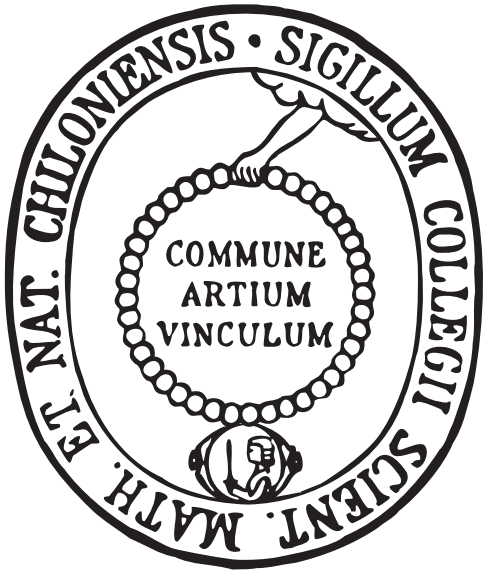
Vom Isophthalamid zum supramolekularen Dendrimer



Dissertation

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„Man muss nicht nur mehr Ideen haben als andere, sondern auch die Fähigkeit besitzen, zu entscheiden, welche dieser Ideen gut sind.“

Linus Pauling

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Schönborn, Heiko Bannick, Saskia Buller und Christian Stoltenberg bleibt unvergessen – Apfelzähne sind viel besser! Ich freue mich, dass unsere Tradition des Semesteressens die anderen Semester mittlerweile übernommen haben. Es ist eine schöne Tradition! Auch bei Adrian Frej und Carsten Grabosch möchte ich mich für die letzten Jahre in der WG bedanken. Ich drücke euch die Daumen, dass ihr auch bald eure Doktorarbeit abgeschlossen habt!

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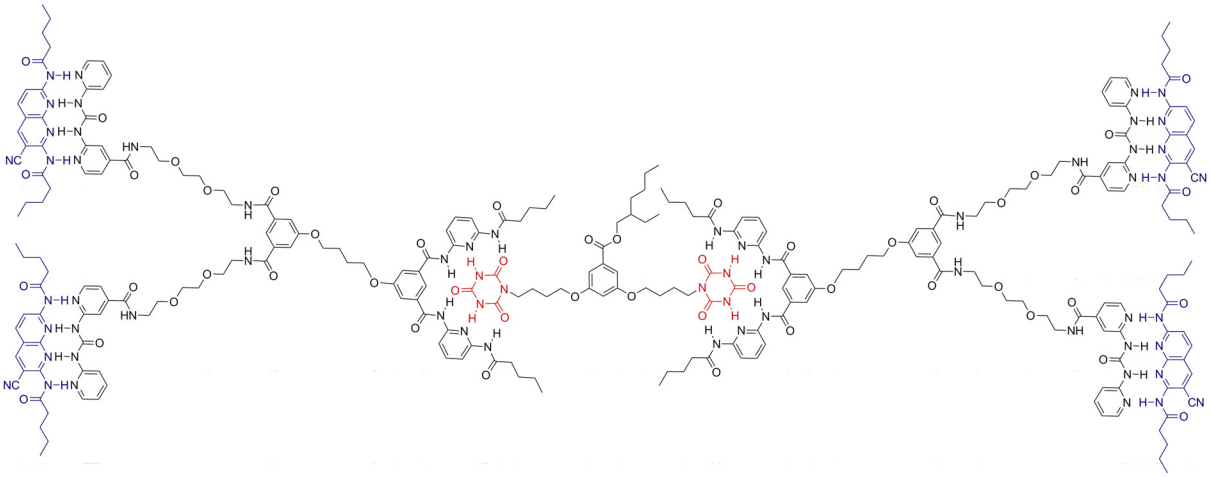
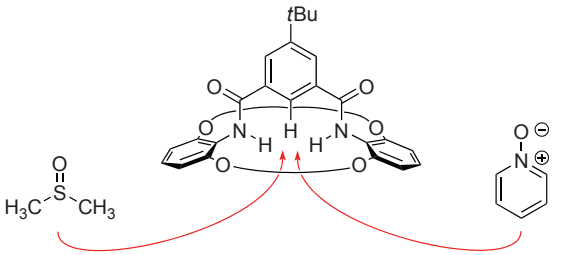
Zusammenfassung

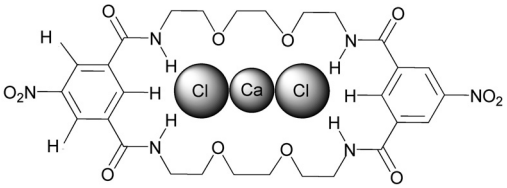
Erstmals konnte ein supramolekulares Dendrimer mit Hilfe von orthogonalen Erkennungsdomänen aufgebaut und untersucht werden. Hierzu wurden im Rahmen dieser Dissertation viele verschiedene Erkennungsbausteine synthetisiert und mit den entsprechenden Bindepartnern in ^{1}H-NMR-Titrationen, ^{1}H-NMR-Diffusionsexperimenten und ITC-Messungen analysiert.



Dabei konnte durch die Einführung von verzweigten Alkylketten, Ethylenglykolketten und Ethern bzw. Estern die Löslichkeit der einzelnen Bausteine erheblich erhöht werden. Zudem konnten verschiedene Isocyanursäure-Kerne erhalten werden. Die Synthese neuer Hamilton-Rezeptoren ermöglicht nun den Aufbau weiterer Dendrimere.

In Zusammenarbeit mit FISCHMANN und SAGGIOMO konnte ein konkaver Bimakrozyklus erhalten werden, der in der Lage ist, Dimethylsulfoxid und Pyridin-*N*-oxid in organischen Lösungsmitteln zu binden. Durch die Entwicklung einer neuen Berechnungsmethode kann mit wenigen Experimenten eine Vielzahl von möglichen Gästen untersucht werden.

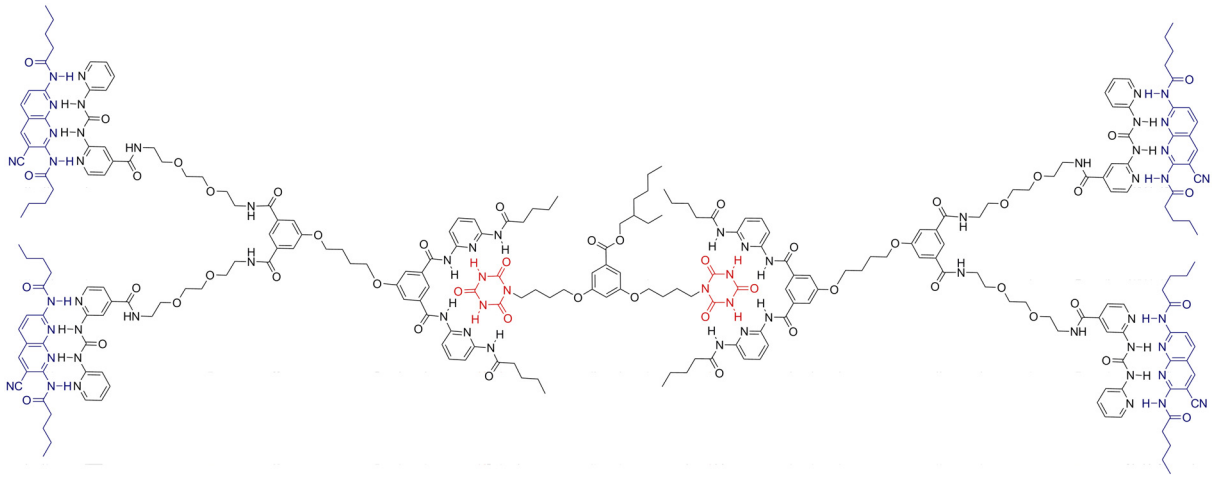




Durch die Synthese eines tritopen Makrozyklus ist es erstmals gelungen, u. a. Calciumchlorid als Ionentriplett in einem organischen Lösungsmittel zu binden. Der Makrozyklus ist in der Lage, die Salze aus dem Feststoff in die Lösung zu extrahieren. Weitere Experimente zum Thema Löslich- und Mischbarkeiten konnten veranschaulichen, dass Vorhersagen zum Verhalten bei Extraktionsversuchen nicht immer möglich sind.

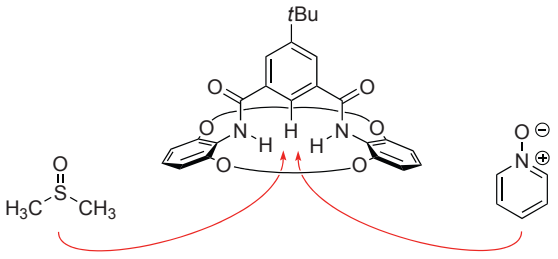
Abstract

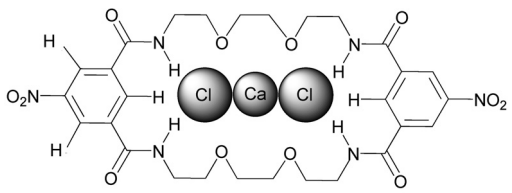
For the first time, a supramolecular dendrimer with orthogonal recognition domains was built up. In this thesis, several different recognition motifs were synthesized and analyzed. Their binding was investigated by ^{1}H NMR titration, ^{1}H NMR diffusion experiments and ITC measurements.



To increase the solubility of the building blocks, branched alkyl chains, ethylene glycol chains, ethers and esters were introduced. Furthermore, the synthesis of different isocyanuric acid cores and several Hamilton receptors made the construction of supramolecular dendrimers possible.

A novel concave bimacrocycle was obtained in collaboration with FISCHMANN and SAGGIOMO. This receptor was able to bind dimethyl-sulfoxide and pyridine-*N*-oxide in organic solvents. A new calculation method was developed to scan several possible guests with little effort.





A tritopic macrocycle was synthesized to bind calcium chloride as an ion triplet in organic solvents. This macrocycle was able to extract different salts into the solvent.

Additional experiments on miscibility and solubility demonstrates the complex world of multi layer experiments.

INHALTSVERZEICHNIS

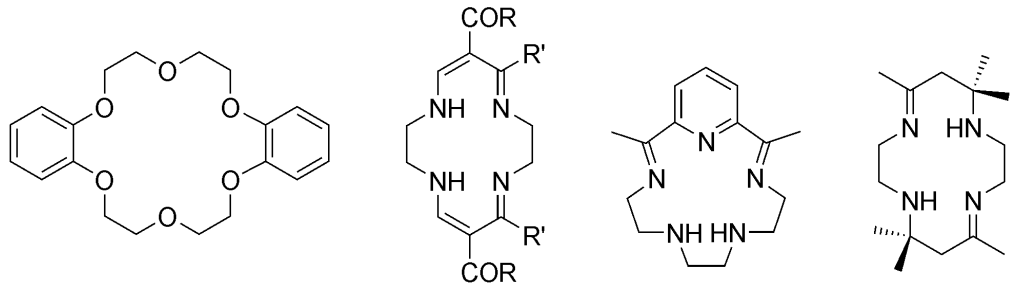
1 Einleitung

1.1 Supramolekulare Chemie

Der Begriff der Supramolekularen Chemie wurde 1978 von LEHN eingeführt. Er beschreibt diesen Bereich als „*chemistry of molecular assemblies and of the intermolecular bond.*“[1,2] Die Forschung im Bereich der Supramolekularen Chemie geht jedoch viel weiter zurück. Bereits 1811 wurde von DAVY ein Gas-Hydrat entdeckt. Er leitete Chlor-Gas bei 0 °C durch eine verdünnte Calciumchlorid-Lösung. Hierbei konnte er grünliche Kristalle abtrennen. Diese Chlor-Hydrat-Kristalle ($Cl_2 \cdot H_2O$) waren aufgrund der Wasserstoffbrückenbindungen zwischen Chlor und Wasser stabil; sie konnten bei Raumtemperatur gelagert werden.[3]

Seit 1811 wurden viele Konzepte entwickelt und erforscht, die heute sehr bekannt sind. Das Schlüssel-Schloss-Prinzip von FISCHER (1894) oder die Strukturuntersuchungen der DNA von WATSON und CRICK (1953) sind nur zwei Beispiele.[4]

In den 1960er Jahren eröffnete die Synthese von Makrozyklen ein neues Kapitel in der Supramolekularen Chemie. Häufig wird dabei PEDERSEN für die Erforschung der Kronenether genannt, aber auch die von CURTIS, BUSCH und JÄGER entwickelten Makrozyklenkonzepte finden in der heutigen Forschung immer noch Anwendung.[1,4]



Pedersen (1967) Jäger (1964) Busch (1964) Curtis (1961)

Seitdem ist die Entwicklung auf diesem Gebiet weit fortgeschritten. Die Synthese von maßgeschneiderten Molekülen für die Molekulare Erkennung ist ebenso eine Herausforderung wie die Nachahmung von biologischen Prozessen. All dieses wäre ohne die Verwendung von Wasserstoffbrücken undenkbar.

1.2 Wasserstoffbrücken

Wasserstoffbrücken findet man an vielen Stellen der Natur und dort haben sie einen großen Einfluss. Die Wasserstoffbrücken im Wasser machen sich besonders beim Verdampfen bemerkbar – um sie aufzulösen, ist sehr viel Energie notwendig. Vergleicht man die Stärke der Wasserstoffbrücken von Wasser mit strukturähnlichen Verbindungen wie zum Beispiel

Schwefelwasserstoff (H_2S), so wird der Unterschied am erheblich höheren Schmelz- und Siedepunkt von Wasser deutlich. Auch die Doppelhelix der DNA wäre ohne vorhandene Wasserstoffbrücken zwischen den Basenpaaren nicht denkbar.

Die Anzahl der Veröffentlichungen pro Jahr mit dem Thema Wasserstoffbrücken ist in den vergangenen Jahren stark angestiegen. Wurden im Jahr 2005 noch 22.685 Arbeiten publiziert, so ist die Zahl in 2011 auf 31.876 angestiegen. Das entspricht immerhin 87 Publikationen pro Tag. Insgesamt sind bis heute über 530.000 Arbeiten mit dem Thema Wasserstoffbrücken im SciFinder® verzeichnet. Auch die IUPAC hat sich in 2011 mit dem Thema der Wasserstoffbrücken beschäftigt und eine neue Definition veröffentlicht.[5,6]

Wasserstoffbrücken bilden sich zwischen Verbindungen, die azide Wasserstoffatome tragen (X-H = z. B. Alkohole, Amide, Amine, Säuren) und denen, die freie Elektronenpaare an elektronegativen Elementen besitzen (Y = Stickstoff, Sauerstoff, besonders ausgeprägt bei Carbonylsauerstoff und Pyridinstickstoff). Dementsprechend werden diese Einheiten als Wasserstoffbrücken-Donor (D) und als Wasserstoffbrücken-Akzeptor (A) bezeichnet.

Die Energie dieser Bindungen (4-120 kJ/mol) und somit auch die Stabilität ist sehr variabel.[4] Die Wasserstoffbrückenbindung wird dabei als eine Überlagerung von vielen Energiebeiträgen betrachtet.[7] Auf große Entfernungen dominiert der Beitrag der elektrostatischen Energie, während bei starker Annäherung die Abstoßung zwischen den Elektronen dominiert.

Ein wesentlicher Aspekt für die Stabilität der Wasserstoffbrücken ist das Lösungsmittel. Dabei bilden sich bei wenig polaren Lösungsmitteln (z. B. Dichlormethan) stabile Komplexe, weil die Lösungsmittel nur schwache Wasserstoffbrücken mit den Verbindungen bilden und kaum eine Konkurrenz darstellen. Bei polaren Lösungsmitteln (z. B. Dimethylsulfoxid) ist die Stabilität der Wasserstoffbrücke hingegen gering. Da das Lösungsmittel selbst als Wasserstoffbrücken-Akzeptor fungieren kann, sind die Bindungskonstanten zwischen Akzeptor und Donor klein.[8-10]

1.3 Wasserstoffbrücken für die Erkennung von Anionen

Bereits 1968 verwendeten PARK und SIMMONS in ihren Katapinanden Wasserstoffbrücken für die Erkennung von Anionen.[11] Ihnen folgten unter anderem SCHMIDTCHEN und LEHN, die viele weitere Kryptanden entwickelten.[12]

Doch erst Anfang der 1990er bekam dieses Forschungsgebiet größere Aufmerksamkeit mit den Arbeiten von SESSLER, GALE, CRABTREE und SMITH.[13-16] Im Jahr 2006 erschien dann das erste Buch, das sich alleine mit dem Thema Anionen-Rezeptor-Chemie befasste.[17] Das Gebiet der Anionen-Erkennung ist seitdem enorm gewachsen, bereits 2008 erschien von VILAR ein weiteres Buch mit dem Titel Anionenerkennung.[18] GALE und DEHAEN konnten 2010 ein weiteres umfassendes Buch mit dem Titel „Anionenerkennung in der Supramolekularen Chemie“ herausgeben.[19]

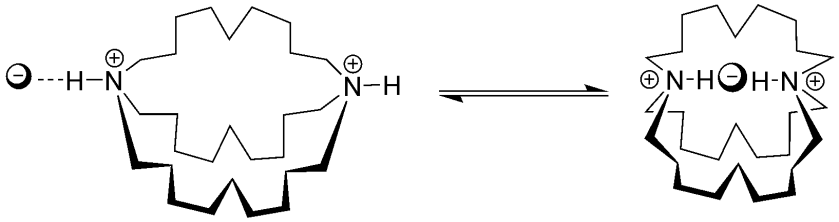
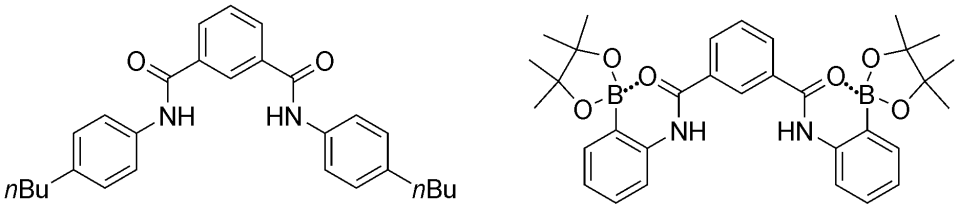


Abb. 1.1: Präorganisierter Katapinand. Die Konformation ändert sich durch den Bindevorgang.

Am Beispiel der Katapinanden (s. Abb. 1.1) erkennt man, dass viele dieser Strukturen für die Anionenerkennung präorganisiert sind. Maßgeschneiderte Systeme für die verschiedensten Anionen zu entwickeln, ist hierbei eine Herausforderung. Nicht nur Amine finden dabei als Donor Anwendung, sondern auch Amide. Die Arbeiten von CRABTREE zur selektiven Bindung von Anionen sind ebenso bedeutsam gewesen wie die zeitgleich entwickelten präorganisierten Boronsäurederivate von SMITH.[20,21]



1.4 Wasserstoffbrückenmuster in der molekularen Erkennung

Zwei Aspekte sind für die selektive Bindung von Molekülen über Wasserstoffbrücken wichtig. Die Moleküle müssen ein geeignetes Muster besitzen, um einen passenden Partner zu binden. Zusätzlich hängt die Stärke der Bindung von der Anzahl der Wasserstoffbrücken ab.

Als Beispiel an dieser Stelle dient erneut die DNA. Kennzeichnet man die Wasserstoffbrücken in den Basenpaaren entsprechend mit „A“ für Akzeptor und „D“ für Donor, erkennt man auf der Seite des Adenins das Muster DA und komplementär dazu im Uracil (RNA) bzw. Thymin (DNA) das Muster AD.

Vergleicht man dieses Basenpaar nun mit dem Paar Guanin-Cytosin, so tragen diese das Muster ADD bzw. DAA. Diese Eigenschaft macht deutlich, dass die Moleküle sich gegenseitig „erkennen“ können und nicht kovalente Bindungen eingehen.

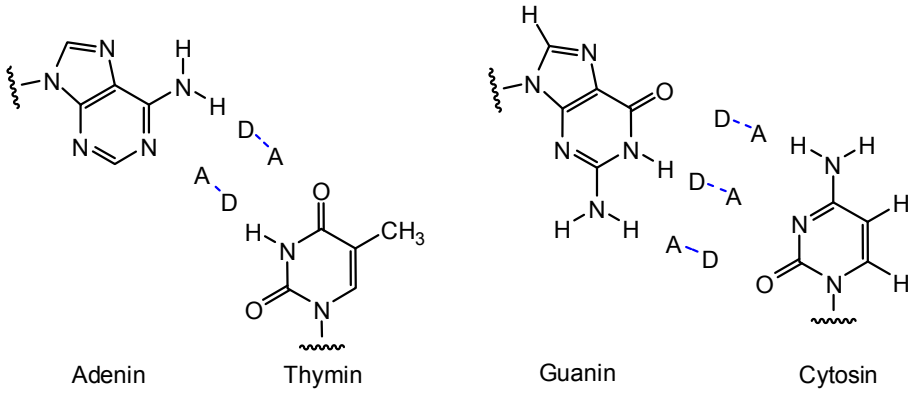


Abb. 1.2: Akzeptor-Donor-Muster in den Watson-Crick-Basenpaaren.[22,23]

TIMMERMAN beschrieb diese Eigenschaft sehr prägnant in der Angewandten Chemie: „*Wasserstoffbrücken ähneln Menschen insofern, als dass sie zur Gruppenbildung neigen. Einzeln sind sie schwach, leicht zu brechen und manchmal schwer zu finden. Handeln sie jedoch gemeinsam, so werden sie viel stärker und unterstützen einander. Bei diesem unter dem Begriff Kooperativität bekannten Phänomen ist 1+1 mehr als 2.*“[7]

Dieses Zitat macht deutlich, dass die Bindungsstärke nicht proportional zur Anzahl der gebildeten Wasserstoffbrücken ist. Dieser Sachverhalt wurde in vielen Arbeiten bereits untersucht und beschreibt diese Eigenschaft als sekundäre Wechselwirkungen. Hierbei kommt es zu einem zusätzlichen positiven Beitrag zur Bindung aus der elektrostatischen Wechselwirkung zwischen Donor und dem diagonal gegenüber liegenden Akzeptor der Komplexpartner bzw. zu einem zusätzlichen negativen Beitrag zur Bindungsstärke aus der Wechselwirkung zwischen Donor und Donor bzw. Akzeptor und Akzeptor (s. Abb. 1.3).

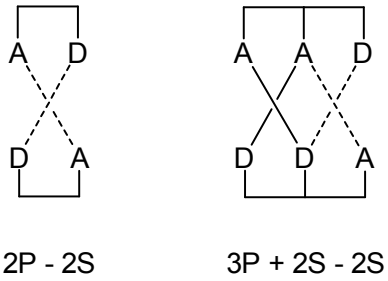


Abb. 1.3: Schematische Darstellung sekundärer Wechselwirkungen von Wasserstoffbrücken, wobei P für primäre (nicht gezeichnet) und S für sekundäre Wechselwirkungen stehen und „—“ einen positiven bzw. „- - -“ einen negativen Beitrag zur Komplexstabilität darstellen.

In der Supramolekularen Chemie wurden bereits viele Bausteine mit Wasserstoffbrückenmustern gezielt synthetisiert. Es handelt sich dabei häufig um Heterocyclen, die von Carbonyl- oder Aminogruppen umgeben sind. Dieses verleiht den Molekülen eine wohldefinierte Abfolge von Wasserstoffbrückendonoren und -akzeptoren und erlaubt die Verwendung als Erkennungsdomäne.[24-27]

Betrachtet man nun ein System aus vier Wasserstoffbrücken, so erhält man aus der Kombination von AAAA bis DDDD zehn verschiedene Muster. Die Muster AADD und ADAD bilden Homodimere. Hierzu sind in der Literatur unter anderem Arbeiten von MEIJER bekannt.[28] Für den Aufbau von orthogonalen Erkennungsdomänen sind sie jedoch nicht von Interesse. Obwohl die restlichen vier Heterodimere (AAAA·DDDD, ADDA·DAAD, AAAD·DDDA und AADA·DDAD) alle über vier Wasserstoffbrücken verfügen, so unterscheidet sich ihre berechnete Assoziationskonstante aufgrund der unterschiedlichen sekundären Wechselwirkungen.[29] Untersuchungen am Muster DDDD konnten durch Protonierung am System DADD von TAUBITZ durchgeführt werden, weiter gelang ihm die Synthese eines löslichen AAAA-Musters.[30,31] LEIGH und HUNTER konnten 2011 ein weiteres AAAA·DDDD System veröffentlichen. Die in Dichlormethan erhaltene Assoziationskonstante von $3 \cdot 10^{12}$ M^{-1} ist bemerkenswert.[32]

In den Arbeiten von KÜHL, UPHOFF und BRAMMER wurden unter anderem Systeme mit Vierfach-Wasserstoffbrücken entwickelt und untersucht.[25-27,33-35] Hierbei wurden die Kombinationen (AADA, DAAD) und komplementäre Partner (DDAD, ADDA) synthetisiert und getestet.

Das Musterpaar ADDA·DAAD besteht zur einen Hälfte aus einem Harnstoffderivat (ADDA) und zur anderen Hälfte aus einem Naphthyridinderivat (DAAD). Dabei besitzt der Komplex neben den vier primären Wechselwirkungen auch zwei positive und vier negative sekundäre Wechselwirkungen (s. Abb. 1.4).

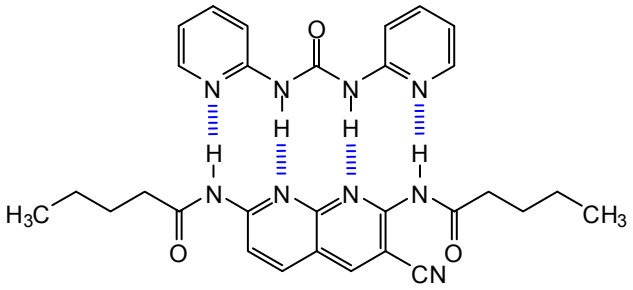


Abb. 1.4: Das Paar ADDA·DAAD mit vier Wasserstoffbrückenbindungen.

Ein häufig wiederkehrendes Erkennungsmuster haben HAMILTON und CHANG 1987 veröffentlicht. Sie entwickelten einen Rezeptor, der das Muster DAD^DAD trägt (^ = gewinkelt). Dieser ist in der Lage, ein komplementäres Muster ADA^ADA, wie es zum Beispiel in Barbital (Diethylbarbitursäure) vorkommt, zu binden. (s. Abb. 1.5). Die Bindung erfolgt über sechs Wasserstoffbrücken und gehört somit zu den stabileren Wasserstoffbrückenkomplexen, obwohl sie ausschließlich über negative sekundäre Wechselwirkungen verfügt. Die für diesen Komplex bestimmte Assoziationskonstante, die ein Maß für die Komplexstabilität ist, wurde mit $K_{ass} = 1.37 \cdot 10^6$ M^{-1} bestimmt.[36]

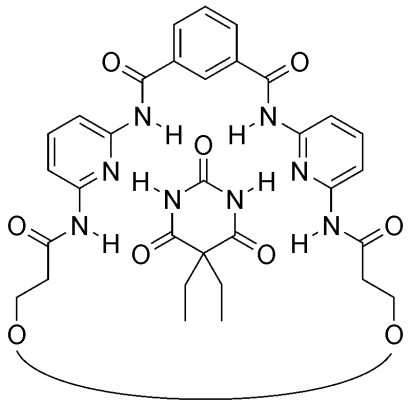


Abb. 1.5: Schematische Darstellung des Komplexes aus Hamilton-Rezeptor und Barbital.[36]

BRAMMER konnte zeigen,[34] dass sich das Bindungsmuster-Paar ADDA·DAAD orthogonal zu dem von HAMILTON entwickelten DAD^DAD-Muster verhält. Dieses hat zur Folge, dass die beiden Muster nebeneinander verwendet werden können, ohne dass es zur Ausbildung von falschen Musterpaaren kommt.

Die Komplexassoziationskonstante K_{ass} bestimmt sich aus den Konzentrationen von freiem Wirt [W], freiem Gast [G] und der Konzentration vom Komplex [WG] gemäß der Gleichung (**1**).

$$K_{ass} = \frac{[WG]}{[W] \cdot [G]} \qquad (\mathbf{1})$$

Für die obigen Beispiele wurden mit Hilfe von ^{1}H-NMR-Titrationen die Assoziationskonstanten bestimmt. Hierbei nutzt man den Effekt aus, dass sich die Protonen der Amide, während sie sich im Komplex befinden, einen Tieffeldshift erfahren. Aufgrund des schnellen Austauschs erhält man einen Mittelwert aus freien und gebundenen Molekülen und kann mit Hilfe der chemischen Verschiebung eine Aussage treffen, welcher Anteil der Moleküle gebunden ist.

Neben der ^{1}H-NMR-Titration können solche Komplexe auch mit Hilfe von ^{1}H-NMR-Diffusionsexperimenten untersucht werden. Bei diesem Experiment werden die Diffusionsgeschwindigkeiten der Komplexpartner bestimmt. Je größer der Komplex ist, desto langsamer diffundiert dieser im angelegten Gradientenfeld. Hieraus erhält man Informationen über die Komplexstabilität. Im Idealfall, der Komplex dissoziiert nicht in Wirt W und Gast G, diffundieren alle Moleküle mit der gleichen Diffusionsgeschwindigkeit. Abweichungen von diesem Wert bedeuten, dass ein Teil ungebunden vorliegt, da die Einzelkomponenten schneller diffundieren als der Komplex.

Eine sehr weit verbreitete Methode ist zudem die Isotherme Titrationskalorimetrie (isothermal titration calometry, ITC). Auch bei dieser Titrationsmethode wird der Gast schrittweise zu einem Wirt zugegeben. Das Gerät besteht aus zwei Zellen (Mess- und Referenzzelle), die adiabatisch von der Umgebung entkoppelt sind und auf gleiche Temperatur beheizt werden. Die beim Komplexierungsvorgang freiwerdende bzw. aufgenommene Energie führt zu einer Temperaturänderung in der Messzelle. Dieser Unterschied wird durch das Regeln eines Heizelementes ausgeglichen und registriert. Das Resultat ist eine Titrationskurve, die die Leistung in µcal/s über die Titrationsdauer wiedergibt. Mit dieser quantitativen Messmethode lässt sich neben der Bindungskonstanten K_{ass} und Bindungsenthalpie ΔH auch die Bindungsstöchiometrie n bestimmen. Weitere Parameter lassen sich über die Gibbs-Helmholtz-Gleichung berechnen (**2**).

$$\Delta G = RT \ln K = \Delta H - T\Delta S \quad (\mathbf{2})$$

1.5 Wasserstoffbrücken für den Aufbau von Dendrimeren

Die Entwicklung der Dendrimere begann mit den ersten Kaskadenmolekülen, die VÖGTLE, BUHLEIER und WEHNER 1978 herstellen konnten.[37] Für seine Kaskadenreaktion wählte VÖGTLE eine zweifache Michael-Addition mit Acrylnitril und eine anschließende Reduktion (s. Abb. 1.6). Durch Wiederholung dieser Synthesesequenz gelang es erstmals, regelmäßig verzweigte Moleküle herzustellen.

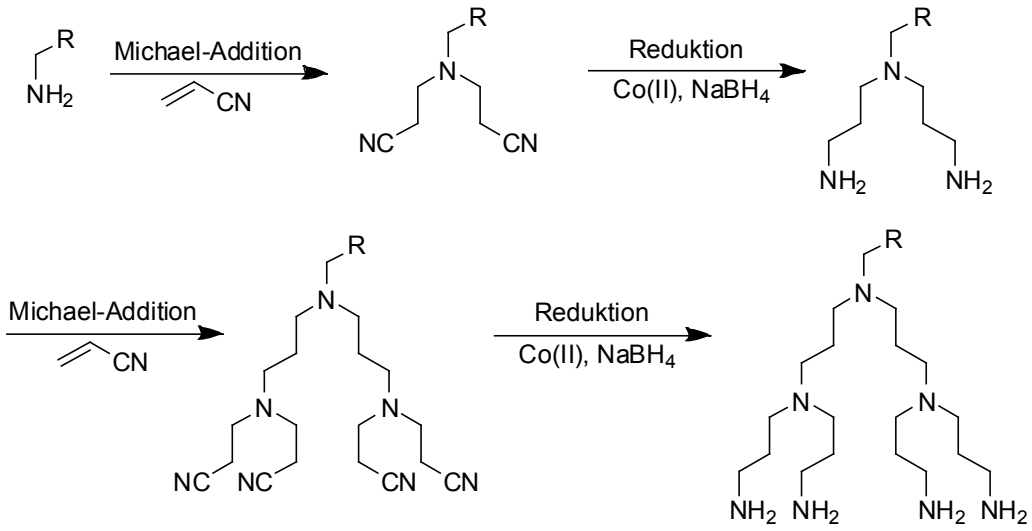


Abb. 1.6: Synthese eines Kaskadenmoleküls nach VÖGTLE ausgehend von einem primären Amin und Acrylnitril.

Erst 1986 führte TOMALIA den Begriff des Dendrimers ein, der sich bis heute durchgesetzt hat. Dabei nutzte er für die verzweigten Poly(amidoamine) [PAMAM] den Namen „Starburst-Dendrimere“.[38] Das Aussehen der Moleküle erinnert an einen Strahlenkranz und die verzweigte Struktur ähnelt Baumverästelungen (s. Abb. 1.7). Die hierbei gebildeten Schichten werden als Generationen bezeichnet, wobei der Kern die 0. Generation (G0) bildet.

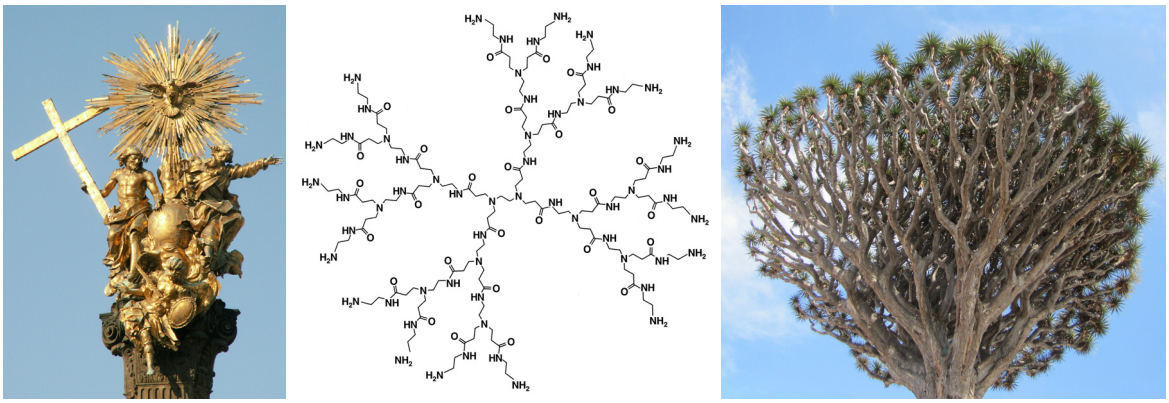


Abb. 1.7: Barocksäule der Heiligen Dreifaltigkeit mit Strahlenkranz, Olmütz, Tschechische Republik (Foto: Jan Kameníček), Starburst-Dendrimer PAMAM, Drachenbaum (Foto: Ulrich Lüning).

1.5.1 Synthese von Dendrimeren

Bei der Synthese von Dendrimeren werden verschiedene Methoden verwendet: Bei der divergenten Synthese werden die Dendrimere schrittweise von innen nach außen aufgebaut. Startend von einem multifunktionalisierten Kernbaustein (K) schließen sich Verzweigungsbausteine an, die schließlich durch Endgruppen abgeschlossen werden. Durch die Verwendung von Schutzgruppen kann über eine repetitive Synthesesequenz bestehend aus Kupplung und Aktivierung das Dendrimer aufgebaut werden.[39]

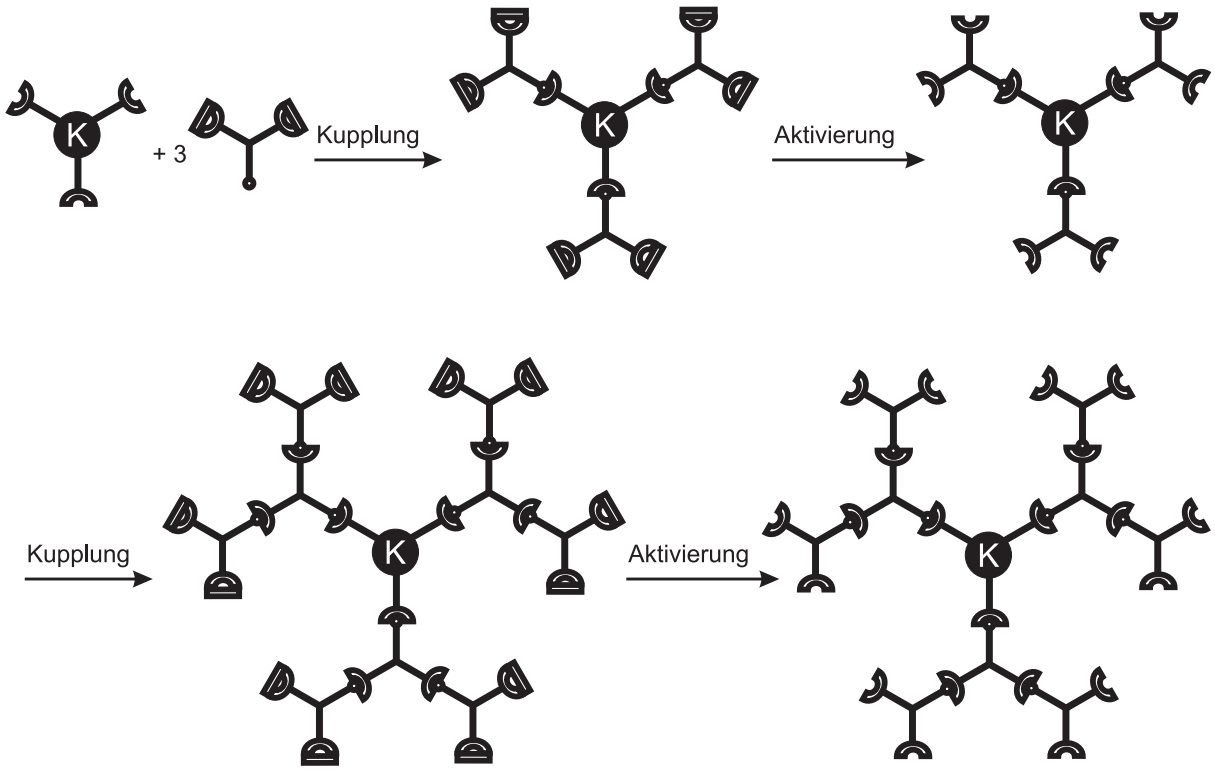


Abb. 1.8: Schematische Darstellung der divergenten Synthesemethode. Ausgehend von einem Kernbaustein und drei Verzweigungsbausteinen erfolgt der Aufbau des Dendrimers. Nach jeder Kupplung erfolgt die Aktivierung z. B. durch Abspaltung einer Schutzgruppe.

Ein wesentliches Problem bei der Synthese ist, dass durch den exponentiellen Anstieg der Endgruppen bei nicht quantitativen Reaktionen Defekte im Dendrimer entstehen können. Das Abtrennen dieser defekten Dendrimere von den perfekten ist aufgrund der Strukturähnlichkeit kaum möglich. Auch die von VÖGTLE und TOMALIA vorgestellten Dendrimere wurden über divergente Synthesen erhalten.

Eine weitere Methode zum Aufbau ist die konvergente Synthese, wobei die Dendrimere von außen nach innen aufgebaut werden. Dabei werden Dendrimer-Teilstücke (Dendrone) mit einem Kernstück verbunden. Ein wesentlicher Vorteil dieser Methode ist, dass die Aufarbeitung vereinfacht ist und weniger Strukturdefekte erhalten werden.

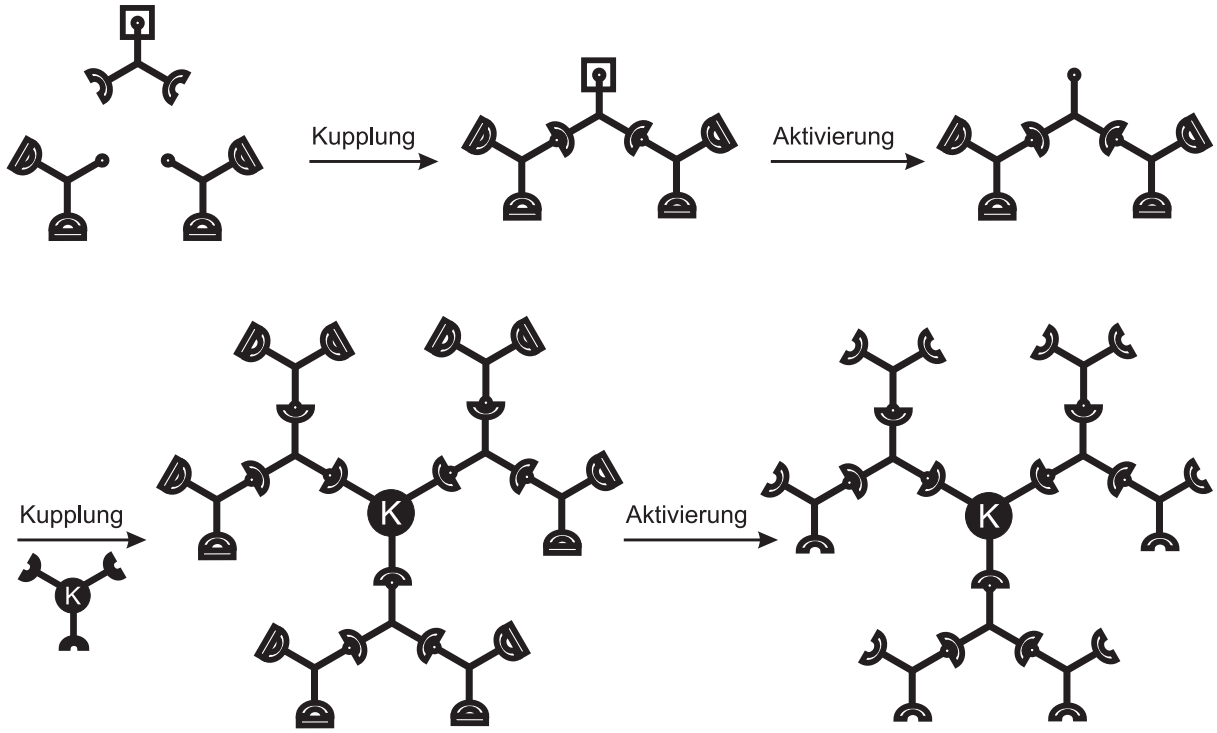
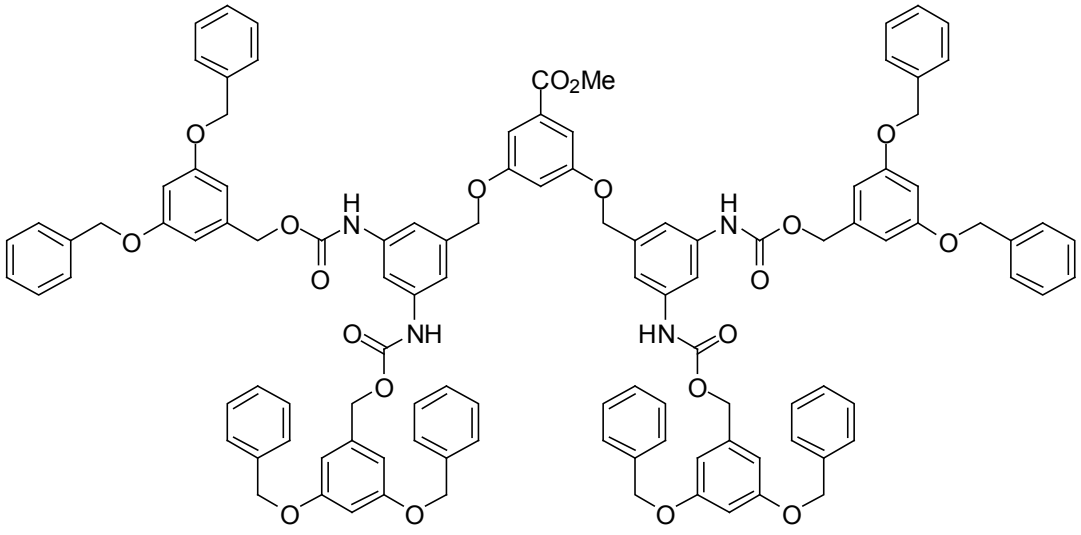


Abb. 1.9: Schematische Darstellung der konvergenten Synthesemethode. Ausgehend von Verzweigungs- bzw. Endbausteinen werden Dendronen aufgebaut, die dann nach Aktivierung mit dem Kern gekuppelt werden.

Eine moderne Synthesemethode ist die orthogonale Synthese. Hierbei werden abwechselnd zwei verschiedene Verzweigungseinheiten verwendet, die über orthogonale Kupplungsfunktionen verfügen. Dadurch, dass Schutzgruppen nicht mehr notwendig sind, ist es möglich, das Dendrimer mit weniger synthetischen Schritten aufzubauen. Erstmals gelang SPINDLER und FRÉCHET diese Methode beim Aufbau des unten abgebildeten Dendrons der dritten Generation.[40]



ZIMMERMAN gelang es 1996 auf diese Art und Weise, ein Dendrimer mit sechs Generationen herzustellen. Die hierfür verwendeten orthogonalen Synthesen sind in Abb. 1.10 vorgestellt.[41]

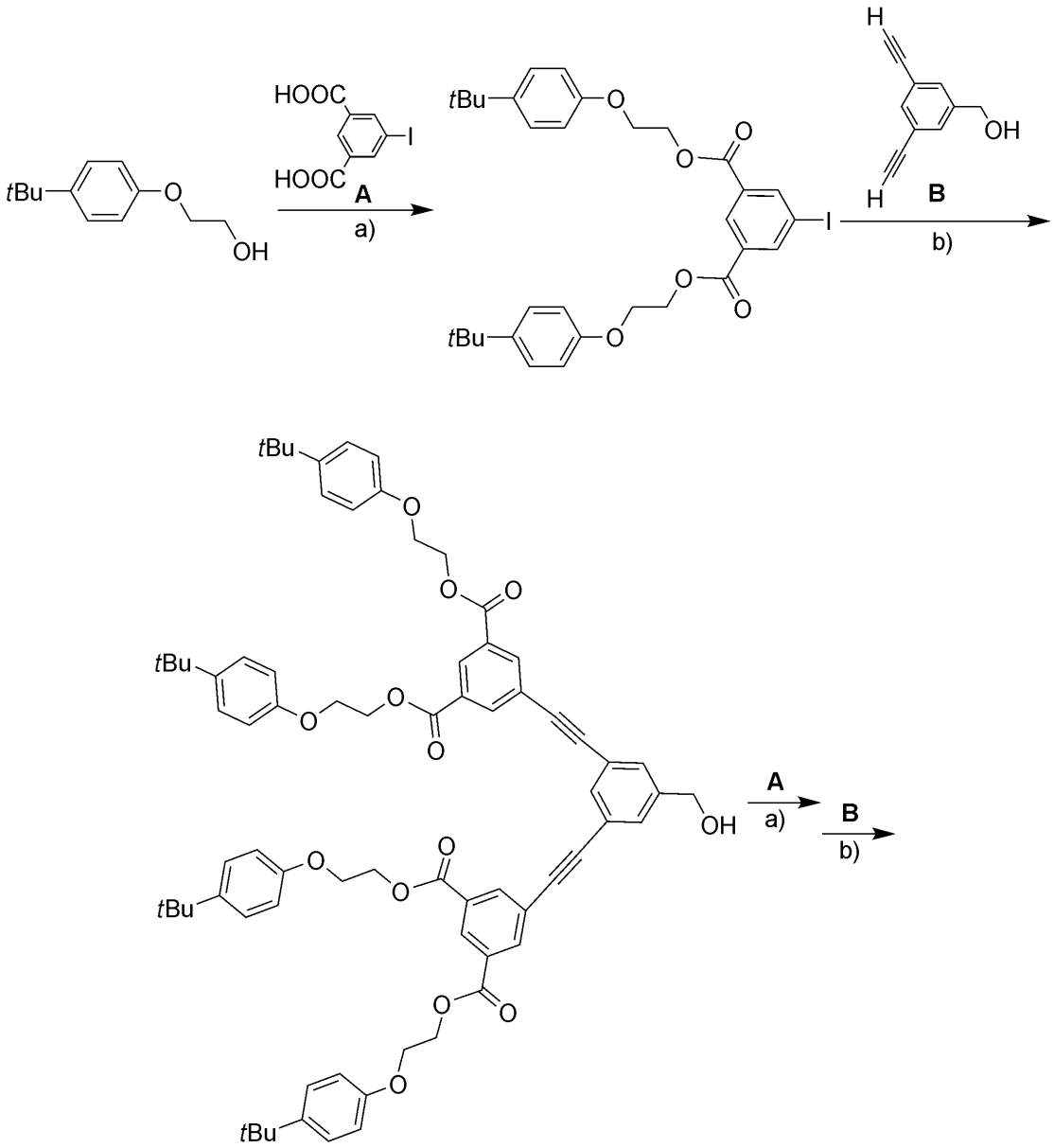


Abb. 1.10: Dendrimer-Aufbau durch die Verwendung von orthogonalen Kupplungsreaktionen. a) PPh_3, Diethylazodicarboxylat (DEAD), THF. b) $Pd(PPh_3)_2Cl_2$, CuI, oder $Pd_2(dba)_3$, CuI, PPh_3, Et_3N, $PhCH_3$.

Die bisher vorgestellten Synthesen beruhen auf der Ausbildung von konvalenten Bindungen. Beim Aufbau der Dendrimere über eine supramolekulare Synthese werden jedoch nicht-kovalente Wechselwirkungen verwendet. Eine Möglichkeit ist, den Kern durch ein Metall zu ersetzen, welches die Dendrone entsprechend koordiniert. FRÉCHET konnte auf diese Art und Weise Polyether-Dendrone über ein Lanthanoid-Ion zu einem Dendrimer koordinieren.[42]

Verzichtet man nun aber nicht nur auf einen kovalent gebundenen Kernbaustein, sondern versucht man, auch die Dendrone über nicht-kovalente Wechselwirkungen aufzubauen, so liegt die Verwendung von Wasserstoffbrückenmustern nahe.

Diese Idee ermöglicht den Selbstaufbau des Dendrimers nach einfachem Zusammenmischen der einzelnen Bausteine im richtigen Verhältnis von Kern zu Verzweigungseinheit und Kappe. HIRSCH konnte 2005 erstmals dieses Konzept realisieren,[43,44] jedoch hat das von ihm verwendete System einen wesentlichen Nachteil. Da Kern, Verzweigungseinheit und Termini die gleichen Erkennungsmuster haben, ist ein fehlerfreier Aufbau nicht gewährleistet.

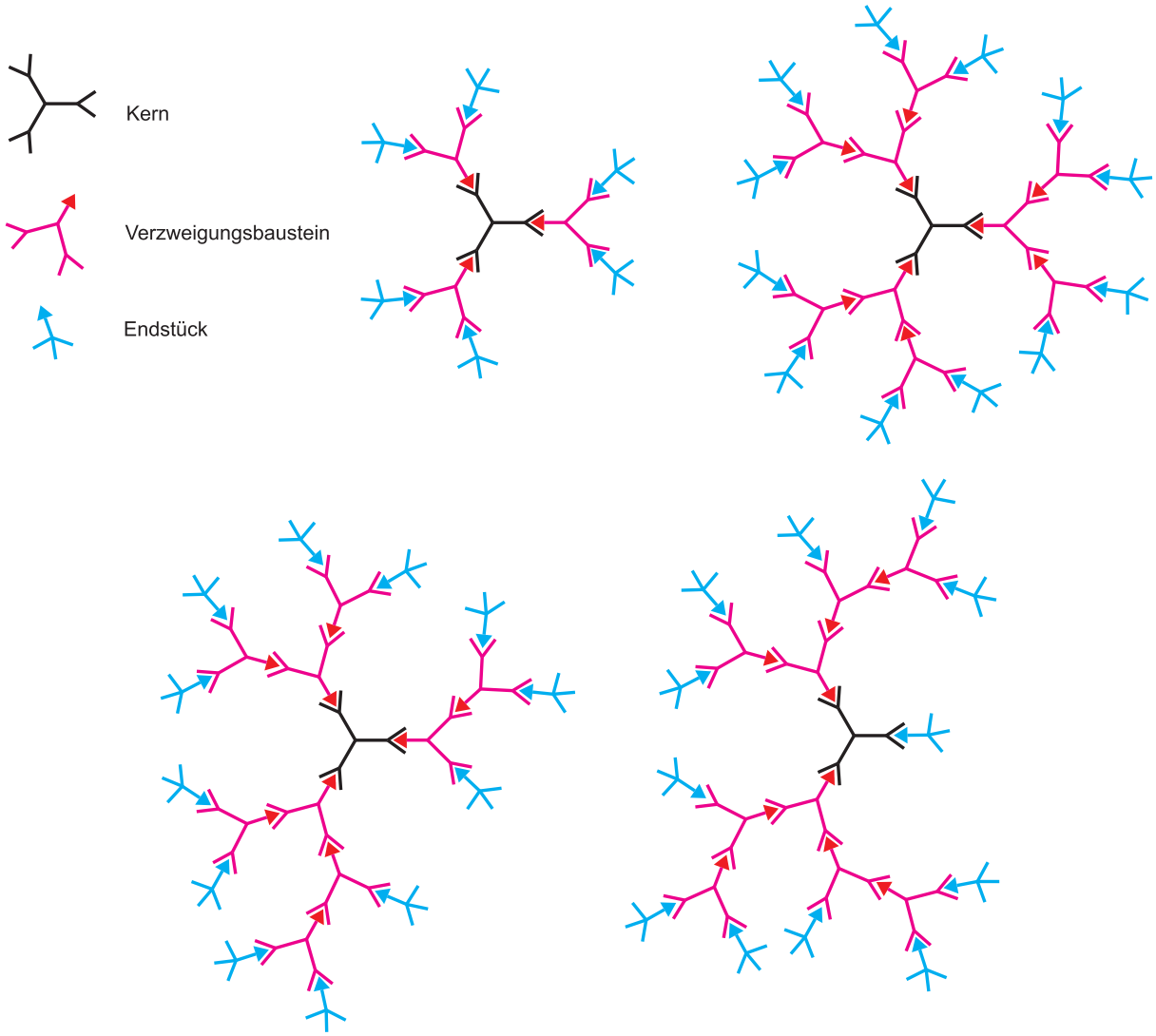


Abb. 1.11: Schematische Darstellung der von HIRSCH entwickelten Dendrimere (1:3:6 und 1:9:12) im Baukastenprinzip (oben). Die unteren beiden Dendrimere demonstrieren, dass bei nicht orthogonalen Erkennungsdomänen ein einheitlicher Aufbau nicht garantiert ist. Die Anzahl an Kern-, Verzweigungs- und Endbausteinen ist jeweils identisch mit 1:9:12.

Abb. 1.11 macht deutlich, dass bei gleicher Stöchiometrie verschiedene Dendrimere erhalten werden können. Um dieses Problem zu umgehen, ist es notwendig, dass Kern, Verzweigungsbaustein und Endkappe über orthogonale Wasserstoffbrückenmuster verbunden werden. Nur

so ist ein fehlerfreier Aufbau Schale für Schale möglich, und das Dendrimer kann sich später nicht, im Gleichgewicht mit den Bausteinen, falsch aufbauen.

Im Arbeitskreis Lüning wurden hierzu in den vergangenen Jahren eine Vielzahl von orthogonalen Wasserstoffbrückenrezeptoren entwickelt, die den fehlerfreien Aufbau eines Dendrimers ermöglichen sollen (vgl. Abb. 1.10).[26,27,35]

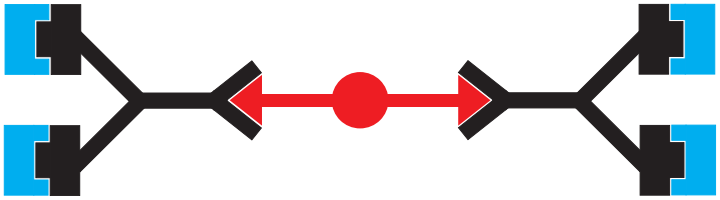
1.5.2 Anwendung von Dendrimeren

Die Anwendung von Dendrimeren ist ebenso vielfältig wie deren Synthese. Sie finden nicht nur in der Katalyse Anwendung,[45-47] sondern auch als Pigmente, Klebstoffe und Additive.[48-50] Verglichen mit Polymeren zeichnen sie sich durch ihre Monodispersität, Variabilität und Funktionalisierungsmöglichkeiten aus. XEROX CORP. verwendet für einen Trockentoner Dendrimere als Additive, sie fungieren als ladungserhöhende Spezies.[51] Auch die Verwendung von Dendrimeren in Displays ist möglich. Die dendritisch modifizierten **p**olymeren **l**icht**e**mmitierenden **D**ioden (PLED) beeindrucken durch eine deutlich höhere Helligkeit und Lebensdauer im Vergleich zu gewöhnlichen LEDs.[52] In der Medizin finden Dendrimere unter anderem ihre Anwendung beim Verkapseln von Wirkstoffen. KOJIMA konnte ein PAMAM-Dendrimer mit Polyethylenglycolketten entwickeln, das in der Lage ist, Antikrebsmedikamente langsam und gleichmäßig abzugeben.[53]

Als SuperFect® befindet sich ein von der Fa. Qiagen entwickeltes Transfektionsmittel im Handel. Es handelt sich um ein gelandenes PAMAM-Dendrimer, das in der Lage ist, DNA-Bausteine in Zellen einzuschleusen.[54,55] Ein Dendrimer auf Gadoliniumbasis ist von Bayer Healthcare unter dem Namen Gadomer® auf dem Markt. Es findet als Kontrastmittel im MRT Anwendung.[56,57]

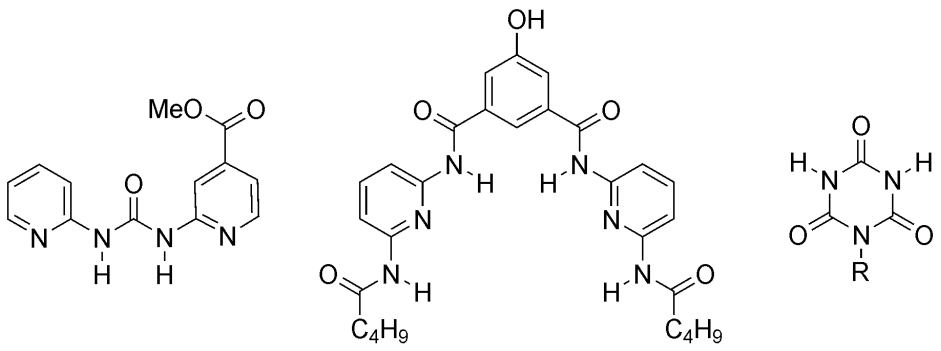
2 Aufgabenstellung

Für den fehlerfreien Aufbau eines supramolekularen Dendrimers sind unterschiedliche orthogonale Bindedomänen notwendig (vgl. Kapitel 1.5). In den vergangenen Jahren wurden im Arbeitskreis LÜNING bereits eine Vielzahl von verschiedenen orthogonalen Wasserstoffbrückenmustern entwickelt und untersucht. Dabei gibt es neben den linearen Mustern z. B. in Dipyridylharnstoffderivaten (ADDA) auch gewinkelte Muster, wie sie in der Barbitur- bzw. Isocyanursäure (ADA^ADA) vorkommen. Das Ziel, diese Einheiten in einem supramolekularen Dendrimer zu vereinen, konnte bisher nicht erreicht werden.



Neben einem entsprechenden multitopen Kern fehlte auch eine Verzweigungseinheit, die das baumartige Wachstum des Dendrimers ermöglichen sollte (vgl. Kapitel 1.5). Ein wesentliches Problem war die schlechte Löslichkeit der einzelnen Bausteine, so dass zwar die notwendigen Erkennungsdomänen isoliert werden konnten, aber eine Verknüpfung bisher nicht gelang. DETHLEFS gelang es erstmals, analytische Mengen einer Verzweigungseinheit zu isolieren.[58] Die Synthese war aber noch nicht optimiert, und eine ungünstige Schutzgruppenstrategie führte zu einer hohen Stufenanzahl bis zur Verzweigungseinheit (s. Abb. 2.1).

Ein Ziel dieser Arbeit war die Verbesserung der Löslichkeit der einzelnen Bausteine. Besonders die Erkennungsmuster ADDA (Pyridylharnstoffderivate) und ADA^ADA (Isocyanursäurederivate) waren bisher schlecht löslich. Aber auch die Hamilton-Rezeptoren (DAD^DAD), die bisher mit *n*-Butyl-Ketten endeten, hatten, je nach Substituent an der Isophthalsäure, keine ausreichende Löslichkeit in Chloroform bzw. Dichlormethan.



ADDA **DAD^DAD** **ADA^ADA**

Ein weiteres Ziel war die Entwicklung einer effizienteren Synthese für den Verzweigungsbaustein, damit dieser in ausreichenden Mengen zum Aufbau eines supramolekularen Dendrimers zur Verfügung steht.

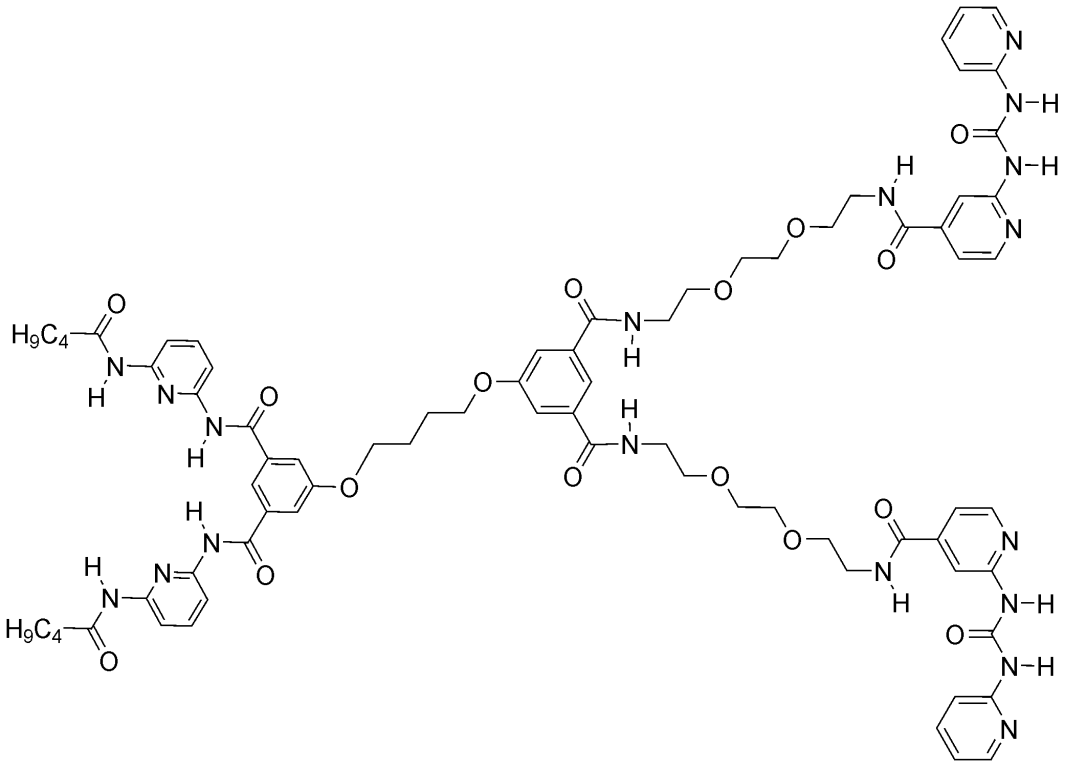


Abb. 2.1: Von DETHLEFS erhaltene Verzweigungseinheit mit dem Erkennungsmuster DAD^DAD und zwei ADDA-Domänen.

Weiter mussten in dieser Arbeit passende lösliche Kernbausteine hergestellt werden. Bevor komplexere Dendrimere aufgebaut und untersucht werden können, sollte man hierfür mit einem mono- und ditopen Kern beginnen. Schließlich sollte das erste supramolekulare Dendrimer zweiter Generation mit orthogonalen Erkennungsdomänen aufgebaut und untersucht werden.

Ein zentraler Baustein beim Aufbau der Erkennungsdomänen sind Isophthalamide. Zwar wurden diese bisher im Arbeitskreis LÜNING im Wesentlichen für den Aufbau von Wasserstoffbrückenmustern genutzt, es gibt jedoch auch zahlreiche Beispiele für die Erkennung von Anionen und/oder Ionenpaaren durch Isophthalamide (vgl. Kapitel 1.3).

Darum soll versucht werden, das Isophthalamidmuster in ein konkaves Molekül einzubauen, damit neben der bekannten Anionenerkennung auch eine größenselektive Erkennung erfolgen könnte. Die Entwicklung eines tritopen Makrozyklus, der in der Lage ist, Ionentripletts (z. B. $CaCl_2$) zu binden, ist eine Herausforderung und wäre ein Fortschritt auf dem Gebiet der Supramolekularen Erkennung.

Die Löslichkeit der Komponenten spielt bei der Synthese der Bausteine und bei den Untersuchungen eine wichtige Rolle. Aber auch die Mischbarkeit von Lösungsmitteln und Salzen darf bei Extraktionsexperimenten nicht vernachlässigt werden. Es soll gezeigt werden, dass Vorhersagen zur Löslichkeit und Mischbarkeit nicht immer einfach sind und der Aufbau von mehrphasigen Systemen möglich ist. Diese Ergebnisse könnten für spätere Transport- und Extraktionsexperimente genutzt werden.

3 Ergebnisse und Diskussion

Das Themengebiet der Supramolekularen Chemie ist vielfältig. Der Aufbau von supramolekularen Strukturen und die Erkennung von Gästen sind dabei wichtige Elemente. Werden größere Strukturen aufgebaut oder werden Wasserstoffbrücken für die Erkennung verwendet, so spielt die Löslichkeit der Bausteine eine zentrale Rolle. Diese drei Themengebiete wurden deshalb in dieser Arbeit untersucht.

Diese kumulative Dissertation besteht aus sieben Veröffentlichungen, die im Folgenden zusammengefasst sind. Dabei wird jede Veröffentlichung durch eine eigene Seite eingeleitet.

Die ersten beiden Veröffentlichungen beschäftigen sich mit dem Thema der Löslich- und Mischbarkeit. Sie machen die Komplexität des Themas auf eine didaktisch ansprechende Methode deutlich (Kapitel 3.1 und Kapitel 3.2). Sie veranschaulichen, dass bereits eine kleine Änderung des Lösungsmittels bzw. der Verbindung einen großen Einfluss auf die Löslichkeit bzw. die Mischbarkeit haben kann.

Die Erkennung von Barbitursäuren mit Hilfe von Hamilton-Rezeptoren über Wasserstoffbrücken wird im Kapitel 3.3 diskutiert. Die hierbei verwendeten Wirte und Gäste sind aufgrund ihrer sechs Wasserstoffbrücken ein wichtiger Baustein für den Aufbau von Dendrimeren, weil sie einerseits eine starke Bindung ausbilden und andererseits über ein Wasserstoffbrückenmuster codiert sind. Durch das Einfügen von verzweigten Alkylketten konnte die Löslichkeit erheblich verbessert werden.

Die Verwendung von orthogonalen Wasserstoffbrückenmustern ermöglicht einen fehlerfreien Aufbau von supramolekularen Dendrimeren. In den vergangenen Jahren konnte dieses im Arbeitskreis Lüning nicht realisiert werden, besonders die Löslichkeit der Einzelkomponenten war ein großes Problem. Erstmals gelang es nun, ein solches Dendrimer herzustellen und zu untersuchen. Die bisherigen Probleme, besonders die Löslichkeit der Einzelkomponenten, konnten behoben werden (Kapitel 3.4).

Isophthalamide können nicht nur im Hamilton-Rezeptor für die Erkennung von Barbitur- und Isocyanursäuren genutzt werden, sie werden auch für die Anionenerkennung verwendet. Im Kapitel 3.5 wird gezeigt, dass auch die Erkennung von ungeladenen Gästen wie Dimethylsulfoxid und Pyridin-*N*-oxid möglich ist. Ein konkaver Bimakrozyklus ermöglicht zudem eine Größenselektivität.

Durch die Verwendung zweier Nitroisophthalamide, die über Ethylenglykolketten verbunden sind, wurde es erstmals möglich, Calciumchlorid als Ionentriplett in einem Makrozyklus zu binden (Kapitel 3.6). Weitere Experimente mit einer Vielzahl von Alkali- und Erdalkalisalzen haben gezeigt, dass der Makrozyklus noch weitere Salze binden kann (Kapitel 3.7).

3.1 James-Bond-Cocktail – Gerührt oder geschüttelt?

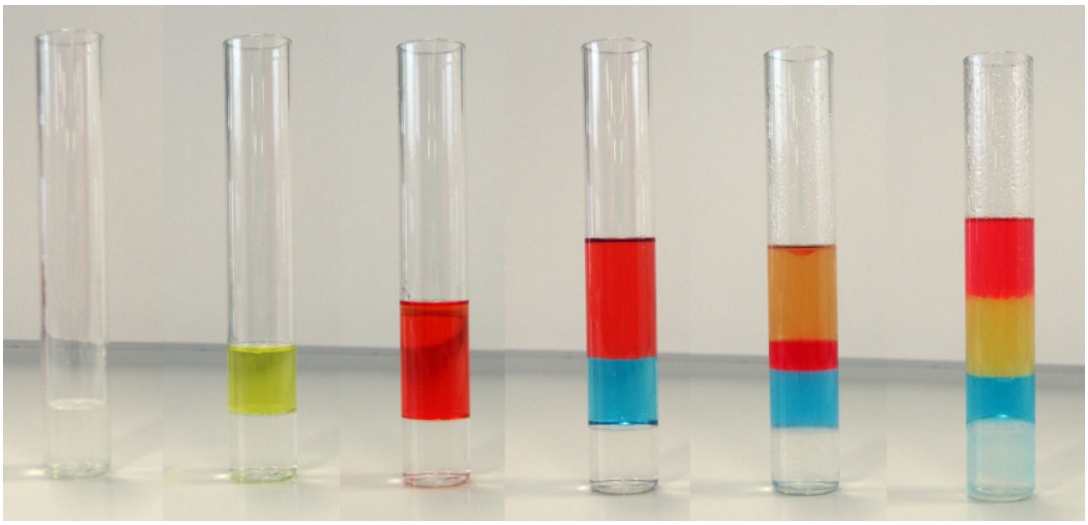
J. Eckelmann, U. Lüning, *Chem. Unserer Zeit* **2009**, *43*, 210-212.

DOI: 10.1002/ciuz.200900484

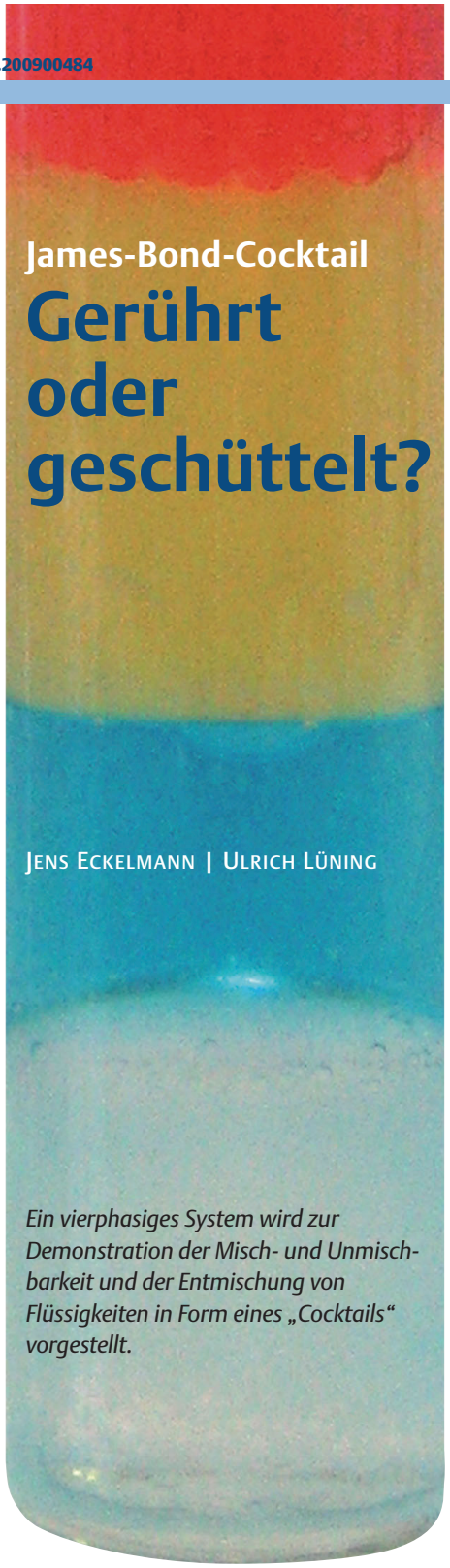
Ob eine Verbindung in Lösungsmitteln löslich ist, hängt von vielen Faktoren ab. Während beim Aufarbeiten von Synthesen häufig zwei Phasen erwünscht sind, kann es dabei auch zur Ausbildung von mehreren Phasen kommen. Die Chemische Ampel ist seit vielen Jahren in der Literatur bekannt und findet in Vorlesungen häufig Anwendung. Sie besteht aus drei nicht mischbaren Phasen, die verschieden eingefärbt sind.

In dieser Arbeit konnte ein besonderer Cocktail hergestellt werden. Die Zugabe der Lösungsmittel und die unterschiedliche Art der Durchmischung machen die Komplexität des Themas deutlich. Ausgehend von Perfluorheptan, gesättigter wässriger Kaliumcarbonatlösung, Methanol, Toluol wurde eine dreiphasige Mischung hergestellt, die sich nach Schütteln – nicht nur Rühren – in vier Phasen trennte. Durch die anschließende Zugabe von *n*-Pentan konnte die Reihenfolge zweier Phasen verändert werden. Durch die Verwendung von geeigneten Farbstoffen wurden die Phasen unterschiedlich eingefärbt. Die erhaltenen vier Phasen sind über viele Monate stabil und trennen sich innerhalb von einigen Sekunden, wenn man versucht, sie zu vermischen. Das besondere Verhalten macht den Versuch für Demonstrationsexperimente sehr interessant.

Der Aufsatz wurde 2010 vom Wiley-VCH Verlag als einer der beliebtesten ChiuZ-Aufsätze in 2009 ausgezeichnet.



DOI: 10.1002/ciuz.200900484



James-Bond-Cocktail

Gerührt oder geschüttelt?

Jens Eckelmann | Ulrich Lüning

Ein vierphasiges System wird zur Demonstration der Misch- und Unmischbarkeit und der Entmischung von Flüssigkeiten in Form eines „Cocktails“ vorgestellt.

Mehrphasige Systeme sind wohlbekannt und gut beschrieben [1, 2]. Der klassische Vertreter ist das Zweiphasensystem bestehend aus Wasser und einer organischen Verbindung, zum Beispiel Öl. Auch ein dreiphasiges System wurde aus den Arbeiten von Schunk unter dem Namen „chemische Ampel“ in der Literatur bekannt und findet in der chemischen Lehre seine Anwendung. Diese einfach durchzuführenden Versuche veranschaulichen die komplexe Welt der Mischbarkeit auf eine beeindruckende Weise.

Das Entmischen einer Phase – die „chemische Ampel“

Zum Aufbau eines dreiphasigen Systems nutzt man den Effekt aus, dass sich Alkohole mit gesättigten Salzlösungen nicht mischen lassen. Hierzu gibt es verschiedene Versuche, die dieses einfach demonstrieren. Allgemein ist bekannt, dass sich Wasser und Methanol oder Ethanol unbegrenzt mischen lassen. Gibt man nun zu einer Mischung von beispielsweise Ethanol und Wasser (je 100 mL) zügig 60 g festes Natriumhydroxid und löst dieses unter Rühren, trennen sich bereits nach kurzer Zeit die Phasen und lassen sich auch nicht mehr vereinen. Die Wärmefreisetzung beim Lösen des festen Natriumhydroxids sollte dabei nicht vernachlässigt werden. Vorsicht: Bei zu schneller Zugabe kann es besonders bei Verwendung von Methanol sogar zu Siedeverzügen kommen – was für die Verwendung des höher siedenden Ethanols spricht.

In Abbildung 1 wurde ein in Ethanol gut löslicher Indikator (Methylrot) zugegeben, um die Entmischung sichtbar zu machen. Dieser Effekt ist die Grundlage für die chemische Ampel [1,2], bei der aber an Stelle von Natriumhydroxid festes Kaliumcarbonat verwendet wird.

Der James-Bond-Cocktail – gerührt oder geschüttelt?

Wie jeder gute Cocktail benötigt auch der hier beschriebene einige ausgewählte Zutaten: Grundlage für den Cocktail ist etwas „klares Hochprozentiges“ (Perfluorheptan, Abbildung 2a). Im zweiten Schritt wird zunächst etwas „Pfirsichlikör“ (Methanol mit Methylrot, Abbildung 2b) und „Grenadine“ (Toluol mit Sudan-III) zugegeben, und es wird geschüttelt. Es bilden sich zwei Phasen (Abbildung 2c). Nun kommt ein Schluck „Blue Curaçao“ (wässrige Kaliumcarbonat-/Kupfersulfat-Lösung) hinzu, und es bilden sich bereits drei Phasen. Anschließend wird der Cocktail mit einem Glasstab gerührt, die drei Phasen bleiben erhalten (Abbildung 2d).

In guter 007-Tradition (oder nicht?) [3] wird nun der Cocktail geschüttelt, und nach kurzer Zeit bilden sich vier Phasen (Abbildung 2e). Für den feinen Geschmack kommt abschließend noch etwas „Wodka“ (*n*-Pentan) hinzu, und die oberen beiden Phasen tauschen ihre Reihenfolge (Abbildung 2f). Egal ob gerührt oder geschüttelt, der Cocktail ist *für den Verzehr leider nicht geeignet*. In Abbildung 2 sind alle Schritte der Entstehung des 007-Cocktails in einer Übersicht zusammengefasst.

Die verwendeten Lösungen

Als Grundlage dienen 15 mL Perfluorheptan [4], die nicht weiter vorbereitet werden müssen.

15 mL Methanol wurden mit etwas Methylrot eingefärbt. Diese Lösung ist zunächst orange, wird aber beim Schütteln mit Kaliumcarbonat gelb.

Die rote Phase wird erzeugt, indem 15 mL Toluol mit etwas Sudan-III angefärbt werden.

Für die blaue, gesättigte wässrige Kaliumcarbonat-Lösung wird solange festes Kaliumcarbonat in 100 mL Wasser gelöst, bis sich kein weiteres Salz mehr löst. Anschließend wird vom Rückstand abgetrennt und mit 50 mL Methanol gewaschen. Dies verhindert, dass bei der Durchführung des Versuchs weiteres Kaliumcarbonat ausfällt. Die Lösung wird mit etwas Kupfer(II)sulfat-Pentahydrat eingefärbt. Von dieser Lösung werden ebenfalls 15 mL benötigt. Es empfiehlt sich, diese Mischung eventuell über Nacht rühren zu lassen, weil sich das Kupfersulfat nur sehr langsam in der gesättigten Kaliumcarbonat-Lösung löst. In der chemischen Ampel [1,2] wird zusammen mit Kupfersulfat auch Kaliumdichromat verwendet, um die grüne Farbe der Ampel zu erhalten. Der Verzicht auf den Chromatzusatz hat neben der geringeren Toxizität den Vorteil, dass der hier vorgestellte Cocktail kein Problem für Rot-Grün-Farbenblinde darstellt.

n-Pentan bedarf keiner weiteren Vorbereitung, es werden 4 mL benötigt.

Benötigte Geräte

Das für diesen Versuch benötigte Material ist nicht sehr aufwändig. Es werden lediglich ein paar Reagenzgläser, vorzugsweise mit einem Durchmesser von 3 cm, und neben einem passenden Stopfen noch ein Glasstab benötigt.

Das vierphasige System – was dahinter steckt

Der 007-Cocktail kombiniert die „chemische Ampel“ mit einem Perfluoralkan und nutzt darüber hinaus aus, dass sich reines Methanol und Toluol zunächst mischen lassen, nach Zugabe von Kaliumcarbonat (durch Extraktion aus der wässrigen Phase) aber entmischen. Schließlich verändert die Zugabe von Pentan die relativen Dichten, so dass es zu einer Umkehr der gelben Methanol- und der roten Toluolphase kommt.

Hochfluorierte Phasen zeichnen sich durch drei wesentliche Eigenschaften aus. Sie besitzen eine sehr hohe Dichte, sind sehr hydrophob, aber in der Regel nicht ölmischbar. Hierdurch lassen sie sich mit wässrigen und auch mit vielen organischen Lösungsmitteln nicht mischen. Endres und Maas beschreiben in ihren Arbeiten diesen Effekt sehr ausführlich und untersuchen die Mischbarkeit von fluorierten Lösungsmitteln mit organischen Lösungsmitteln in Abhängigkeit von der Temperatur. [5] Zum Aufbau von vier Phasen hat man sich daher bei diesem Versuch für das hochfluorierte Lösungsmittel Perfluorheptan entschieden. Es zeigt bei Hörsaaltemperaturen (ca. 20 °C) keine Mischbarkeit mit Toluol.

Die Zugabe der Komponenten erfolgt über einen neu entwickelten Weg, und die gewählte Art der Durchmischung verdeutlicht dem Zuschauer die Komplexität der Mischbarkeit von Lösungen.

Die vier Phasen sind auch noch nach Wochen stabil und entmischen sich nach kräftigem Schütteln innerhalb von kurzer Zeit wieder.

Zusammenfassung

Ausgehend von Perfluorheptan, gesättigter wässriger Kaliumcarbonatlösung, Methanol, Toluol und geeigneten Farb-

Abb. 1 *Mischung von Wasser und Ethanol (angefärbt mit Methylrot, links). Nach der Zugabe von festem Natriumhydroxid bilden sich zwei Phasen (Mitte). Die „chemische Ampel“ (rechts) [1,2] mit drei Phasen besteht aus Toluol (oben, mit Sudan III angefärbt), Methanol (Mitte, mit Methylrot) und gesättigter Kaliumcarbonatlösung (unten, mit Kupfersulfat und Kaliumdichromat).*

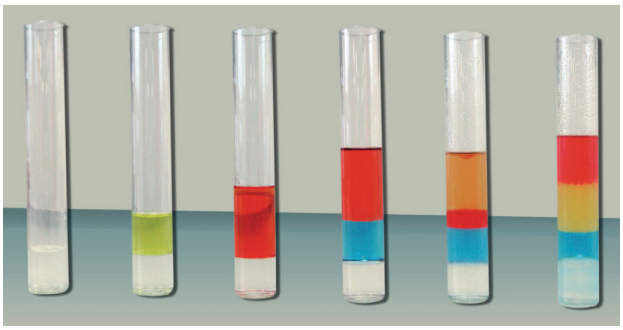


Abb. 2 *(von links nach rechts: a – f). a) Die „hochprozentige“ Grundlage ist Perfluorheptan. b) Der zugegebene „Pfirsichlikör“ besteht aus Methanol mit Methylrot. c) Anschließend wird „Grenadine“ (Toluol mit Sudan-III) zugegeben und die Mischung geschüttelt. d) Zugabe wässriger Kaliumcarbonat-/Kupfersulfat-Lösung, es wird gerührt, nicht geschüttelt. e) Nun wird geschüttelt, nicht gerührt. f) Zur Verfeinerung wird „Wodka“ (n-Pentan) zugegeben.*

stoffen wird eine zunächst dreiphasige Mischung hergestellt, die sich nach Schütteln – nicht nur Rühren – in vier Phasen trennt. Zugabe von Pentan kehrt die Reihenfolge zweier Phasen um. Die Zugabe der Komponenten erfolgt über einen neu entwickelten Weg, und die gewählte Art der Durchmischung verdeutlicht dem Zuschauer die Komplexität mehrphasiger Lösungen.

Summary

Starting from perfluoroheptane, saturated aqueous potassium carbonate solution, methanol, toluene and suitable dyes, a three-phasic mixture is prepared initially. After shaking – not only stirring – four layers develop. Addition of pentane changes the sequence of two layers. The layers are added in a new sequence and the way of mixing demonstrates the complexity of multi-phasic systems.

Schlagworte

chemische Ampel, Entmischung, Mehrphasensystem, Mischbarkeit, Perfluorheptan

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[2] A. Schunk und S. Lauterborn, Chemische Versuche am Büchertisch der Universität Ulm, 2. Aufl., Universitätsverlag Ulm, Ulm, **1996**, S. 9.

[3] Ist der James-Bond-Dry-Martini nun gerührt oder geschüttelt? Es kommt auf den jeweiligen 007-Film an, den man sieht. Für endlose Diskussionen zu diesem Thema sei auf das Internet verwiesen.

[4] Perfluorheptan (Isomerengemisch), AlfaAesar (CAS 335-57-9).

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Die Autoren

Prof. Dr. Ulrich Lüning, geboren 1956 in Dortmund, studierte an der Technischen Hochschule Darmstadt und promovierte dort. Nach einem Post-Doc-Aufenthalt an der Pennsylvania State University habilitierte er sich an der Albert-Ludwigs-Universität Freiburg und lehrt und forscht seit 1994 in Organischer und Supramolekularer Chemie an der Christian-Albrechts-Universität zu Kiel.

Dipl.-Chem. Jens Eckelmann, geboren 1983 in Hannover, studierte Chemie an der Christian-Albrechts-Universität zu Kiel und erhielt 2008 sein Diplom. Derzeit fertigt er bei U. Lüning eine Doktorarbeit über Supramolekulare Dendrimere an. Der 007-Versuch wurde für die Weihnachtsvorlesung James Potter & Harry Bond entwickelt.

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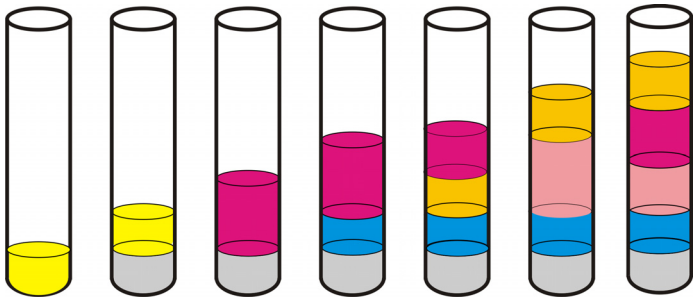
3.2 Mixing Liquids – Mission Impossible? An Experiment on Immiscible Systems

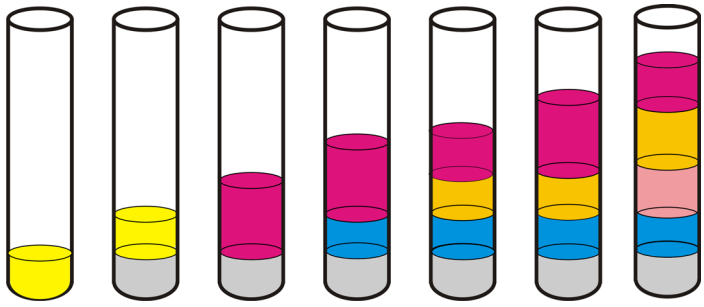
J. Eckelmann, U. Lüning, eingereicht bei *Journal of Chemical Education*.

Im vorherigen Experiment, dem James-Bond-Cocktail, konnte gezeigt werden, dass Anzahl und Reihenfolge der unmischbaren Phasen gezielt verändert werden können, je nachdem, ob die Lösungsmittel geschüttelt oder gerührt wurden. Nun stellte sich die Frage, ob analoge Experimente auch mit mehr als vier Phasen möglich sind. In der Literatur findet man siebenphasige Systeme, die jedoch mit Quecksilber, geschmolzenem Phosphor bzw. Gallium arbeiten. Diese Systeme funktionieren einerseits nicht bei Raumtemperatur und sind andererseits aufgrund ihrer Giftigkeit für Unterrichtsversuche ungeeignet.

Es gelang nun, zwei fünfphasige Systeme zu entwickeln, die ein besonderes Verhalten zeigen. Dazu wurden Methanol, Perfluorheptan, Toluol (System A), *n*-Pentan (System B), gesättigte wässrige Kaliumcarbonatlösung, Silikonöl und Petrolether verwendet, die entsprechend eingefärbt wurden. Obwohl sich anfangs Lösungsmittel miteinander vermischen, entmischen sie sich nach der Zugabe eines weiteren Lösungsmittel wieder. Dabei hängt das Mischungsverhalten auch davon ob, ob die Phasen gerührt oder geschüttelt werden.



System A



System B

Auch dieses Systeme entmischen sich nach einigen Minuten wieder vollständig, wenn man versucht, sie durch Schütteln zu vereinen – getreu dem Motto: Mission Impossible.

In der Literatur wird vermutet, dass fünf organische Phasen das Maximum an unmischbaren Phasen darstellt.

Mixing Liquids - Mission Impossible?[#]

An Experiment on Immiscible Systems

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Two experiments are presented which demonstrate the immiscibility of five or six layers of liquids. The set-up of both experiments is such that one homogeneous layer in a multi-phasic mixture separates into two new layers upon shaking. The solvents used are methanol, toluene, petroleum ether or *n*-pentane, silicone oil, perfluoroheptane and water for the five layer experiment. Addition of mercury results a sixth phase.

Keywords
Demonstration /Liquids / Phases / Solvents / Solutions / Separation

[#] To homogenize immiscible liquids for instance by shaking is a "Mission Impossible". The German word for mixing is "mischen" – pronounced as mission...

Due to different densities, liquids and solutions can be filled in containers layer by layer, for example water and sirup, but eventually many of them mix. A Tequila Sunrise is a nice example. However, such bi- or even multilayer systems can be stable if immiscible liquids are used. A classic example for a biphasic system consists of water and an organic compound. Thus vinegar and olive oil, for instance, form a biphasic system and for this reason, in a classic vinaigrette, additives which stabilize an emulsion are added. The "chemical traffic light", a triphasic system described by Schunk,[1,2] is often used to demonstrate immiscible phases. These experiments which can simply be carried out illustrate the complex world of the miscibility in an impressing way.[3] And there are even more complex systems described in the literature.

Already in 1934, Hildebrand published a pentaphasic system containing mercury, phosphorus, water, aniline, and hexane (bottom-up).[4] He modified this system in 1944 by the addition of gallium (above mercury) as a sixth phase, and in 1949 he added perfluorokerosene (above phosphorus) as a seventh phase.[5,6] Hildebrand's system was optimized in 1950 by Kittsley and Goeden.[7] They created an eight-layer system with mercury, gallium, perfluorodimethylcyclohexane, aniline, water, silicone oil, and paraffin oil.

All these complex systems have two major drawbacks. First of all, white phosphorus and gallium are not liquid at room temperature, so the mixture needs to be heated to 45 °C. Furthermore, some chemicals [bis(2-chloroethyl)ether, white phosphorus and mercury] are highly toxic and highly reactive (phosphorus), risks of carcinogenicity have been reported for aniline and carbon tetrachloride, and finally hexane has a possible risk of impaired fertility.[8] In summary, these experiments are not acceptable as class room experiments.

In 1991, Kuchansky presented a hexaphasic system, that differs from those used previously. He mixed mineral oil, silicone oil, water, benzyl alcohol, perfluoro(*N*-ethylpiperidine), and mercury (top-down).[9] In 1999, Shakhashiri published two tetraphasic systems. The first mixture contained bis(2-chloroethyl)ether, perfluoro-1,3-dimethylcyclohexane, water, and mineral oil and the second one mercury, carbon tetrachloride, water, and mineral oil.[10] Other recent polyphasic systems exploit the immiscibility of ionic liquids with many solvents.[11] Some of these systems are acceptable for class room experiments, but not as exciting as possible.

In 2009, we published a stable tetraphasic system which can be generated from a triphasic system upon agitation. Whether four layers develop or not depends on the conditions: stirred

or shaken. In view of James Bond's Martini (shaken, not stirred),[12] this experiment was called "James Bond Cocktail".[13,14]

Starting from perfluoroheptane (a), methanol (b), toluene (c), saturated aqueous potassium carbonate solution, and suitable dyes, a triphasic mixture is prepared initially (d). This combination is stable if it is stirred. However after shaking, a fourth layer develops (e). The addition of pentane changes the order of two layers (f).

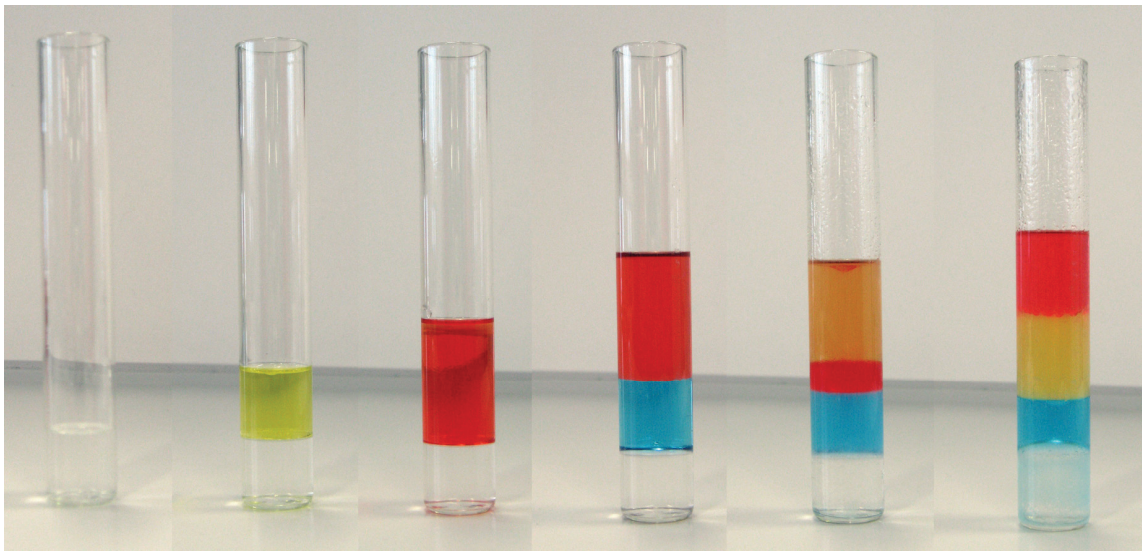

Figure 1: A stable and well separating tetraphasic system called James Bond Cocktail.[13]

This simple but impressive experiment was the basis for further research on this topic. Here, we present two pentaphasic systems in which an additional layer only forms when the mixture is shaken.

The first experiment starts with methanol colored with methyl red (Figure 2: a). Addition of perfluoroheptanes results in a simple biphasic mixture (b). In the next step, toluene colored with Sudan III is added (c). It does not matter whether stirred or shaken, it is impossible to obtain three layers. After carefully addition of saturated aqueous potassium carbonate solution, colored by copper(II) ions, the solution is stirred with a glass bar and three layers remain (d). Now, the solution is shaken, not stirred, and a fourth layer develops (e). In the next step, silicone oil is added, and the solution is stirred again. But there are still four layers (f). Finally, petroleum ether ($d_{20} = 0.89$) is added, and the solution is shaken, not stirred, and left for some minutes. The former toluene/silicone oil layer separates and five layers are observed (g).

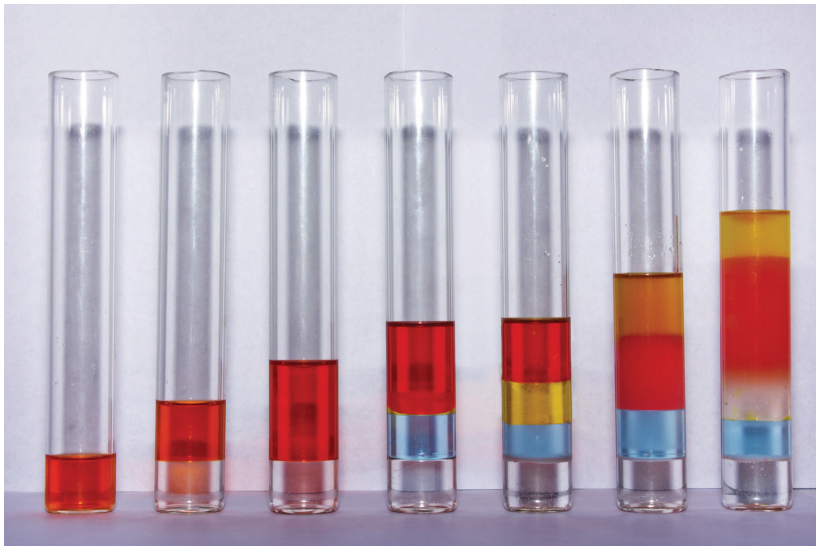

Figure 2 (from left to right: a-g): (a) Methanol/methyl red. (b) After addition of perfluoroheptanes. (c) Toluene/Sudan III was added and the solution was stirred and shaken. (d) Aqueous saturated potassium carbonate solution [colored with copper(II) sulfate] was carefully added and the solution was stirred. (e) Four layers develop after shaking the mixture. (f) Silicone oil was added, stirred, again four layers. (g) Addition of petroleum ether produces five layers.

The second system again starts from methanol colored with methyl red (Figure 3: a). Addition of perfluoroheptanes yields a mixture with two layers (b). *n*-Pentane colored with Sudan III is added, the mixture is stirred and shaken, but only two layers can be observed (c). A three-phase system can be obtained by careful addition of saturated aqueous potassium carbonate solution, colored by copper(II) ions (d). The mixture is stirred, not shaken, and three layers remain. Next, the test tube is shaken and an additional fourth layer develops (e). Silicone oil is added, the mixture is stirred again, and four layers remain (f). Finally, after the addition of petroleum ether and shaking of the mixture, five layers develop (g). Like Kochansky's system, our mixture can be shaken and separates after 20 minutes.

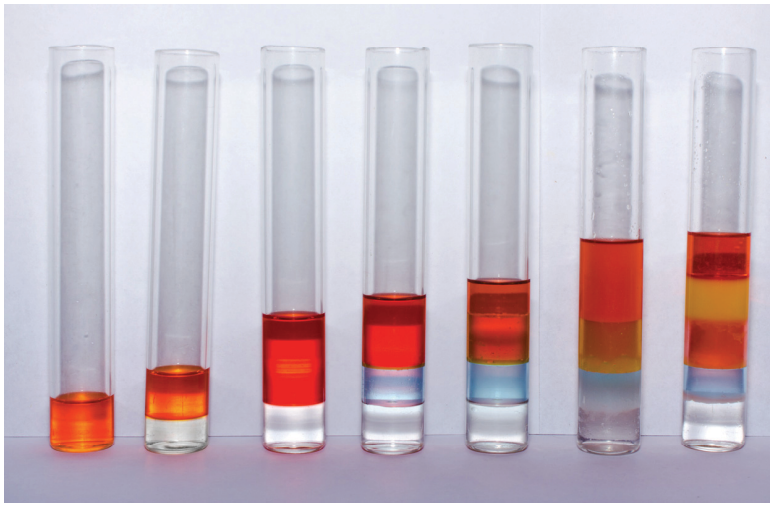

Figure 3 (from left to right: a-g): A second system with five layers. Suitable dyes are used to color the different layers. (a) Methanol/methyl red, (b) perfluoroheptanes and methanol, (c) after the addition of *n*-pentane/Sudan III, (d) carefully addition of aqueous saturated potassium carbonate solution [colored with copper(II) sulfate] and stirring, (e) after shaking, (f) silicone oil is added, stirred again. (g) Petroleum ether is added, the mixture is shaken, and left for some minutes.

Is it possible to add a sixth phase? Yes, it is! True to the motto *The World Is Not Enough*,[15] the addition of mercury results in a beautiful hexaphasic mixture. There is no risk to come in contact with mercury vapors, if a sealed and stable test tube is used. From top to bottom: petroleum ether, methanol, silicone oil, saturated aqueous potassium carbonate solution, perfluoroheptanes, mercury. Shaking does not result in a dissolving of any of the layers.

Figure 4: Hexaphasic system containing petroleum ether (>95°C, colored with Sudan III), methanol (colored with methyl red), silicone oil, saturated aqueous potassium carbonate (colored with copper(II) sulfate), perfluoroheptanes, and mercury.

Hazards:

Mercury is toxic and must only be used in combination with a hood. Mercury spills shall be removed immediately with a mercury spill kit. Different mercury spill kits and instructions are commercially available. Spill kits use sulfur flakes, activated carbon or powdered zinc to absorb mercury.

The immiscibility features can be learned from the penta-layered system as well if mercury shall be avoided.

For all other substances safety precautions have to be applied as to be done with any chemical substance. The solvents toluene, methanol, petroleum ether, and pentane are flammable solvents (some of them are part of fuels). Their MAK values (maximum concentration for long time exposure, 8 h d^{-1}, 40 h $week^{-1}$) are: toluene: 190 mg m^{-3}, methanol: 270 mg m^{-3}, octane (as a representative for petroleum ether): 2400 mg m^{-3}, *n*-pentane: 3000 mg m^{-3}. The inorganic salts are described with lethal doses LD_{50} for potassium carbonate: 1870 mg kg^{-1} (rat, oral), and copper(II) sulfate: 300 mg kg^{-1} (rat, oral). Silicone oils are used in medicinal products and food industry, perfluorheptanes are used in medicinal products. The dyes are described to be irritant.

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[13] Eckelmann, J.; Lüning, U. *Chem. Unserer Zeit* **2009**, *43*, 210-212.

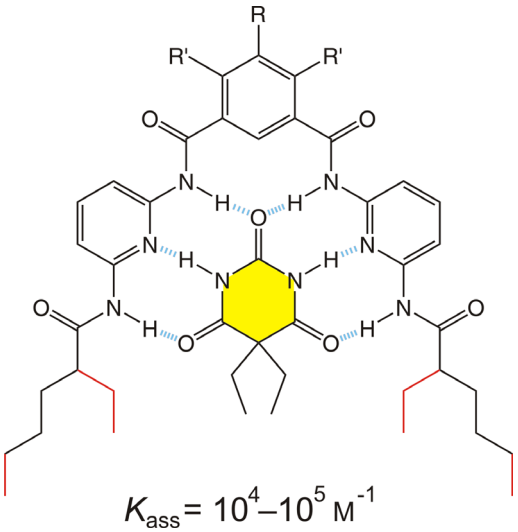
[14] Even if the experiment is called a cocktail, one must not drink it!

[15] ***The World Is Not Enough*** was released in 1999 as the nineteenth spy film in the James Bond movie series.

3.3 Determination of Binding Constants of Hydrogen-Bonded Complexes by ITC, NMR CIS, and NMR Diffusion Experiments

C. Dethlefs, J. Eckelmann, H. Kobarg, T. Weyrich, S. Brammer, C. Näther, U. Lüning, *Eur. J. Org. Chem.* **2011**, 2066-2074. DOI: 10.1002/ejoc.201001684

Ausgehend von substituierten Isophthalsäuren konnten sieben neue Hamilton-Rezeptoren hergestellt werden. Die Synthesen erfolgten analog zu den literaturbekannten Synthesen von HAMILTON und BRAMMER. Dabei gelang es, neben den 5-substituierten auch 4,6-disubstituierte Rezeptoren zu erhalten. Die unterschiedlichen Substituenten der Isophthalsäure zeigten dabei Auswirkung auf die Assoziationskonstante des Komplexes. Durch die Verwendung eines verzweigten Acylrestes in den Verbindungen **1** und **2b** konnte zwar eine bessere Löslichkeit erzielt werden, jedoch hatte dieser sterisch anspruchsvollere Rest einen negativen Effekt auf die Assoziationskonstante. Die in der Veröffentlichung vorgestellten Rezeptoren auf 5-Hydroxyisophthalsäurebasis wurden von DETHLEFS und WEYRICH hergestellt. Hierbei wurde ein anderer Syntheseweg verwendet, bei dem zunächst 2,6-Diaminopyridin einseitig mit dem entsprechenden Alkylcarbonsäurechlorid funktionalisiert wird.



K_{ass} = 10^4–10^5 M^{-1}

R = I, R' = H: **1** R = NO_2, R' = H: **2a**/**2b** R = H, R' = Br: **3**

Anschließend wurden die hergestellten Komplexe aus Hamilton-Rezeptor und Barbital mit drei verschiedenen Messmethoden untersucht. Neben der klassischen ^{1}H-NMR-Titration wurden die Bindekonstanten mit Hilfe von ^{1}H-NMR-Diffusions-Experimenten und Isothermer Titrationskalorimetrie (ITC) bestimmt und verglichen. Die NMR-Experimente wurden hierbei von KOBARG durchgeführt.

FULL PAPER

DOI: 10.1002/ejoc.201001684

Determination of Binding Constants of Hydrogen-Bonded Complexes by ITC, NMR CIS, and NMR Diffusion Experiments[‡]

Christiane Dethlefs,[a] Jens Eckelmann,[a] Hauke Kobarg,[a] Thomas Weyrich,[a] Stefan Brammer,[a] Christian Näther,[b] and Ulrich Lüning*[a]

Keywords: Host–guest systems / Hydrogen bonds / Receptors / Supramolecular chemistry / Association constants

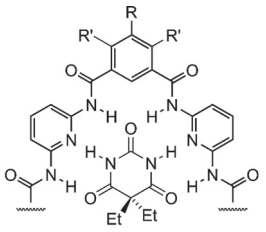
The host–guest complex formation between barbital and various acylaminopyridyl isophthalamides (Hamilton receptors) has been determined quantitatively. The syntheses of nine isophthalamides are described. Their structures differ in the substitution patterns on the central isophthalic unit, and the natures of the acyl residues. Ethylhexanoyl derivatives proved to be more soluble than pentanoyl amides. The association constants were determined by ^{1}H NMR titrations monitoring chemically induced shifts (CIS values), by ^{1}H NMR diffusion experiments, and by isothermal titration calorimetry (ITC), giving K_{ass} values in chloroform at 298 K between 33×10^3 and 100×10^3 M^{-1}.

Introduction

Noncovalent interactions are the fundamental forces in supramolecular chemistry and molecular recognition.[1] In order to design supramolecular structures based on multiple hydrogen bonds, it is necessary to use complementary acceptor and donor patterns.[2,3] Various linear hydrogen-bond acceptor/donor sequences have been synthesized and their host–guest chemistry has been investigated during recent years.

When four hydrogen bonds are situated next to one another, the pattern determines whether homodimers, as described by Meijer,[4,5] or heterodimers, such as the quadruple hydrogen bond system first synthesized in our group,[6] are formed. For controlled self-assembly of large supramolecules through hydrogen bonds it is not enough to use just one complementary pair: various orthogonal recognition domains are necessary. For four neighboring hydrogen bonds, several orthogonal pairs have already been synthesized.[7–12] Another type of orthogonality can be achieved if the recognition domain shows nonlinear geometry.

In 1988, Chang and Hamilton synthesized a macrocyclic angulate receptor.[13] Containing six converging hydrogen bonds, this phthalamide host was able to bind barbituric acid derivatives (Figure 1, R = R′ = H, with the two amide groups in the 6-positions of the pyridine rings being connected to give a macrocycle).[13] ^{1}H NMR titrations of several related receptors with different guests gave association constants in the 10^5 M^{-1} range (in chloroform) for such bent arrays of six hydrogen bonds.[14] The original macrocyclic Hamilton receptors[13] were synthesized from isophthalic acid as starting material. Molecular recognition between open structures such as **1** and barbiturates, however, is also strong and orthogonal to other hydrogen bond patterns.[7] Consequently, nonmacrocyclic "Hamilton receptors" have been used preferentially, and today quite a number of supramolecular systems use the "Hamilton receptor" and barbituric acid derivatives; examples include self-assembled dendrimers,[15,16] multifunctional block copolymers[17] or double dynamers.[18]



R = I	R′ = H	**1a**	**2a**
R = NO_2	R′ = H	**1b**	**2b**
R = H	R′ = Br	**1c**	-
R = OBz	R′ = H	**1d**	**2d**

Figure 1. Host–guest systems **1·3** with *n*-butyl residues and **2·3** with ethylpentyl residues at the amido groups at the 6-positions of the pyridine rings.

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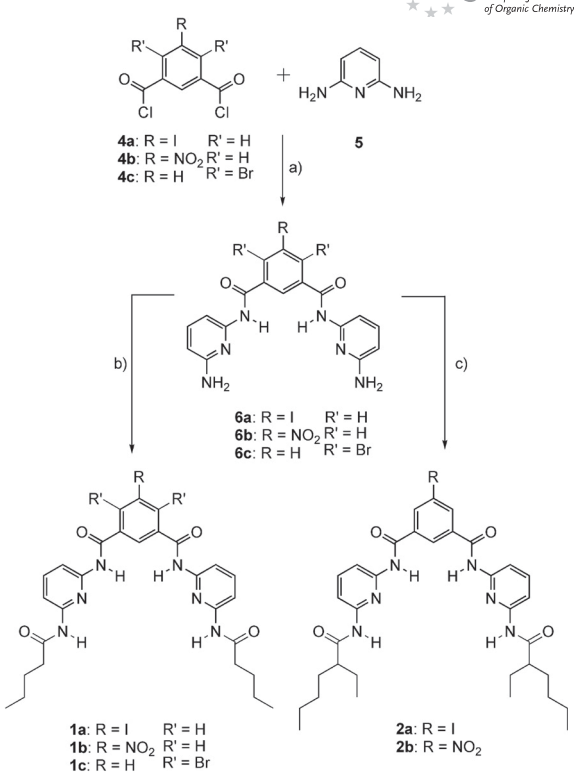
A prerequisite for introduction of a Hamilton receptor into a larger structure is a covalent connection to another moiety, so syntheses of receptors functionalized in the isophthalic component have been carried out. 5-Iodo,[7] -amino,[15] or -hydroxy[16] substitution have been reported. For practical applications, however, not every combination of Hamilton hosts and corresponding guests can be used, due to solubility problems. Firstly, the hosts and guests are flat, so they can stack, and secondly, the heterocycles contain many hetero elements that favor intermolecular interactions through dipole–dipole interactions, including hydrogen bonds. All these forces have to be overcome if applications are to be carried out in solution. To enhance solubility, we therefore synthesized a set of Hamilton receptors **2** (Figure 1), each bearing a branched alkyl residue rather than the *n*-alkyl substituent of receptors **1**.

Here we report on the syntheses of different Hamilton receptors of both families **1** and **2** and on the determination of their association constants when forming a complex with barbital (**3**, Figure 1). Besides the two different residues at the amido group in the 6-positions in the pyridine rings, the receptors differ in the character and position of the functional group(s) in the isophthalic acid moiety. The influence of these changes on binding constants was studied. Three techniques for the determination of the association constants – ^{1}H NMR titrations monitoring chemically induced shifts (CIS values), ^{1}H NMR diffusion experiments, and isothermal titration calorimetry (ITC) – were selected and the results were compared.



Scheme 1. Synthesis of the Hamilton receptors **1a**–**c** and **2a** and **2b**. a) Et_3N, THF, room temp., 3 h; b) pentanoyl chloride, Et_3N, THF, room temp., 16 h; c) 2-ethylhexanoyl chloride, Et_3N, THF, room temp., 16 h.

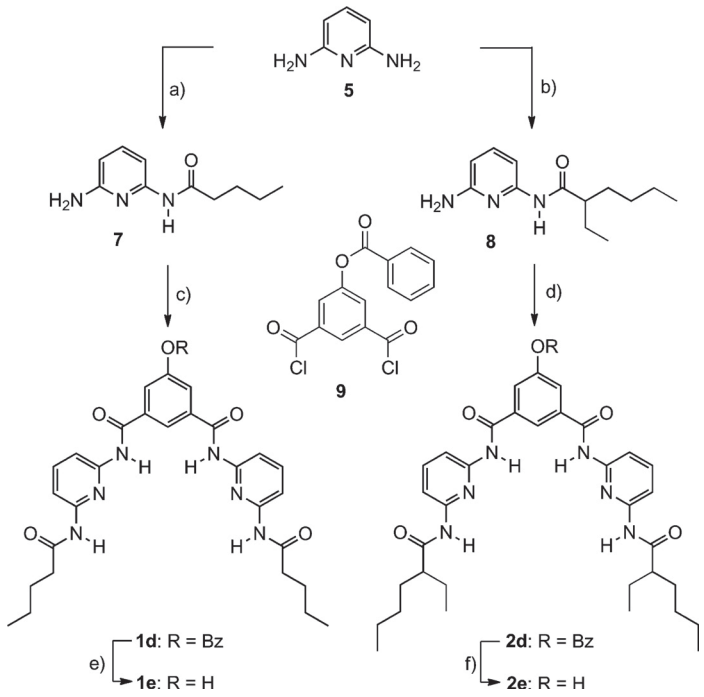
Results and Discussion

Syntheses of the Hamilton Receptors

The syntheses of the Hamilton receptors were carried out by two different reaction pathways. In both cases the parent compounds were isophthalic acid derivatives with functional groups either at their 5- or at their 4- and 6-positions. The next step was the formation of isophthalamides either with 2,6-diaminopyridine (**5**, Scheme 1) or with the already monoacylated diaminopyridines **7** or **8** (Scheme 2, below).

The preparation of the iodine Hamilton receptor **1a** was developed in our group in 2002 in analogy to the synthesis described by Chang and Hamilton.[13] First of all, 5-aminoisophthalic acid was converted into 5-iodoisophthalic acid by a literature procedure, with sodium nitrite, potassium iodide, and a catalytic amount of iodine.[19] 5-Iodoisophthaloyl chloride (**4a**, Scheme 1) could be obtained by treatment with oxalyl dichloride in toluene.[19] 5-Nitroisophthaloyl chloride (**4b**) was synthesized by the same procedure from commercially available 5-nitroisophthalic acid. Furthermore, 4,6-dibromoisophthaloyl chloride (**4c**) was prepared in three steps starting from *m*-xylene, which was first brominated, then oxidized, and finally treated with thionyl chloride.[20–22] These stable isophthaloyl chlorides **4a**–**4c** were each treated with 2,6-diaminopyridine (**5**, excess) to afford the corresponding diamines **6a**–**6c** in a universally applicable precursor. Finally, the different Hamilton receptors **1a**–**c** and **2a** and **2b** with different solubilities were synthesized by use of pentanoyl chloride or 2-ethylhexanoyl chloride. Two factors improve the solubility of the ethylhexanoyl derivatives: the branching itself and the formation of diastereomeric mixtures due to the fact that two chiral centers are introduced.

Since the first description of a synthesis of these isophthalamides, an alternative route to build up the angular receptor has been reported in the literature.[23,24] According to these procedures, we synthesized four additional Hamilton receptors (Scheme 2) by starting from 5-hydroxyisophthalic acid, which was protected with a benzoyl group and afterwards converted into the isophthaloyl chloride **9**.[25] Unlike in the syntheses described above, in this route the side chain was introduced prior to treatment with the acid chloride **9**. 2,6-Diaminopyridine (**5**) was monoacylated with an aliphatic acid chloride such as pentanoyl chloride or 2-ethylhexanoyl chloride. Next, the amidoaminopyridines **7** or **8** were linked to 5-(benzoyloxy)isophthaloyl chloride (**9**) to form the diamides **1d** and **2d**. Crystals were obtained from 5-benzoyloxy-*N*,*N*′-bis(6-pentanoylaminopyrid-2-yl)isophthalamide (**1d**) and the X-ray structure could be solved, although the crystals were non-merohedrally twinned.



Scheme 2. Synthesis of different 5-oxy-substituted Hamilton receptors: a) pentanoyl chloride, NEt_3, THF, 0 °C, 3 h, room temp., 16 h; b) 2-ethylhexanoyl chloride, NEt_3, THF, 0 °C, 3 h, room temp., 16 h; c) and d) 5-(benzoyloxy)isophthaloyl chloride (**9**), NEt_3, THF, room temp., 30 min, reflux, 18 h; e) and f) EtOH, NaOH (1 N), room temp., 3 h, HCl (2 N).

The Hamilton receptor **1d** crystallized in the triclinic space group $P\bar{1}$. The almost planar orientation of the Hamilton receptor binding sites is shown in its X-ray structure (Figure 2). The planarity is comparable to that in another structure published by Vögtle and De Cola.[15,26] Unlike their receptor, which contained tertiary butyl groups, our receptor **1d** has longer unbranched chains; nevertheless, no twist is visible and the binding sites are still in-plane. According to the crystal structure, there is no steric hindrance to binding of a guest.

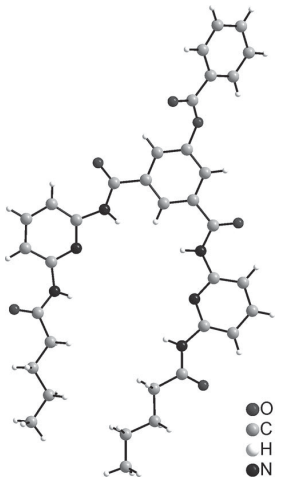


Figure 2. X-ray structure of 5-benzoyloxy-*N*,*N*′-bis(6-pentanoylaminopyrid-2-yl)isophthalamide (**1d**). Only one orientation of the disordered benzoyl protecting group is shown.

The last step in the syntheses of **1e** and **2e** was the deprotection of the hydroxy group. Ester cleavage was achieved in alkaline medium followed by acidification. The solubility of the Hamilton receptor **1e** with unbranched pentanoyl chains was limited, and it dissolved only in DMSO, DMF, and THF. Through the introduction of the branched 2-ethylhexanoyl substituents, the solubility was improved, and less polar and aprotic solvents such as chloroform can be used for further syntheses and measurements. Thanks to these results, the two chloroform-soluble protected Hamilton receptors **1d** and **2d** were used for the determination and comparison of binding constants with barbital (**3**). The hydroxy derivatives **1e** and **2e** were only synthesized to allow incorporation of Hamilton receptors into larger arrays, so investigation of the esters **1d** and **2d**, rather than the corresponding phenols **1e** and **2e**, seemed more relevant.

Investigation of the Host–Guest Systems

The determination of association constants is an essential element when dealing with supramolecular structures or self-assembly. Various methods for the determination of association constants for host–guest complexes are known. In this work, ^{1}H NMR CIS titrations, ^{1}H NMR diffusion experiments, and isothermal titration calorimetry (ITC)

were selected to investigate several Hamilton receptor/barbital systems (see Figure 1). All measurements were carried out in $CDCl_3$ or $CHCl_3$ at 25 °C.

The determination of binding constants by ^{1}H NMR titrations, by recording of changes in the chemically induced shifts (CISs), is an easily applicable and well established method.[27] The association constants for host–guest formation between the Hamilton receptors **1a**, **1d**, **2a**, and **2d** as hosts and barbital (**3**) as guest were calculated from the CIS of the N–H signal of barbital (**3**) upon addition of increasing amounts of the Hamilton host to a solution of the guest (see Table 1 and Figure 3 for an example). The reason for the inverse titration was the parallel determination of the diffusion parameters (see below). The results for the receptors **1a**, **1d**, **2a**, and **2d** are compared in Table 1.

Table 1. K_{ass} values of complexes **1·3** and **2·3** determined by ^{1}H NMR CIS titration and ^{1}H NMR diffusion experiments in $CDCl_3$ at 298 K with a concentration of **3** of 0.4 mM. All errors were smaller than 20% except for values in parentheses. For exact errors see the Supporting Information.

	K_{ass} [10^3 M^{-1}] (CIS)	K_{ass} [10^3 M^{-1}] (diffusion)
1a	64	59
2a	34	(33)
1d	(76)	85
2d	44	37

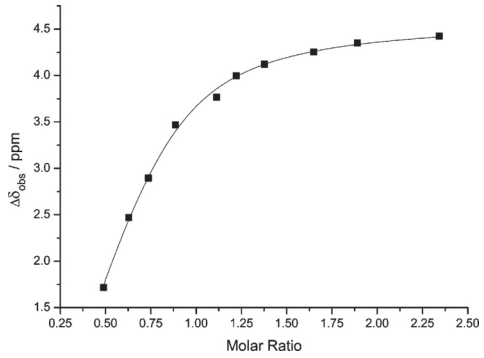


Figure 3. ^{1}H NMR CIS titration curve of barbital (**3**, 5 mM) with the Hamilton receptor **2d** in $CDCl_3$. The CIS of the NH signals of **3** is plotted against the **2d/3** molar ratio.

All four host–guest systems **1a/2a·3** and **1d/2d·3** show association constants (K_{ass}) of the same order of magnitude. Nevertheless, a difference between the Hamilton receptors with unbranched acyl residues (**1a**, **1d**) and those with the branched chains (**2a**, **2d**) is detectable. The smaller association constants (K_{ass}) for receptors **2a** and **2d** are probably the result of greater steric hindrance during complexation. With regard to the substituents at the isophthalic acid part, there is only a marginal difference in the association constants (K_{ass}).

For the determination of association constants (K_{ass}) through ^{1}H NMR diffusion experiments, the solutions from the titrations of barbital (**3**) with increasing amounts of the Hamilton receptors **1** or **2** were used. By detection of spin echoes with pulsed gradients the diffusion constant (D) of barbital (**3**) in each mixture was measured, and finally the association constants (K_{ass}) were calculated.[28] The signals of the guest **3** were chosen because of the larger difference in molecular weight, and thus diffusion constant, between barbital (**3**) and the complexes **1·3** or **2·3** (for an example see Figure 4).

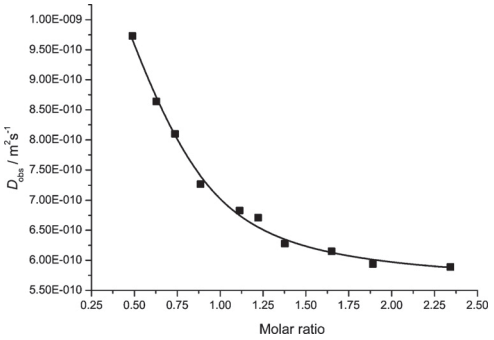


Figure 4. Titration curve of barbital (**3**, 5 mM) with the Hamilton receptor **2d** determined by ^{1}H NMR diffusion spectroscopy in $CDCl_3$. The signal of the CH_2 groups of barbital (**3**) was used to determine the diffusion constant (D_{obs}), which is plotted against the **2d/3** molar ratio.

Table 1 summarizes the association constants (K_{ass}) determined by the diffusion method and compares them with the constants (K_{ass}) obtained from ^{1}H NMR CIS titrations. The latter analyze the chemically induced shifts of certain H atoms, preferentially those participating in hydrogen bond formation (see above). The K_{ass} values determined this way thus only register the complexes that are indeed bound by hydrogen bonds. In contrast, the hydrodynamic radius of a guest will always increase when it is coordinated to a host, regardless of whether it is bound by hydrogen bonds or by other intermolecular forces such as van der Waals interactions or π–π stacking. If such other forces play a role, it is obvious that K_{ass} values determined from diffusion experiments may be larger than those determined by CIS titrations. Despite these differences, the binding constants (K_{ass}) for **1·3** or **2·3** determined by diffusion experiments are in the expected range, and they even have a smaller calculation error than the CIS titration data.

The Hamilton receptors **2a** and **2d** with the branched acyl groups show weaker binding of barbital (**3**) than the unbranched **1a** and **1d**. Furthermore, the substituent on the isophthalic acid moiety appears to be irrelevant for the binding; K_{ass} is not influenced. These results are in accordance with the measurements described in the NMR CIS titration section.

In addition to the applied NMR methods, the association constants (K_{ass}) of the receptors **1a**, **2a**, **1d**, and **2d** and three other complexes **1b·3**, **1c·3**, and **2b·3** were determined by isothermal titration calorimetry. ITC is a calorimetric method increasingly used to determine the thermodynamic parameters of supramolecular interactions. The results for the association constants (K_{ass}), the enthalpy changes (ΔH), and also the changes in entropy (ΔS) are summarized in Table 2.

Table 2. Association constants (K_{ass}) and thermodynamic parameters ΔH and ΔS for titration of the Hamilton receptors **1** or **2** (ca. 0.4 mM) with barbital (**3**) in chloroform as determined by ITC. Note that kcal rather than kJ is used.

	K_{ass} [10^3 M^{-1}]	ΔH [kcal mol^{-1}]	ΔS [cal mol^{-1} K^{-1}]
1a	98	–37	–103
1b	100	–36	–99
1c	40	–37	–104
1d	91	–39	–109
2a	59	–40	–115
2b	67	–37	–103
2d	58	–40	–113

The ITC association constants had larger values than those obtained in the NMR CIS experiments. This is not too surprising, because the CIS changes observed during a ^{1}H NMR titration only occur when the corresponding proton becomes part of a hydrogen bond – in contrast to calorimetric measurements, which register any binding regardless of whether this binding is caused by hydrogen bonds or by other interactions.[9b] In this respect, ITC measurements are similar to NMR diffusion experiments. The measurements confirm the expected results: the differences between the association constants (K_{ass}) for the interaction of the Hamilton receptors bearing unbranched (**1a**, **1d**) and branched acyl groups (**2a**, **2d**) with barbital (**3**) became obvious (for an example see Figure 5). Again, the substituents at the central phthaloyl moiety had only a minor influence on the association constants (K_{ass}). In addition to the pairs

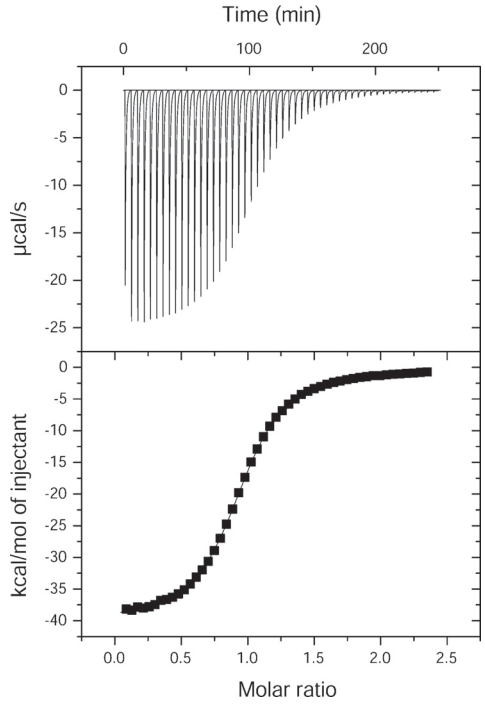


Figure 5. Isothermal titration calorimetry (ITC). Titration of barbital (**3**, 0.5 mM) with the Hamilton receptor **2d** (5 mM) in chloroform (energy in kcal and not in kJ.).

1a/1d·3 and **2a/2d·3**, measurements of three more Hamilton receptors – **1b**, **1c**, and **2b** – with barbital (**3**) were carried out. The two Hamilton receptors with a nitro group at the 5-position in the isophthalic acid component (**1b**, **2b**) did not differ from other 5-substituted receptors. With regard to the only receptor with substituents in the *ortho* positions (**1c**), there is a decrease in the association constant (K_{ass}) comparable to that when the acyl groups are branched.

Table 2 also shows that the negative Gibbs free enthalpy (ΔG) for the binding results from an enthalpic contribution. Although there is a considerable entropic compensation of ca. 30 kcal mol^{-1} (298 K times ca. 100 cal mol^{-1} K^{-1}), ΔH is ca. 30% larger, resulting in negative Gibbs free enthalpies and corresponding association constants of 40–100×10^3 M^{-1}.

Conclusions

Nine different Hamilton receptors **1** and **2** were synthesized from substituted isophthalic acids, 2,6-diaminopyridine (**5**), and different acyl chlorides. The Hamilton receptors **1** each bear two linear pentanoyl residues, whereas branched substituents were introduced in class **2**, resulting in enhanced solubilities in low-polarity organic solvents such as chloroform. The two amide bonds in the 2- and 6-positions of the pyridine rings in the receptors **1** and **2** could be formed in either sequence. For **1d** it was possible to obtain an X-ray crystal structure showing the planar preorganization of the binding sites. The association constants of the receptors **1** and **2** with barbital (**3**) were determined by monitoring of the chemically induced shifts (CISs) in ^{1}H NMR titrations, by ^{1}H NMR diffusion experiments, and by isothermal titration calorimetry (ITC). The K_{ass} values were found to be between 35×10^3 and 100×10^3 M^{-1} by the three methods, displaying differences of a factor of 3 at most. Slight decreases in the K_{ass} values were detected for Hamilton receptors with branched acyl groups (**2a**, **2b**, and **2d**) or for receptor **1c** with two *ortho* substituents at the phthaloyl unit, possibly due to greater steric hindrance.

Experimental Section

General Remarks: NMR spectra were recorded with Bruker AC 200, DRX 500, or AV 600 instruments. Assignments are supported by COSY, HSQC, and HMBC. Even when obtained by DEPT, the type of ^{13}C signal is always listed as singlet, doublet, etc. All chemical shifts are referenced to TMS or to the residual proton or carbon signal of the solvent. All diffusion and titration measurements were carried out with a Bruker AV 600 spectrometer with a triple-resonance cryo probehead with a maximum *z*-gradient strength of 5.67 G mm^{-1}. As pulse sequence a double stimulated echo with bipolar gradient pulses was chosen. The diffusion time in all these experiments was 100 ms and each gradient pair was applied for 2500 µs. The maximum gradient strength was varied between 5 and 95% of the gradient strength in 16 steps. EI/CI mass spectra were recorded with a Finnigan MAT 8200 or MAT 8230. MALDI mass spectra were recorded with a Bruker–Daltonics Biflex III instrument and Cl-CCA (α-cyano-4-chlorocinnamic acid)

as matrix. ESI mass spectra were recorded with an Applied Biosystems Mariner Spectrometry Workstation. IR spectra were recorded with a Perkin–Elmer Paragon 1000, Perkin–Elmer Spectrum 100 fitted with an MKII Golden GateTM Single Reflection ATR unit. Elemental analyses were carried out with a Euro EA 3000 Elemental Analyzer from Euro Vector. 5-(Benzoyloxy)isophthaloyl chloride (**9**) was synthesized by the literature procedure.[25] 5-Iodoisophthaloyl acid and 5-iodoisophthaloyl dichloride (**4a**) were synthesized by the literature procedure.[19] *N*,*N*′-Bis(6-aminopyrid-2-yl)-5-nitroisophthalamide (**6b**) was synthesized analogously to Hamilton et al.[29]

^{1}H NMR CIS Titrations and Diffusion Experiments: A new sample was prepared for each titration measurement. For each component a stock solution in $CDCl_3$ (dry, as purchased) with a concentration of about 5 mmol L^{-1} was prepared. TMS (ca. 10 μL) was added as internal reference to the stock solution of barbital (**3**). The samples were prepared by injecting the stock solution of barbital (**3**, 50 μL) into a 5 mm NMR tube with a standard microliter syringe. A corresponding volume of a stock solution of a Hamilton receptor (**1a**, **2a**, **1d**, **2d**) in $CDCl_3$ was added and the NMR tube was filled up to 600 μL with $CDCl_3$.

The final concentrations of the Hamilton receptors **1** and **2** in the mixtures were checked by integration of the CH_2 group of barbital (**3**) and the CO–CH or CO–CH_2 signals of **1** or **2**, respectively. The barbital (**3**) concentration was assumed to be constant in all measurements. The same signals were used for the diffusion analysis. In cases of slight signal overlap, biexponential fits with respect to two components were applied to the diffusion data to provide more exact integrals for concentration calculations on the one hand and more accurate diffusion constants on the other.

The diffusion analyses were carried out with the aid of Bruker's Topsin 2.1 software. In the case of biexponential fitting, Origin 7.5 including the ONMR plug-in was used for further analyses and plotting/fitting options.[30]

Statistical errors are usually calculated for curve fittings of NMR titrations but in most cases they do not include all errors (weighing error, temp., how many measurements have been carried out at what ratios, systematic error when always adding the same aliquot of a guest solution to a given host solution, etc.). In our experiments, for every data point in the NMR measurements, new solutions were prepared so that weighing errors etc. of each single experiment should cancel out. In this regard, each titration curve is a set of several independent experiments, and the calculated errors include the other errors. The specific statistical error for each titration can be found in the Supporting Information

Isothermal Titration Calorimetry: Experiments were carried out with a VP-ITC microcalorimeter (MicroCal LLC, GE Healthcare) in anhydrous chloroform. A Hamilton receptor **1** or **2** (ca. 1.4 mL, 0.3–0.5 mM) was placed in the calorimeter cell. The titration syringe was loaded with barbital (**3**) at a 10 times higher concentration than in the cell. The titrations were usually carried out with 50 injections of 6 μL each with time intervals of 5 min. The solution was stirred at 300 rpm as suggested by the manufacturer. Titrations were carried out at a cell temperature of 298 K (shield: 297 K) and with a reference power of 10 μcal s^{-1}. ITC data analyses were carried out in Origin 7 SR 2 (OriginLab Corp.) with the provided microcal ITC routines. Please note that all energies are listed as kcal mol^{-1} rather than kJ mol^{-1} by this routine. Each experiment was carried out at least twice. In cases of larger deviations (due to, for instance, changes in room temperature stability), more titrations were carried out. One representative titration curve for the titrations of each host guest pair is shown in the Supporting Information.

5-Iodo-*N*,*N*′-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (1a): *N*,*N*′-Bis(6-aminopyrid-2-yl)-5-iodoisophthalamide (**6a**, 4.94 g, 10.4 mmol) and triethylamine (3.0 mL, 22 mmol) were dissolved in anhydrous tetrahydrofuran (80 mL) under nitrogen. A solution of pentanoyl chloride (2.7 mL, 22 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise. After the system had been stirred at room temp. for 3 h, the solvent was evaporated in vacuo and the residue was dissolved in chloroform (80 mL) and water (80 mL). The organic layer was washed with sodium hydrogen carbonate (50 mL, 5%) and dried with magnesium sulfate, and the solvent was removed. The residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:1, R_f = 0.38); yield 5.90 g (88%); m.p. 170–173 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.56 (br. s, 2 H, Ar-CON*H*), 8.33 (s, 2 H, Ar-*H*-4,6), 8.32 (s, 1 H, Ar-*H*-2), 7.98 (br. s, 2 H, H_9C_4CONH), 7.95–7.88 (m, 4 H, Pyr-*H*-3,5), 7.70 (t, $^3J_{H,H}$ = 8.1 Hz, 2 H, Py-4-*H*), 2.38 (t, $^3J_{H,H}$ = 7.5 Hz, 4 H, $COCH_2$), 1.70 (quin, $^3J_{H,H}$ = 7.5 Hz, 4 H, $COCH_2CH_2$), 1.40 (sext, $^3J_{H,H}$ = 7.5 Hz, 4 H, CH_2CH_3), 0.94 (t, $^3J_{H,H}$ = 7.5 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9 (s, *C*OC_4H_9), 163.0 (s, Ar-*C*ONH), 149.8 (s, Py-*C*-2), 149.0 (s, Py-*C*-6), 141.0 (d, Py-*C*-4), 139.7 (d, Ar-*C*-4,6), 136.2 (s, Ar-*C*-1,3), 125.0 (d, Ar-*C*-2), 110.4 (d, Py-*C*-3), 109.7 (d, Py-*C*-5), 94.8 (s, Ar-*C*-5), 37.5 (t, CO*C*H_2), 27.4 (t, $COCH_2CH_2$), 22.3 (t *C*H_2CH_3), 13.8 (q, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3428, 3302 (N–H), 2958, 2930, 2871 (aliph. C–H), 1688, 1586, 1514 (C=O), 1295 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 642 (24) $[M]^{+\cdot}$, 600 (100) $[M - C_3H_6]^{+\cdot}$, 585 (90) $[M - C_4H_9]^+$, 516 (35) $[M - I]^{+\cdot}$. MS (CI, isobutane): *m*/*z* (%) = 643 (26) $[M + H]^+$, 517 (18) $[M - I + H]^+$, 194 (100) $[H_9C_4CONHPyNH + H]^+$. HRMS (EI): calcd. $C_{28}H_{31}IN_6O_4$: 642.14514; found 642.14180, calcd. $C_{27}{}^{13}CH_{31}IN_6O_4$: 643.14850; found 643.14570. $C_{28}H_{31}IN_6O_4$ (642.49): calcd. C 52.34, H 4.86, N 13.08. $C_{28}H_{31}IN_6O_4{\cdot}0.5H_2O$ (651.15): calcd. C 51.62, H 4.95, N 12.90; found C 51.60, H 4.96, N 12.90.

5-Nitro-*N*,*N*′-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (1b): Compound **1b** was synthesized by the same procedure as used for receptor **1a**, from *N*,*N*′-bis(6-aminopyrid-2-yl)-5-nitroisophthalamide (**6b**, 1.00 g, 2.54 mmol), triethylamine (1.65 mL, 7.50 mmol), and pentanoyl chloride (920 μL, 7.50 mmol) in anhydrous tetrahydrofuran (10 mL). The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 1:1, R_f = 0.30); yield 1.06 g (74%) as a slightly yellow solid; m.p. 193–195 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.92 (br. s, 2 H, Ar-CON*H*), 10.12 (br. s, 2 H, H_9C_4CONH), 8.92 (d, $^4J_{H,H}$ = 1.5 Hz, 2 H, Ar-*H*-4,6), 8.90 (d, $^4J_{H,H}$ = 1.5 Hz, 1 H, Ar-*H*-2), 7.88–7.78 (m, 6 H, Pyr-3,4,5-*H*), 2.41 (t, $^3J_{H,H}$ = 7.5 Hz, 4 H, $COCH_2$), 1.58 (quin, $^3J_{H,H}$ = 7.5 Hz, 4 H, $COCH_2CH_2$), 1.32 (sext, $^3J_{H,H}$ = 7.5 Hz, 4 H, CH_2CH_3), 0.90 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 172.2 (s, *C*OC_4H_9), 163.4 (s, Ar-*C*ONH), 150.6 (s, Py-*C*-2), 149.8 (s, Py-*C*-6), 147.7 (s, Ar-*C*-5), 140.1 (d, Py-*C*-4), 135.8 (s, Ar-*C*-1,3), 133.6 (d, Ar-*C*-2), 125.7 (d, Ar-*C*-4,6), 110.5 (d, Py-*C*-3), 110.3 (d, Py-*C*-5), 35.8 (t, CO*C*H_2), 27.1 (t, $COCH_2CH_2$), 21.7 (t *C*H_2CH_3), 13.7 (q, *C*H_3) ppm. IR (ATR): $\tilde{\nu}$ = 3332, 3274 (N–H), 3087 (arom. C–H), 2959, 2931, 2872 (aliph. C–H), 1663 (C=O), 1583, 1443 (arom. C=C), 1511 (C–NO_2) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 504 (5) $[M - C_4H_9]^{+\cdot}$. MS (CI, isobutane): *m*/*z* (%) = 562 (3) $[M + H]^+$. MS (MALDI): *m*/*z* = 562 $[M + H]^+$, 584 $[M + Na]^+$. $C_{28}H_{31}N_7O_6$ (561.59): calcd. C 59.88, H 5.56, N 17.46; found C 59.60, H 5.55, N 17.34.

4,6-Dibromo-*N*,*N*′-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (1c): Compound **1c** was synthesized by the same procedure as used

for receptor **1a**, from *N*,*N*′-bis(6-aminopyrid-2-yl)-4,6-dibromoisophthalamide (**6c**, 450 mg, 0.889 mmol), triethylamine (2.00 mL, 9.09 mmol), and pentanoyl chloride (433 μL, 3.56 mmol) in anhydrous tetrahydrofuran (10 mL). The residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:1, R_f = 0.39); yield 475 mg (70%); m.p. 199–201 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.47 (br. s, 2 H, Ar-CON*H*), 8.05 (br. s, 1 H, Ar-*H*-5), 7.83 (s, 1 H, Ar-*H*-2), 8.20 (br. s, 2 H, H_9C_4CONH), 7.93 (d, 2 H, Py-5-*H*), 7.86 (br. d, 4 H, Py-3-*H*), 7.61 (t, $^3J_{H,H}$ = 8.2 Hz, 2 H, Py-4-*H*), 2.38 (t, $^3J_{H,H}$ = 7.5 Hz, 4 H, COCH_2), 1.68 (quin, $^3J_{H,H}$ = 7.5 Hz, 4 H, COCH$_2$CH_2), 1.37 (sext, $^3J_{H,H}$ = 7.4 Hz, 4 H, CH_2CH$_3$), 0.91 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, CH$_2$CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2 (s, *C*OC_4H_9), 164.0 (s, Ar-*C*ONH), 150.0 (s, Py-*C*-2), 148.5 (s, Py-*C*-6), 141.0 (d, Py-*C*-4), 137.9 (s, Ar-*C*-4,6), 136.2 (s, Ar-*C*-1,3), 130.3 (d, Ar-*C*-5), 122.1 (d, Ar-*C*-2), 110.6 (d, Py-*C*-3), 109.8 (d, Py-*C*-5), 37.6 (t, CO*C*H$_2$), 27.4 (t, COCH$_2$*C*H$_2$), 22.3 (t *C*H$_2$CH$_3$), 13.8 (q, *C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3289 (N–H), 3025 (arom. C–H), 2958, 2930, 2871 (aliph. C–H), 1674 (C=O), 1582, 1505 (arom. C=C), 1445 (CH$_2$, CH$_3$) 1052 (arom. C–Br) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 672 (5) $[M]^{+\cdot}$, 615 (8) $[M - C_4H_9]^+$. MS (MALDI): *m*/*z* = 673 $[M + H]^+$, 695 $[M + Na]^+$, 711 $[M + K]^+$. $C_{28}H_{30}Br_2N_6O_4$ (674.38): calcd. C 49.87, H 4.48, N 12.46; found C 49.67, H 4.53, N 12.25.

5-Benzoyloxy-*N*,*N*′-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (1d): *N*-(6-Aminopyrid-2-yl)pentanamide (**7**, 1.12 g, 6.18 mmol) and anhydrous triethylamine (1.12 mL, 8.03 mmol) were dissolved in anhydrous tetrahydrofuran (60 mL) under nitrogen. A solution of 5-(benzoyloxy)isophthaloyl chloride (**9**, 1.00 g, 2.37 mmol) in anhydrous tetrahydrofuran (15 mL) was then added dropwise. After the system had been stirred at room temp. for 30 min it was heated to reflux for 18 h. The resulting dispersion was filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 3:2, R_f = 0.8); yield 911 mg (60%); m.p. 115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (s, 1 H, Ar-*H*-2), 8.21 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, Py-*H*-5), 8.05–7.94 (m, 6 H, Ar-*H*-4,6, Bz-*H*-2,6, Py-*H*-3), 7.81–7.74 (m, 2 H, Bz-*H*-3,5), 7.70 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, Bz-*H*-4), 7.56 (t, $^3J_{H,H}$ = 8.1 Hz, 2 H, Py-*H*-4), 2.38 (t, $^3J_{H,H}$ = 7.5 Hz, 4 H, COCH_2), 1.73 (quint, $^3J_{H,H}$ = 7.5 Hz, 4 H, COCH$_2$CH_2), 1.42 (sext, $^3J_{H,H}$ = 7.5 Hz, 4 H, COCH$_2$CH$_2$CH_2), 0.96 (t, $^3J_{H,H}$ = 7.3 Hz, 6 H, CH_3), ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.1 (s, NH*C*O), 165.1 (s, NH*C*O), 163.7 (s, O*C*O), 151.5 (s, Ar-*C*-5), 150.0 (s, Py-*C*-2), 149.1 (s, Py-*C*-6), 140.9 (d, Py-*C*-4), 136.1 (s, Ar-*C*-1,3), 134.3 (d, Bz-*C*-4), 130.3 (s, Bz-*C*-1), 128.8 (d, Bz-*C*-2,6), 128.3 (d, Bz-*C*-3,5), 125.0 (d, Ar-*C*-4,6), 122.9 (d, Ar-*C*-2), 110.3 (d, Py-*C*-3), 109.4 (d, Py-*C*-5), 37.4 (t, *C*H$_2$), 27.4 (t, *C*H$_2$), 22.4 (t, *C*H$_2$), 13.8 (q, *C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3408 (N–H), 2962 (aliph. C–H), 1686 (C=O), 1584, 1523 (arom.), 1260 (N–H) cm^{-1}. MS (ESI): *m*/*z* (%) = 637 $[M + H]^+$, 659 $[M + Na]^+$. $C_{35}H_{36}N_6O_6$ (636.7): calcd. C 66.02, H 5.70, N 13.20. $C_{41}H_{48}N_6O_6 \cdot 2.5\,H_2O$: calcd. C 61.66, H 6.06, N 12.33; found C 61.81, H 6.04, N 12.23.

5-Hydroxy-*N*,*N*′-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (1e): 5-Benzoyloxy-*N*,*N*′-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (**1d**, 570 mg, 896 μmol) was dissolved in ethanol (5 mL). After addition of sodium hydroxide (1 N, 10 mL), the solution was stirred for 3 h and then acidified with hydrochloric acid (2 N). The mixture was filtered, and the solid was washed with tetrahydrofuran. The organic filtrate was dried with sodium sulfate and the solvent was evaporated in vacuo; yield 449 mg (94%); m.p. 172 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.4 (br. s, 2 H, CON*H*), 10.2 (br. s, 2 H, CON*H*), 8.00 (s, 1 H, Ar-*H*-2), 7.52 (s, 2 H, Ar-*H*-4,6), 7.86–7.75 (m, 6 H, Py-*H*-3,4,5), 2.41 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, COCH_2), 1.58 (quint, $^3J_{H,H}$ = 7.4 Hz, 4 H, COCH$_2$CH_2), 1.32 (sext, $^3J_{H,H}$ = 7.5 Hz, 4 H, COCH$_2$CH$_2$CH_2), 0.86 (t, $^3J_{H,H}$ = 7.3 Hz, 6 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1 (s, $CH_3CH_2CH_2CH_2CO$), 166.1 (s, NH*C*O), 150.5 (s, Ar-*C*-5), 150.3 (s, Py-*C*-2), 139.9 (Py-*C*-6, Py-*C*-4), 135.1 (s, Ar-*C*-1,3), 119.5 (Ar-*C*-4,6, Ar-*C*-2), 110.1 (d, Py-*C*-3), 109.4 (d, Py-C-5), 35.8 (t, CO*C*H$_2$), 27.1 (t, COCH$_2$*C*H$_2$), 21.7 (t, *C*H$_2$CH$_3$), 13.7 (q, *C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3376 (O–H, N–H), 1654 (C=O), 1585, 1530 (arom.), 1293 (N–H) cm^{-1}. MS (ESI): *m*/*z* (%) = 533 $[M + H]^+$, 555 $[M + Na]^+$. $C_{28}H_{32}N_6O_5$ (532.6): calcd. C 63.14, H 6.06, N 15.78. $C_{28}H_{32}N_6O_5 \cdot 0.5\,H_2O$: calcd. C 62.05, H 6.14, N 15.52; found C 61.85, H 6.15, N 15.59.

***N*,*N*′-Bis[6-(2-ethylhexanoylamino)pyrid-2-yl]-5-iodoisophthalamide (2a):** Compound **2a** was synthesized by the same procedure as used for receptor **1a**, from *N*,*N*′-bis(6-aminopyrid-2-yl)-5-iodoisophthalamide (**6a**, 1.23 g, 2.60 mmol), triethylamine (750 μL, 5.50 mmol), and 2-ethylhexanoyl chloride (950 μL, 5.50 mmol). Column chromatography (silica gel, ethyl acetate/cyclohexane 1:1, R_f = 0.59); yield 1.51 g (80%); m.p. 130–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (br. s, 2 H, Ar-CON*H*), 8.40–8.35 (m, 3 H, Ar-*H*-2,4,6), 8.03, 7.97 (2 × d, $^3J_{H,H}$ = 8.0 Hz, 4 H, Pyr-3,5-*H*), 7.90 (br. s, 2 H, $H_{15}C_7CONH$), 7.73 (t, $^3J_{H,H}$ = 8.0 Hz, 2 H, Py-4-*H*), 2.19 (m_c, 2 H, COC*H*), 1.80–1.50 (m, 8 H, COCHCH_2), 1.32 (m_c, 8 H, CH_2CH_2CH$_3$), 0.97 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, CHCH$_2$CH_3) 0.88 (m_c, 6 H, CHCH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.9 (s, *C*OC_7H_{15}), 162.8 (s, Ar-*C*ONH), 149.8 (s, Py-*C*-2), 148.9 (s, Py-*C*-6), 141.0 (d, Py-*C*-4), 139.6 (d, Ar-*C*-2), 136.3 (s, Ar-*C*-1,3), 125.0 (d, Ar-*C*-4,6), 110.5 (d, Py-*C*-3), 109.7 (d, Py-*C*-5), 94.8 (s, Ar-*C*-5), 50.7 (d, CO*C*H), 32.4 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 29.8 (t, CH$_2$*C*H$_2$CH$_2$CH$_3$), 26.1 (t, CH*C*H$_2$CH$_3$), 22.8 (t, CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.0 (q, CH$_2$CH$_2$CH$_2$*C*H$_3$), 12.0 (q, CHCH$_2$*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3279 (N–H), 3071 (arom. C–H), 2958, 2929, 2859 (aliph. C–H), 1668 (C=O), 1580, 1504 (arom. C=C), 1441 (alkyl C–H) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 726 (15) $[M]^{+\cdot}$, 670 (72) $[M - C_4H_8]^{+\cdot}$, 627 (100) $[M - C_7H_{15}]^+$, 600 (5) $[M - I]^{+\cdot}$. MS (CI, isobutane): *m*/*z* (%) = 727 (100) $[M + H]^+$, 601 (18) $[M - I + H]^+$. MS (ESI): *m*/*z* (%) = 727 $[M + H]^+$. MS (MALDI): *m*/*z* (%) = 727 $[M + H]^+$, 749 $[M + Na]^+$, 765 $[M + K]^+$. $C_{34}H_{43}IN_6O_4$ (726.24): calcd. C 56.20, H 5.96, N 11.57; found C 56.20, H 6.13, N 11.60.

***N*,*N*′-Bis[6-(2-ethylhexanoylamino)pyrid-2-yl]-5-nitroisophthalamide (2b):** Compound **2b** was synthesized by the same procedure as used for receptor **1a**, from *N*,*N*′-bis(6-aminopyrid-2-yl)-5-nitroisophthalamide (**6b**, 661 mg, 1.68 mmol), triethylamine (785 μL, 3.56 mmol), and 2-ethylhexanoyl chloride (615 μL, 3.56 mmol). The crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 1:1, R_f = 0.60); yield 500 mg (46%) as a slightly yellow solid; m.p. 119–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.87 (d, $^4J_{H,H}$ = 1.5 Hz, 2 H, Ar-*H*-4,6), 8.83 (t, $^4J_{H,H}$ = 1.5 Hz, 1 H, Ar-*H*-2), 8.76 (br. s, 2 H, Ar-CON*H*), 8.02 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, Pyr-5-H), 7.99 (br. s, 2 H, H_9C_4CONH), 7.95 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, Pyr-3-*H*), 7.74 (t, $^3J_{H,H}$ = 8.0 Hz, 2 H, Py-4-*H*), 2.21 (m_c, 2 H, COC*H*), 1.80–1.50 (m, 8 H, COCHCH_2), 1.32 (m_c, 8 H, CH$_2$CH_2CH$_3$), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 6 H, CHCH$_2$-CH_3), 0.88 (t, $^3J_{H,H}$ = 6.9 Hz, 6 H, CHCH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1 (s, *C*OC_7H_{15}), 162.1 (s, Ar-*C*ONH), 149.9 (s, Py-*C*-2), 148.8 (s, Py-*C*-6), 148.7 (s, Ar-*C*-5), 141.0 (d, Py-*C*-4), 141.0 (d, Ar-*C*-2), 136.5 (s, Ar-*C*-1,3), 125.3 (d, Ar-*C*-4,6), 110.8 (d, Py-*C*-3), 109.8 (d, Py-*C*-5), 50.7 (d, CO*C*H), 32.4 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 29.8 (t, CH$_2$*C*H$_2$CH$_2$CH$_3$), 26.1 (t, CH*C*H$_2$CH$_3$), 22.8 (t, CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.0 (q, CH$_2$CH$_2$CH$_2$*C*H$_3$), 12.0 (q, CHCH$_2$*C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3283 (N–H), 3050 (arom. C–H), 2959, 2931, 2872 (aliph. C–H), 1669 (C=O), 1583, 1505 (arom. C=C), 1441 (alkyl C–H) cm^{-1}. MS

(EI, 70 eV): *m*/*z* (%) = 645 (4) $[M]^{+\cdot}$, 616 (10) $[M - C_2H_5]^{+\cdot}$, 546 (100) $[M - C_4H_9]^+$. MS (CI, isobutane): *m*/*z* (%) = 646 (6) $[M + H]^+$. MS (MALDI): *m*/*z* = 646 $[M + H]^+$, 668 $[M + Na]^+$, 684 $[M + K]^+$. $C_{34}H_{43}N_7O_6$ (645.749): calcd. C 63.24, H 6.71, N 15.18. $C_{34}H_{43}N_7O_6 \cdot 0.1\,CH_3COOCH_2CH_3$ (663.37): calcd. C 63.12, H 6.74, N 14.98; found C 63.28, H 6.94, N 14.82.

5-Benzoyloxy-*N*,*N*′-bis[6-(2-ethylhexanoyl)aminopyrid-2-yl]isophthalamide (2d): *N*-(6-Aminopyrid-2-yl)-2-ethylhexanamide (**8**, 1.24 g, 5.27 mmol) and anhydrous triethylamine (1.24 mL, 8.96 mmol) were dissolved in anhydrous tetrahydrofuran (60 mL) under nitrogen. A solution of 5-(benzoyloxy)isophthaloyl chloride (**9**, 1.10 g, 3.40 mmol) in anhydrous tetrahydrofuran (15 mL) was then added dropwise. After the system had been stirred at room temp. for 30 min it was heated to reflux for 18 h. The resulting dispersion was filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 3:1, R_f = 0.38); yield 850 mg (35%); m.p. 111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (br. s, 2 H, N*H*), 8.31 (br. s, 2 H, N*H*), 8.25 (s, 1 H, Ar-*H*-2), 8.08 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H, Py-*H*-5), 7.98–7.87 (m, 6 H, Ar-*H*-4,6, Bz-*H*-2,6, Py-*H*-3), 7.65–7.59 (m, 3 H, Bz-*H*-3,4,5), 7.46 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, Py-*H*-4), 2.23–2.17 (m, 2 H, C*H*), 1.75–1.68 (m, 4 H, $CHCH_2CH_3$), 1.60–1.48 (m, 4 H, $CHCH_2$), 1.29–1.25 (m, 8 H, $CHCH_2CH_2CH_2$), 0.94 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, $CHCH_2CH_3$), 0.86–0.83 (m, 6 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.2 (s, *C*O), 164.9 (s, O*C*O), 163.5 (s, NH*C*O), 151.5 (s, Ar-*C*-5), 149.9 (s, Py-*C*-2), 149.0 (s, Py-*C*-6), 140.8 (d, Py-*C*-4), 136.1 (s, Ar-*C*-1,3), 134.3 (d, Bz-*C*-4), 130.3 (s, Bz-*C*-1), 128.7 (d, Bz-*C*-2,6), 128.3 (d, Bz-*C*-3,5), 124.7 (d, Ar-*C*-4,6), 122.9 (d, Ar-*C*-2), 110.5 (d, Py-*C*-3), 109.7 (d, Py-*C*-5), 50.6 (d, CO*C*H), 32.4 (t, $COCHCH_2$), 29.8 (t, $COCHCH_2$), 26.9 (t, $COCHCH_2CH_2$), 22.8 (t, $COCHCH_2CH_2CH_2$), 13.9 (q, $COCHCH_2CH_2CH_2CH_3$), 12.1 (q, $CHCH_2CH_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3292 (N–H), 2959 (aliph. C–H), 1670 (C=O), 1582, 1507 (arom.) cm^{-1}. MS (ESI): *m*/*z* = 721 $[M + H]^+$, 743 $[M + Na]^+$. $C_{41}H_{48}N_6O_6$ (720.8): calcd. C 68.31, H 6.71, N 11.66. $C_{41}H_{48}N_6O_6 \cdot 0.5\,H_2O$: calcd. C 67.47, H 6.77, N 11.51; found C 67.85, H 6.75, N 11.65.

***N*,*N*′-Bis[6-(2-ethylhexanoyl)aminopyrid-2-yl]-5-hydroxyisophthalamide (2e):** 5-Benzoyloxy-*N*,*N*′-bis[6-(2-ethylhexanoyl)aminopyrid-2-yl]isophthalamide (**2d**, 570 mg, 791 μmol) was dissolved in ethanol (5 mL). After addition of aqueous sodium hydroxide (1 N, 10 mL), the solution was stirred for 3 h and then acidified to pH 3 with hydrochloric acid (2 N). The mixture was filtered, and the solid was washed with tetrahydrofuran. The organic filtrate was dried with sodium sulfate, and the solvent was evaporated in vacuo; yield 410 mg (84%); m.p. 134 °C. ^{1}H NMR (200 MHz, $[D_6]$DMSO): δ = 10.36 (br. s, 2 H, CON*H*), 10.14 (br. s, 2 H, CON*H*), 8.01 (s, 1 H, Ar-*H*-2), 7.86–7.79 (m, 6 H, Py-*H*-3,4,5), 7.53 (s, 2 H, Ar-*H*-4,6), 2.51–2.50 (m, 2 H, C*H*), 1.57–1.55 (m, 4 H, $CHCH_2CH_3$), 1.46–1.36 (m, 4 H, $CHCH_2$), 1.27–1.23 (m, 8 H, $CHCH_2CH_2CH_2$), 0.87–0.83 (m, 12 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1 (s, *C*O), 165.1 (s, NH*C*O), 157.7 (s, Ar-*C*-5), 150.4 (s, Py-*C*-2), 150.1 (s, Py-*C*-6), 140.1 (d, Py-*C*-4), 135.6 (s, Ar-*C*-1,3), 118.1 (d, Ar-*C*-4,6), 117.6 (d, Ar-*C*-2), 110.3 (d, Py-*C*-3), 110.0 (d, Py-*C*-5), 47.6 (d, CO*C*H), 31.9 (t, $COCHCH_2CH_3$), 29.2 (t, $COCHCH_2$), 26.3 (t, $COCHCH_2CH_2$), 22.2 (t, $COCHCH_2CH_2CH_2$), 13.9 (q, $CH_2CH_2CH_3$), 11.7 (q, $CHCH_2CH_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3270 (O–H, N–H), 1668 (C=O), 1582, 1506 (arom.) cm^{-1}. MS (ESI): *m*/*z* = 617 $[M + H]^+$, 639 $[M + Na]^+$. $C_{34}H_{44}N_6O_5$ (616.7): calcd. C 66.21, H 7.19, N 13.63. $C_{41}H_{48}N_6O_6 \cdot 0.5\,H_2O$: calcd. C 65.26, H 7.25, N 13.43; found C 65.13, H 7.19, N 13.26.

***N*,*N*′-Bis(6-aminopyrid-2-yl)-5-iodoisophthalamide (6a):** 5-Iodoisophthaloyl dichloride (**4a**, 2.52 g, 7.69 mmol) in tetrahydrofuran (50 mL) was added dropwise over a period of 3 h to a solution of 2,6-diaminopyridine (**5**, 8.39 g, 76.9 mmol) and triethylamine (2.13 mL, 15.4 mmol) in anhydrous tetrahydrofuran (150 mL). After the system had been stirred for 2 h, the solvent was removed in vacuo and the residue was washed with water (1 L). Purification by column chromatography (neutral alumina, tetrahydrofuran/dichloromethane 3:1, R_f = 0.52) yielded a light yellow solid; yield 1.54 g (79%); m.p. 248 °C. ^{1}H NMR (200 MHz, $[D_6]$DMSO): δ = 10.35 (br. s, 2 H, N*H*), 8.49 (s, 1 H, Ar-2-*H*), 8.38 (d, $^4J_{H,H}$ = 1.3 Hz, 2 H, Ar-4,6-*H*), 7.45 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, Pyr-4-*H*), 7.36 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 0.9 Hz, 2 H, Pyr-3-*H*), 6.28 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 0.9 Hz, 2 H, Pyr-5-*H*), 5.84 (br. s, 4 H, NH_2) ppm. ^{13}C NMR (125 MHz, $[D_6]$DMSO): δ = 163.4 (s, Ar-*C*ONH), 158.6 (s, Py-*C*-2), 150.1 (s, Py-*C*-6), 139.3 (d, Py-*C*-4), 139.0 (d, Ar-*C*-4,6), 136.2 (s, Ar-*C*-1,3), 126.3 (d, Ar-*C*-2), 104.3 (d, Py-*C*-3), 101.9 (d, Py-*C*-5), 94.6 (s, Ar-*C*-5) ppm. IR (ATR): $\tilde{\nu}$ = 3326 (CON*H*), 1673, 1612 (*C*ONH) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 474 (100) $[M]^{+\cdot}$, 366 (9) $[M - NHPyrNH_2]^{+\cdot}$. MS (CI, isobutane): *m*/*z* (%) = 475 (100) $[M + H]^+$, 349 (18) $[M - I + H]^+$. HRMS (EI): $C_{18}H_{15}IN_6O_2$ calcd. 474.03012; found 474.02408, $C_{17}{}^{13}CH_{15}IN_6O_2$ calcd. 475.03348; found 475.02854.

***N*,*N*′-Bis(6-aminopyrid-2-yl)-4,6-dibromoisophthalamide (6c):** 2,6-Diaminopyridine (**5**, 986 mg, 9 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL), the mixture was stirred for 3 h at room temp., the solution was filtered, and triethylamine (2 mL) was added. The solution was cooled in ice and 4,6-dibromoisophthaloyl chloride (**4c**, 1.08 g, 3.00 mmol) in tetrahydrofuran (10 mL) was added under nitrogen. The reaction mixture was stirred at room temp. for 10 h, concentrated by evaporation, and poured into boiling water (200 mL) to remove excess 2,6-diaminopyridine and triethylamine hydrochloride. The crude product was dried and purified by basic alumina filtration (tetrahydrofuran/methanol 25:1). Recrystallization from tetrahydrofuran/*n*-hexane afforded **6a** as white crystals (1.15 g, 76%); m.p. 250–255 °C (decomp.). ^{1}H NMR (200 MHz, $[D_6]$DMSO): δ = 10.33 (br. s, 2 H, Ar-CON*H*), 8.03 (s, 1 H, Ar-*H*-5), 7.68 (s, 1 H, Ar-*H*-2), 7.42 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, Py-4-*H*), 7.31 (br. d, $^3J_{H,H}$ = 7.8 Hz, 2 H, Py-3-*H*), 6.26 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.0 Hz, 2 H, Py-5-*H*), 5.80 (br. s, 4 H, NH_2) ppm. ^{13}C NMR (125 MHz, $[D_6]$DMSO): δ = 164.51 (s, *C*ONH), 158.6 (s, Py-2-*C*), 149.9 (s, Py-6-*C*), 138.92 (d, Py-4-*C*), 137.0 (s, Ar-1,3-*C*), 136.0 (d, Ar-5-*C*), 129.3 (d, Ar-2-*C*), 120.9 (s, Ar-*C*-4,6), 104.2 (d, Py-3-*C*), 101.4 (d, Py-5-*C*) ppm. IR (ATR): $\tilde{\nu}$ = 3463, 3300, 3197 (N–H), 3056 (arom. C–H), 1668 (C=O), 1620, 1532 1448 (arom. C=C), 1052 (arom. C–Br) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 504 (48) $[M]^{+\cdot}$, 425 (100) $[M - Br]^+$, 345 $[M - Br_2 + H]^+$. MS (CI, isobutane): *m*/*z* (%) = 505 (13) $[M + H]^+$. MS (MALDI): *m*/*z* = 505 $[M + H]^+$, 527 $[M + Na]^+$.

***N*-(6-Aminopyrid-2-yl)pentanamide (7):** 2,6-Diaminopyridine (**5**, 3.25 g, 29.8 mmol) and anhydrous triethylamine (4.35 mL, 29.8 mmol) were dissolved in anhydrous tetrahydrofuran (50 mL). A solution of pentanoyl chloride (3.80 mL, 31.3 mmol) in anhydrous tetrahydrofuran (6 mL) was added dropwise at 0 °C over 30 min. Afterwards, the mixture was stirred at 0 °C for 3 h and then for 16 h at room temp. After filtration, the solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 3:2, R_f = 0.5); yield 3.44 g (60%); m.p. 66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (br. s, 1 H, N–*H*), 7.55 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, Py-*H*-3), 7.45 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H, Py-*H*-4), 6.24 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, Py-*H*-5), 4.29 (br. s, 2 H, NH_2), 2.35 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, $COCH_2$), 1.70 (quint, $^3J_{H,H}$ = 7.6 Hz, 2 H, $COCH_2CH_2$), 1.40 (sext, $^3J_{H,H}$ = 7.6 Hz, 2 H, $COCH_2CH_2CH_2$), 0.94 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.9 (s, *C*O), 156.9

(s, Py-*C*-6), 149.8 (s, Py-*C*-2), 140.3 (d, Py-*C*-4), 104.1 (d, Py-*C*-5), 103.2 (d, Py-*C*-3), 37.3 (t, $CO\mathit{C}H_2$), 27.4 (t, $COCH_2\mathit{C}H_2$), 22.2 (t, $COCH_2CH_2\mathit{C}H_2$), 13.7 (q, $\mathit{C}H_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3410 (N–H), 2961 (aliph. C–H), 1673 (C=O), 1617, 1542 (arom.), 1299 (N–H) cm^{-1}. MS (ESI): *m*/*z* = 194 $[M + H]^+$, 216 $[M + Na]^+$. $C_{10}H_{15}N_3O$ (193.2): calcd. C 62.15, H 7.82, N 21.74; found C 62.09, H 7.97, N 21.62.

***N*-(6-Aminopyrid-2-yl)-2-ethylhexanamide (8):** 2,6-Diaminopyridine (**5**, 3.25 g, 29.8 mmol) and anhydrous triethylamine (4.35 mL, 29.8 mmol) were dissolved in anhydrous tetrahydrofuran (50 mL). A solution of 2-ethylhexanoyl chloride (5.36 mL, 31.3 mmol) in anhydrous tetrahydrofuran (6 mL) was added dropwise over 30 min. Afterwards, the mixture was stirred at 0 °C for 3 h and then for 16 h at room temp. After filtration, the solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:2, R_f = 0.37); yield 3.77 g (54%); m.p. 102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (br. d, $^3J_{H,H}$ = 7.8 Hz, 2 H, Py-*H*-3, N–*H*), 7.44 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H, Py-*H*-4), 6.24 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, Py-*H*-5), 4.30 (br. s, 2 H, NH_2), 2.10–2.06 (m, 1 H, C*H*), 1.83–1.65 (m, 2 H, $CHCH_2$), 1.56–1.47 (m, 2 H, CH_2), 1.32–1.26 (m, 4 H, CH_2CH_2), 0.93 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, $CHCH_2CH_3$), 0.87 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5 (s, *C*=O), 157.0 (s, Py-*C*-6), 149.8 (s, Py-*C*-2), 140.2 (d, Py-*C*-4), 104.2 (d, Py-*C*-5), 103.3 (d, Py-*C*-3), 50.9 (d, CO*C*H), 32.5 (t, $COCHCH_2CH_3$), 29.8 (t, $COCHCH_2$), 26.1 (t, $COCHCH_2CH_2$), 22.8 (t, $COCHCH_2CH_2CH_2$), 13.9 (q, $CH_2CH_2CH_3$) 12.06 (q, $CHCH_2CH_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3201 (N–H), 2922 (aliph. C–H), 1638 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 235 (22) $[M]^+$, 109 (100) $[M - C_8H_{15}O]^+$. MS (MALDI): *m*/*z* = 236 $[M + H]^+$, 276 $[M + Na]^+$. $C_{13}H_{21}N_3O$ (235.3): calcd. C 66.35, H 8.99, N 17.86; found C 66.13, H 9.05, N 17.80.

X-ray Crystal Structure Determination of 1d: Suitable crystals were grown by allowing the test tubes to stand overnight after column chromatography. Empirical formula $C_{35}H_{36}N_6O_6 \cdot 3H_2O$, *Fw* = 690.75 $g\,mol^{-1}$, *a* = 11.6929(9) Å, *b* = 13.1904(10) Å, *c* = 13.2977(9) Å, α = 108.951(8)°, β = 96.455(9)°, γ = 109.105(9)°, *V* = 1777.2(2) $Å^3$, *T* = 170(2) K, $p_{calcd.}$ = 1.291 $Mg\,m^{-3}$, μ = 0.094 mm^{-1}, triclinic, space group $P\bar{1}$, *Z* = 2, STOE Imaging Plate Diffraction System (IPDS-1), Mo-K_α (λ = 0.71073 Å), 7076 measured reflections in the $2.2° < 2\theta < 26.0°$ range, 3762 independent reflections used for refinement. R_{int} = 0.0850. The structure was solved with SHELXS-97. Structure refinement was performed against F^2 with use of SHELXL-97; 514 parameters, R_1 = 0.0704 for 3205 data with $F_o > 4\sigma(F_o)$, R^1 = 0.0784 and wR_2 = 0.1978 for all 3762 data, GoF = 1.104, residual electron density 0.225/–0.283 ($e\,Å^{-3}$). All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned with idealized geometry and were refined by use of a riding model. The O–H hydrogen atoms were located in the difference map, their bond lengths were set to ideal values and finally they were refined by use of a riding model. The terminal six-membered ring is disordered in two orientations and was refined by use of a split model. All crystals investigated were non-merohedrally twinned. The two individual forms were therefore indexed and integrated separately and overlapping reflections were omitted.

CCDC-803919 (for **1d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): NMR spectra and titration curves.

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SUPPORTING INFORMATION

DOI: 10.1002/ejoc.201001684
Title: Determination of Binding Constants of Hydrogen-Bonded Complexes by ITC, NMR CIS, and NMR Diffusion Experiments
Author(s): Christiane Dethlefs, Jens Eckelmann, Hauke Kobarg, Thomas Weyrich, Stefan Brammer, Christian Näther, Ulrich Lüning*

General:

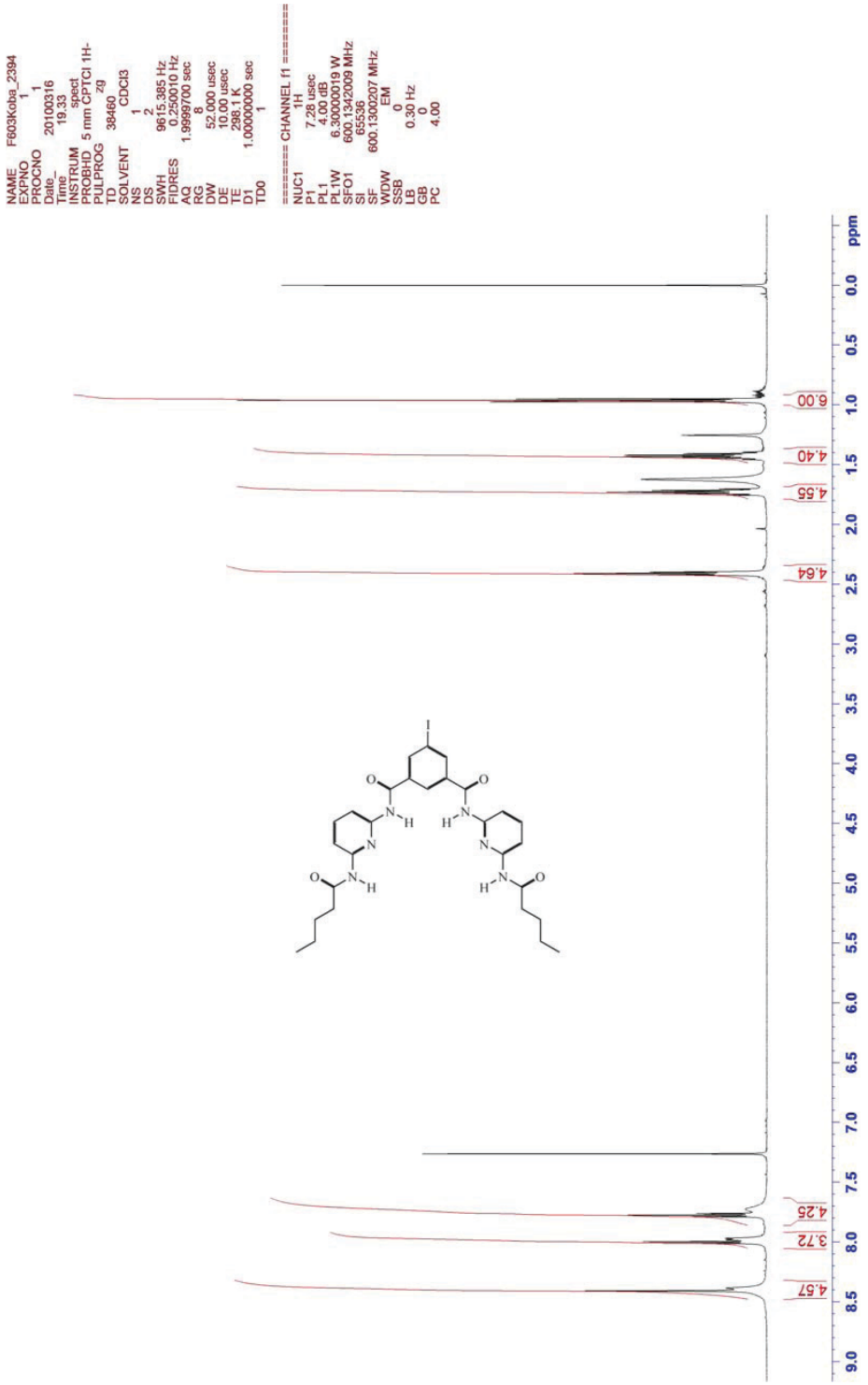
The procedures of ^{1}H NMR CIS titrations, diffusion experiments and isothermal titration calorimetry are described in the experimental part of the paper.

The ^{1}H NMR CIS titration and ^{1}H NMR diffusion analyses were carried out using Brukers Topsin 2.1 and Origin 7.5 software. In the case of biexponential fitting, Origin 7.5 including the ONMR-plugin was used for further analyses and plotting/fitting options.

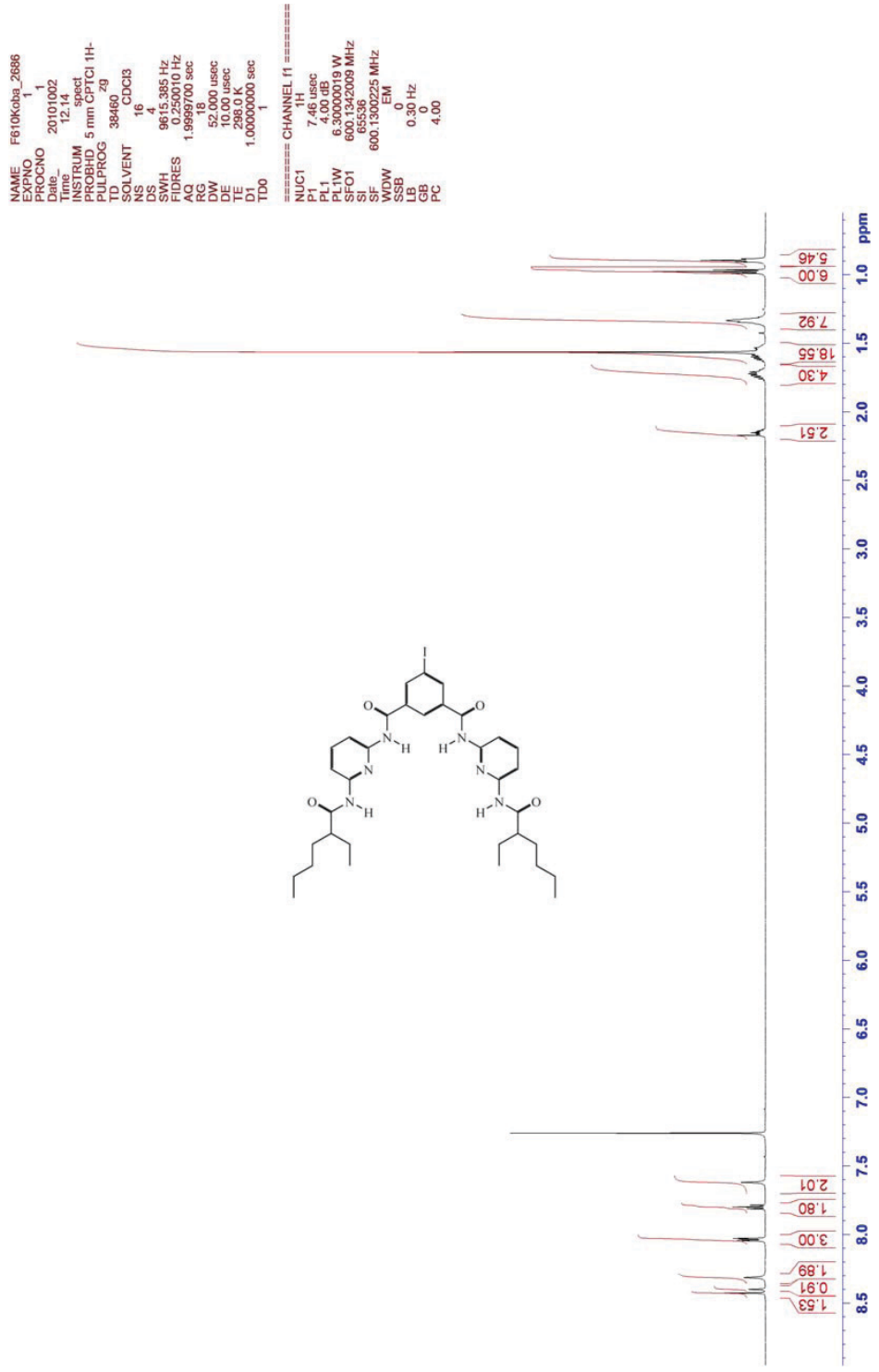
ITC Data Analysis was carried out in Origin 7 SR 2 (OriginLab Corp.) with the provided microcal ITC routines. The sample cell was filled with a solution of Hamilton receptor **1** or **2** in chloroform while the reference cell contained pure solvent. Next, a solution containing a ten fold concentration of barbital **3** was added step by step using a syringe.

^{1}H NMR Spectra

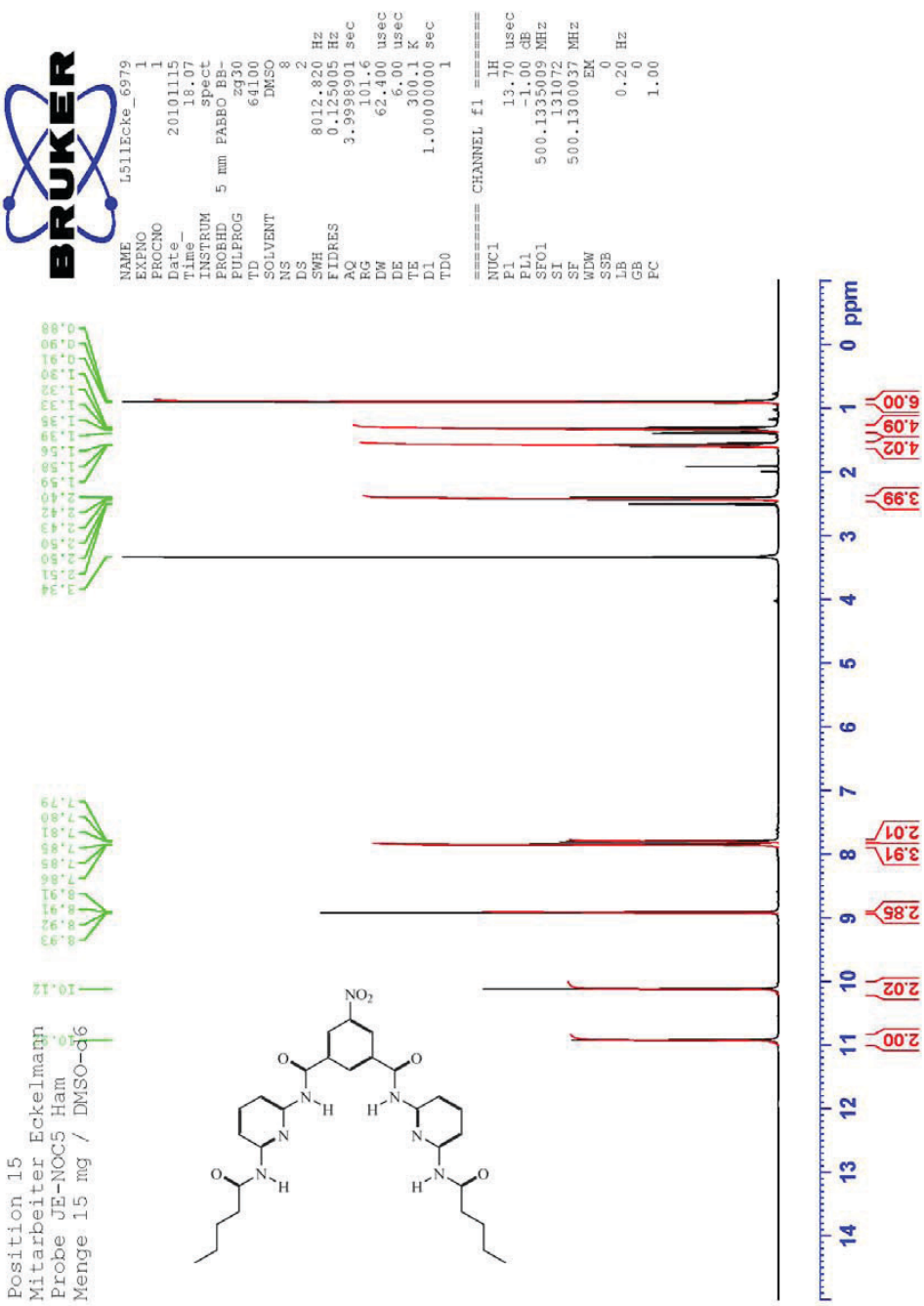
^{1}H NMR spectrum of 5-Iodo-*N*,*N*′-bis(6-pentanoylaminopyrid-2-yl)-isophthalamide (**1a**)



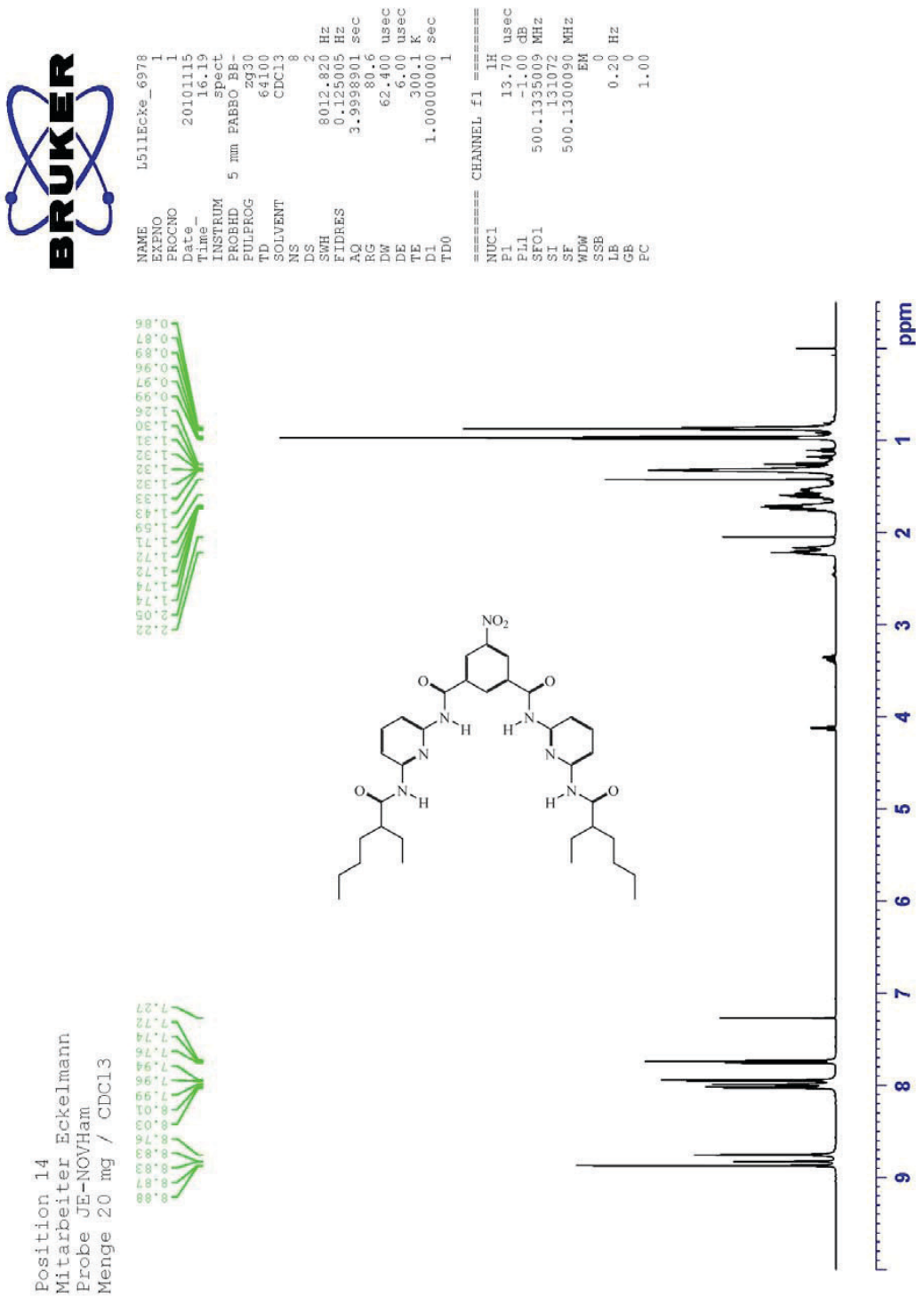
^{1}H NMR spectrum of 5-Iodo-*N*,*N*′-bis[6-(2-ethylhexanoyl)aminopyrid-2-yl]-isophthalamide (**2a**)



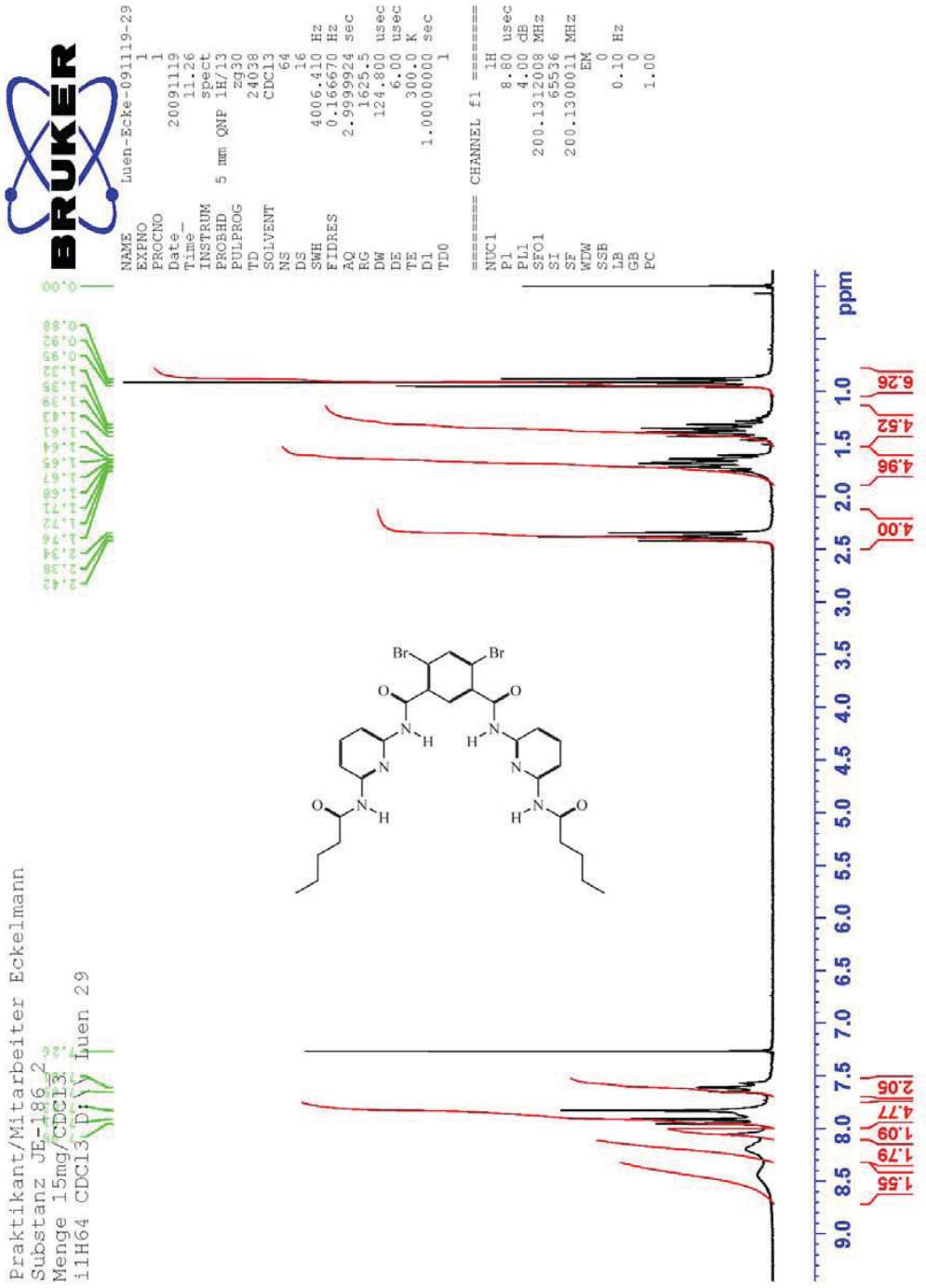
^{1}H NMR spectrum of 5-Nitro-*N,N'*-bis-(6-pentanoylaminopyrid-2-yl)-isophthalamide (**1b**)



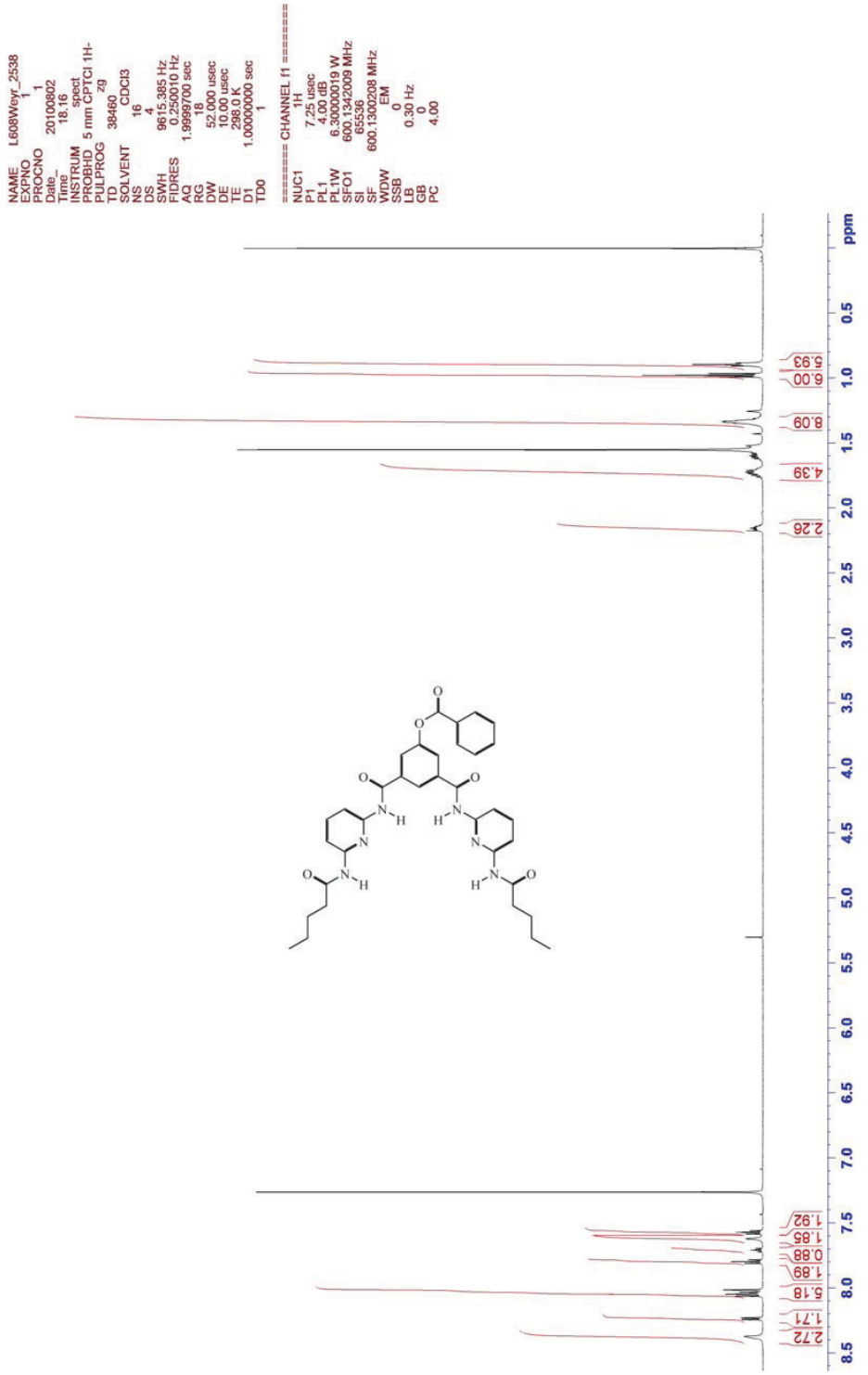
^{1}H NMR spectrum of *N,N'*-Bis-[6-(2-ethylhexanoylamino)-pyrid-2-yl]-5-nitroisophthalamide (**2b**)



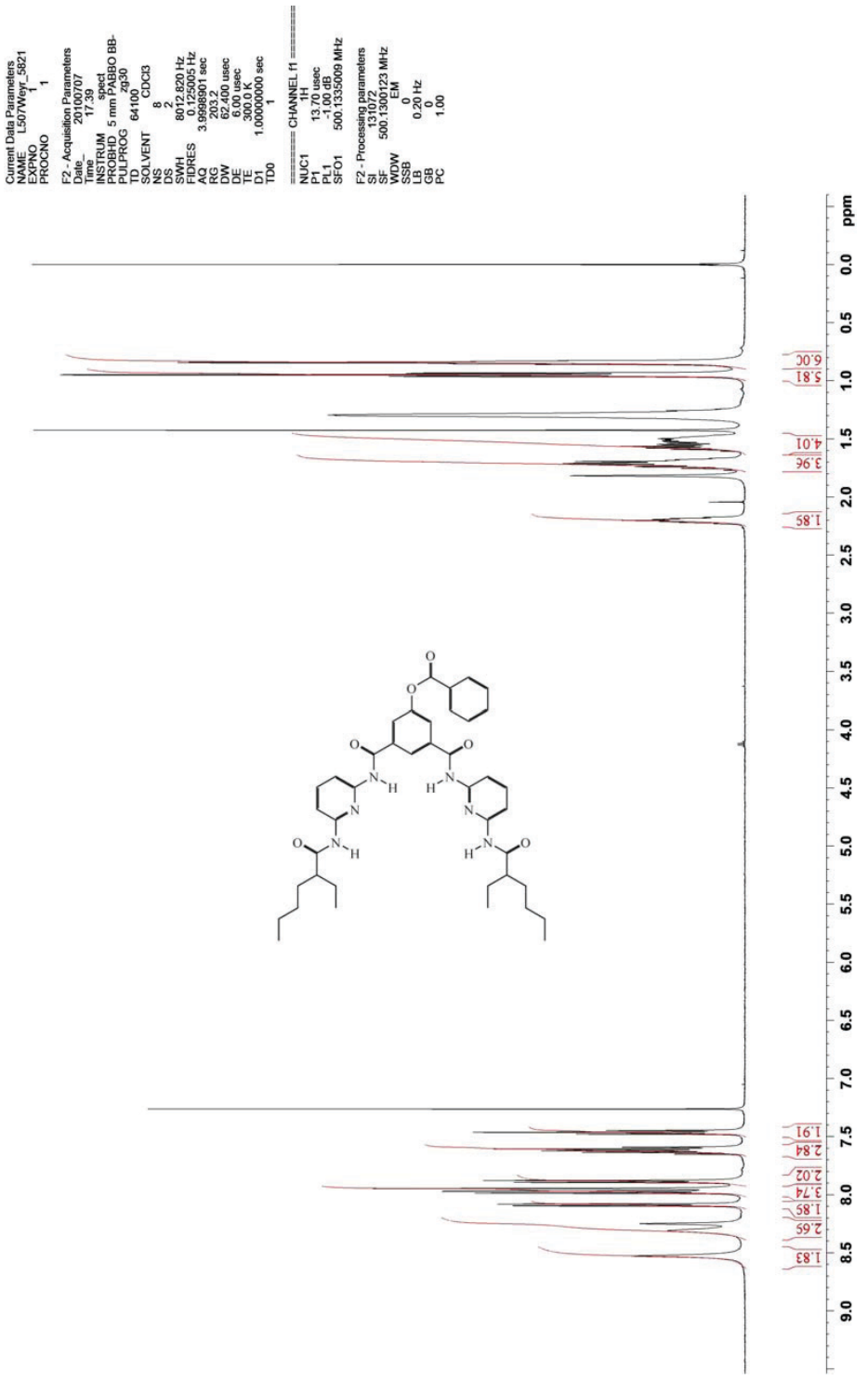
^{1}H NMR spectrum of 4,6-Dibromo-*N,N'*-bis(6-pentanoylaminopyrid-2-yl)-isophthalamide (**1c**)



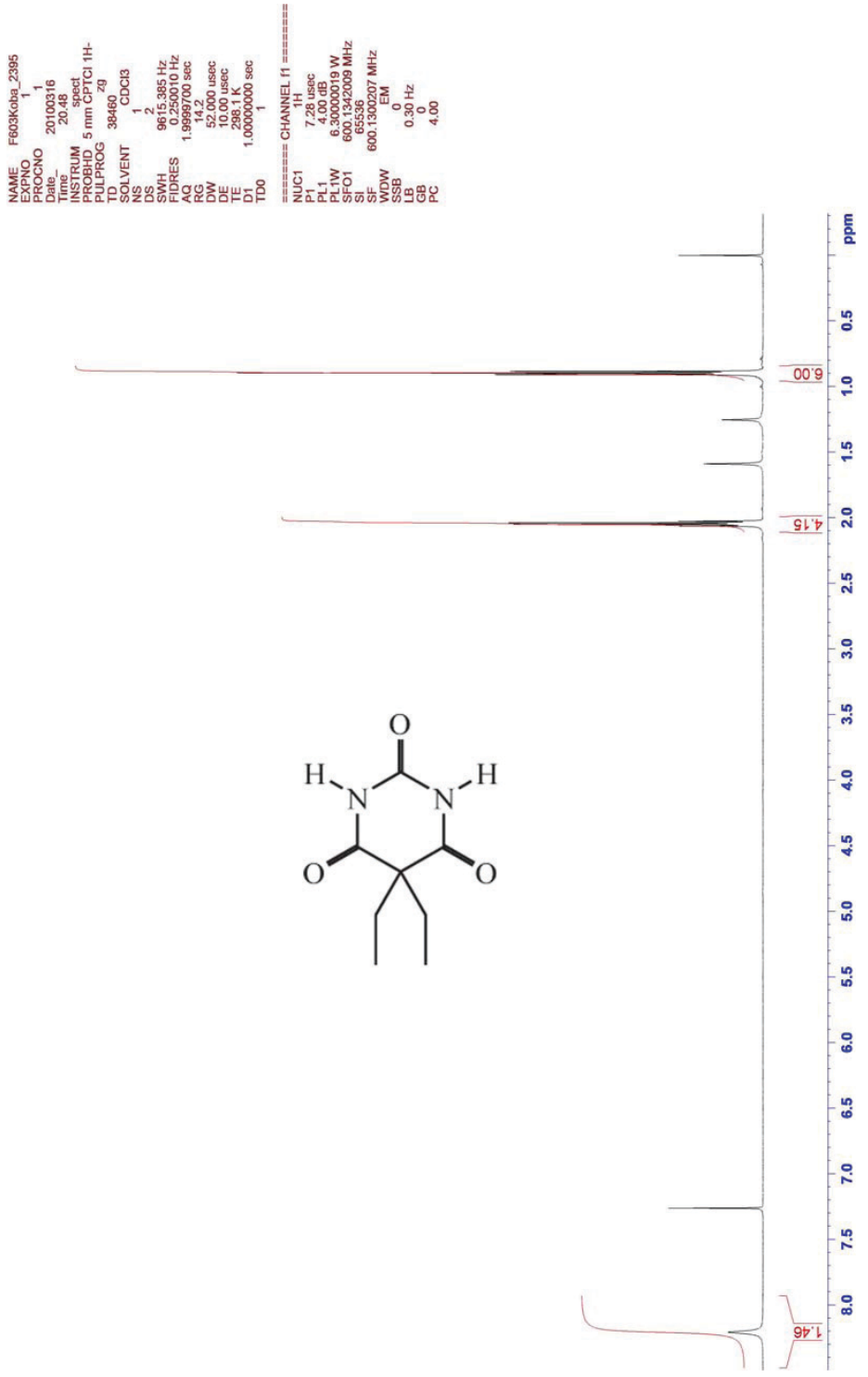
^{1}H NMR spectrum of 5-Benzoyloxy-*N*,*N*'-bis(6-pentanoylaminopyrid-2-yl)-isophthalamide (**1d**)



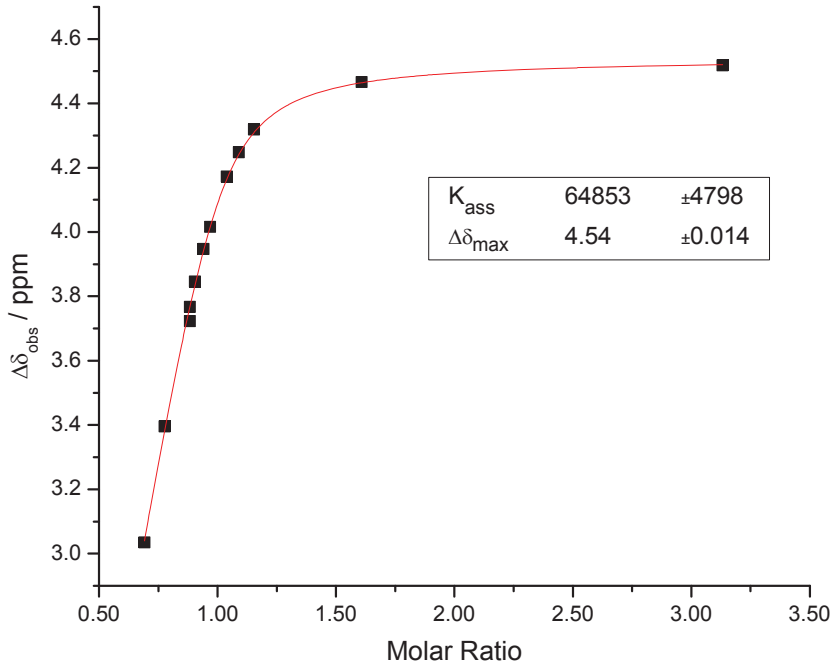
^{1}H NMR spectrum of 5-Benzoyloxy-*N*,*N*'-bis[6-(2-ethylhexanoyl)aminopyrid-2-yl]-isophthalamide (**2d**)



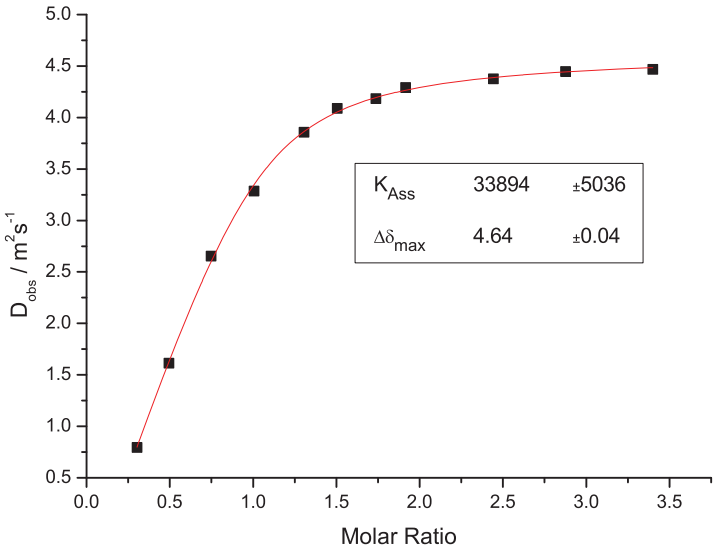
^{1}H NMR spectrum of 5,5-Diethylbarbituric acid (**3**)



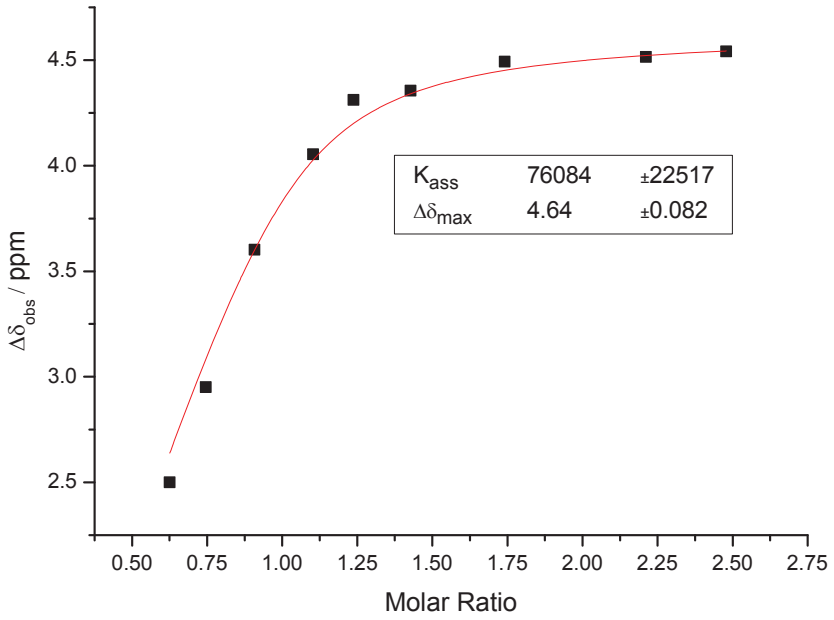
^{1}H NMR Titrations



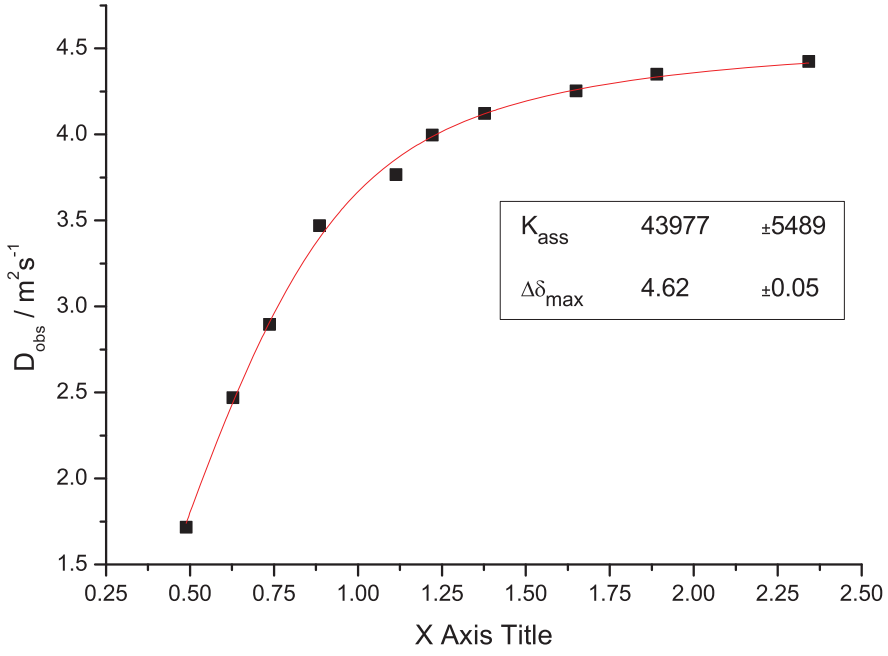
Titration **1a·3**. ^{1}H NMR CIS titration curve of barbital **3** with Hamilton receptor **1a**. The CIS of the NH signals of **3** is plotted against the molar ratio **1a**/**3**.



Titration **2a·3**. ^{1}H NMR CIS titration curve of barbital **3** with Hamilton receptor **2a**. The CIS of the NH signals of **3** is plotted against the molar ratio **2a**/**3**.

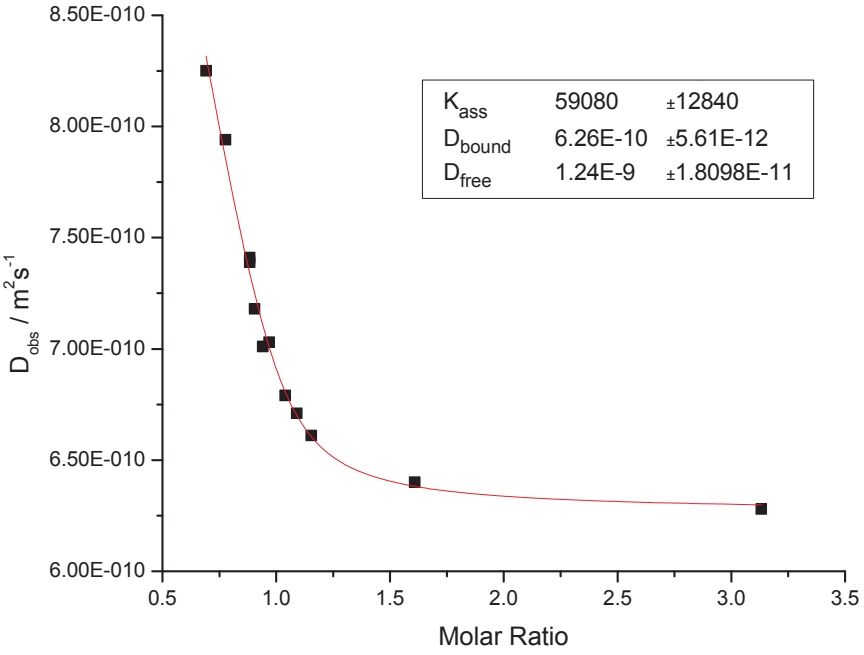


Titration **1d·3**. ^{1}H NMR CIS titration curve of barbital **3** with Hamilton receptor **1d**. The CIS of the NH signals of **3** is plotted against the molar ratio **1d**/**3**.

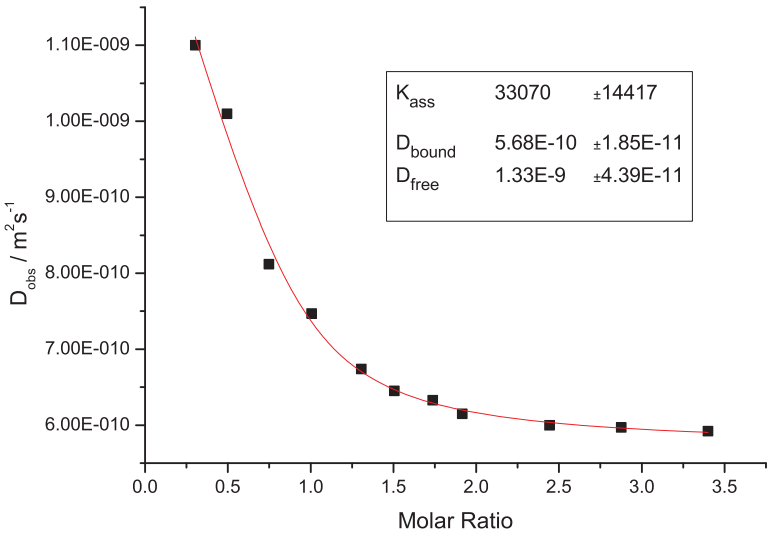


Titration **2d·3**. ^{1}H NMR CIS titration curve of barbital **3** with Hamilton receptor **2d**. The CIS of the NH signals of **3** is plotted against the molar ratio **2d**/**3**.

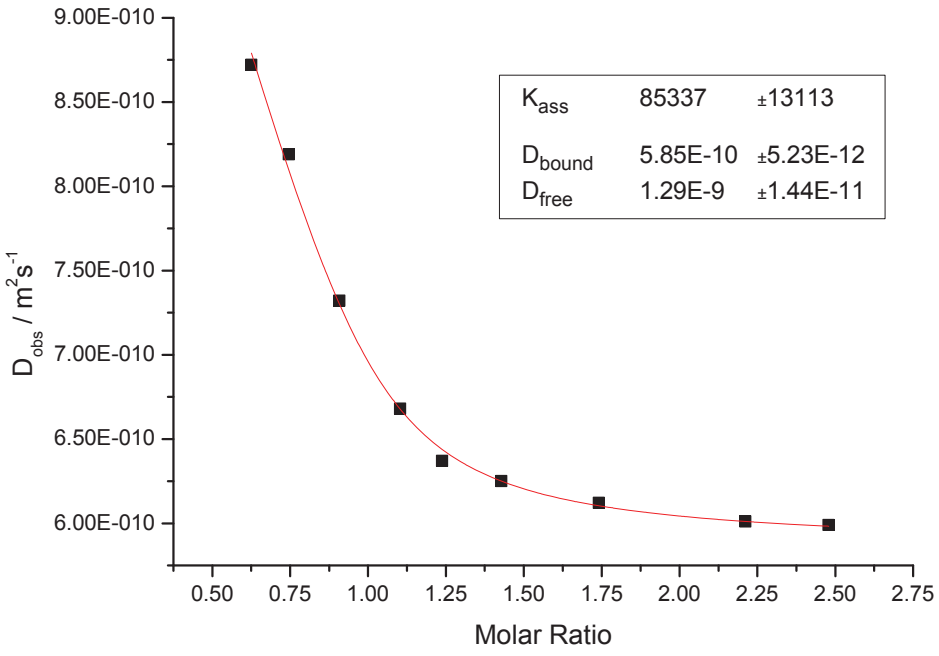
Diffusion NMR Experiments



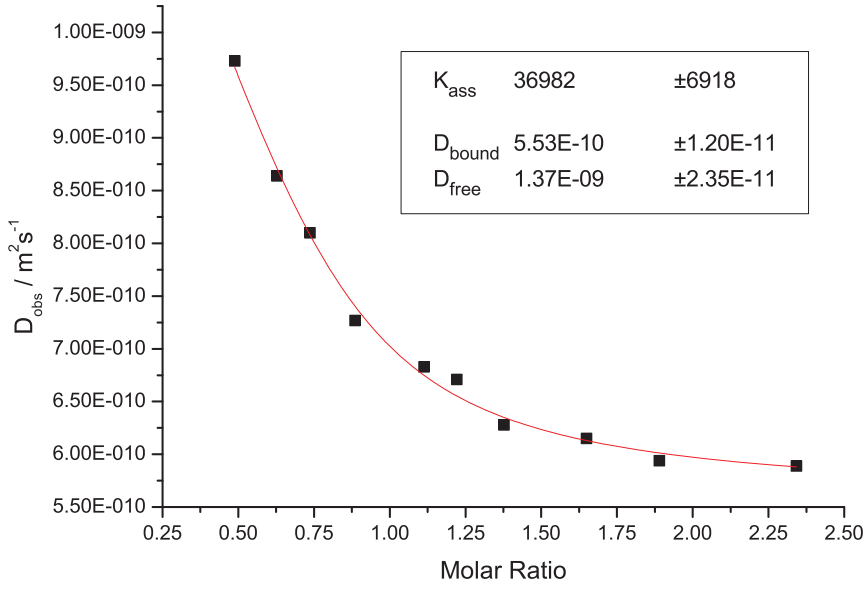
Titration **1a·3**. Titration curve of barbital **3** with Hamilton receptor **1a** determined by ^{1}H NMR diffusion spectroscopy. The signal of the CH_2 groups of barbital **3** was used to determine the diffusion constant D_{obs} which is plotted against the molar ratio **1a**/**3**.



Titration **2a·3**. Titration curve of barbital **3** with Hamilton receptor **2a** determined by ^{1}H NMR diffusion spectroscopy. The signal of the CH_2 groups of barbital **3** was used to determine the diffusion constant D_{obs} which is plotted against the molar ratio **2a**/**3**.



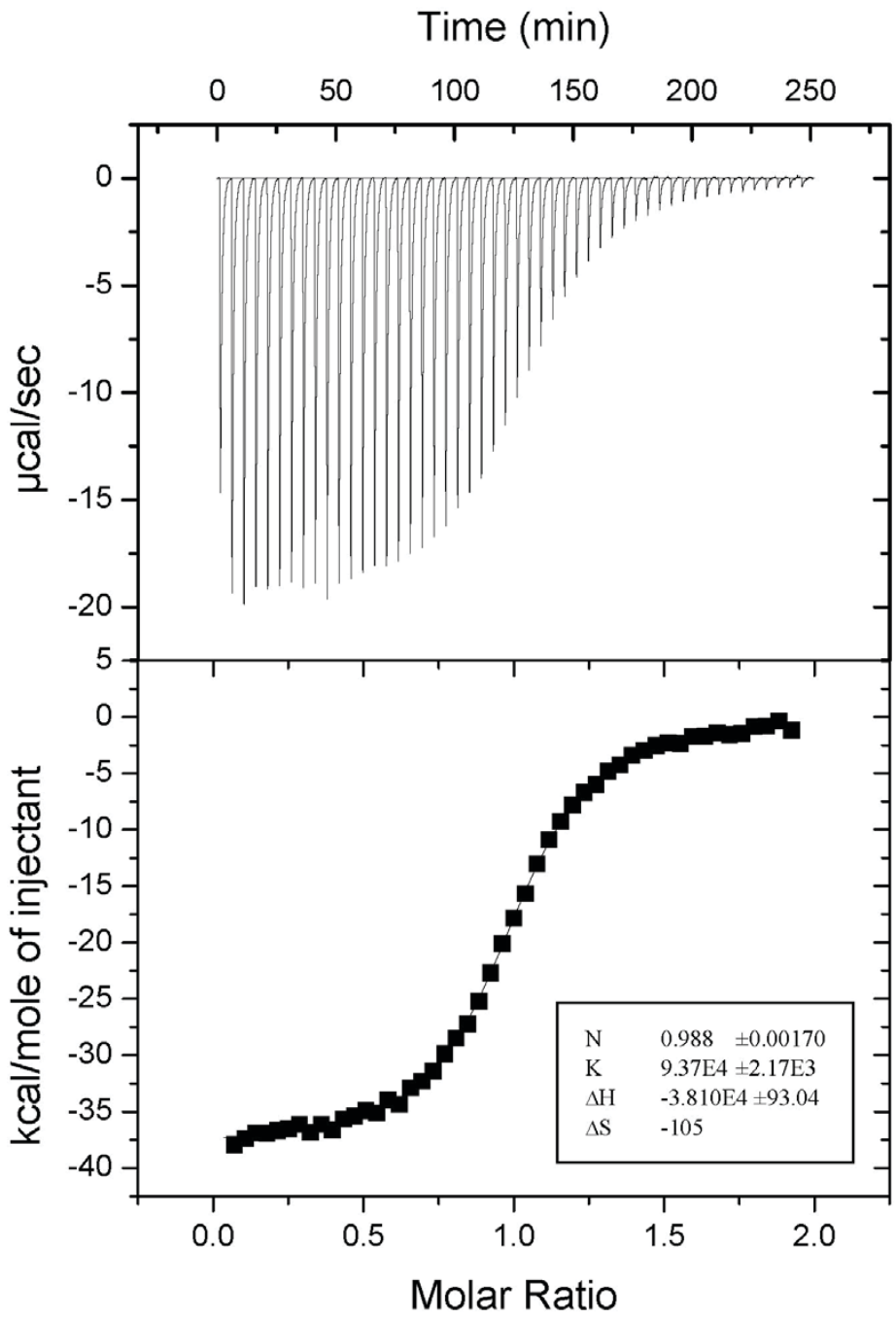
Titration **1d·3**. Titration curve of barbital **3** with Hamilton receptor **1d** determined by ^{1}H NMR diffusion spectroscopy. The signal of the CH_2 groups of barbital **3** was used to determine the diffusion constant D_{obs} which is plotted against the molar ratio **1d**/**3**.



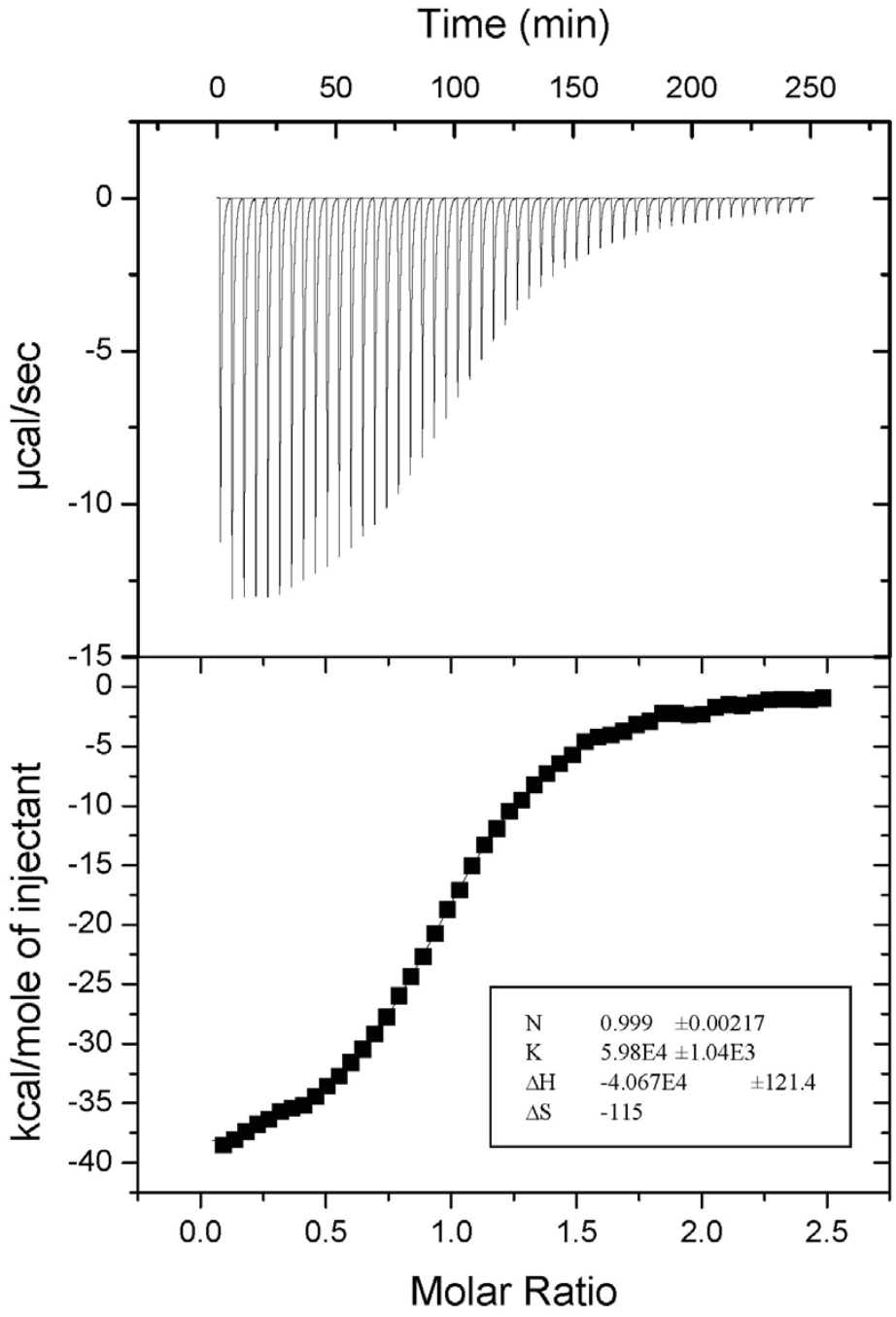
Titration **2d·3**. Titration curve of barbital **3** with Hamilton receptor **2d** determined by ^{1}H NMR diffusion spectroscopy. The signal of the CH_2 groups of barbital **3** was used to determine the diffusion constant D_{obs} which is plotted against the molar ratio **2d**/**3**.

ITC Experiments

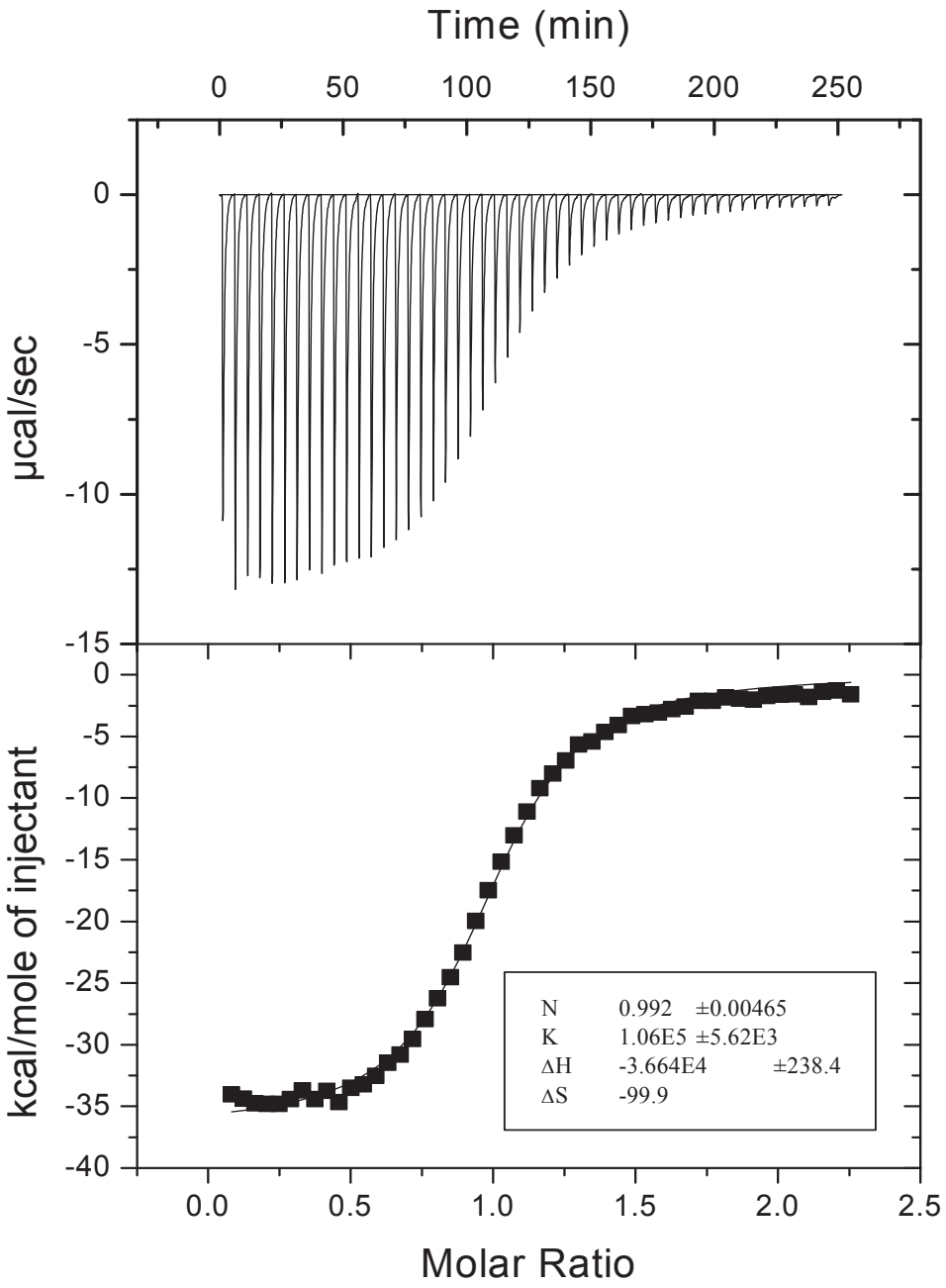
Titration **1a·3** (energy in cal rather than J)



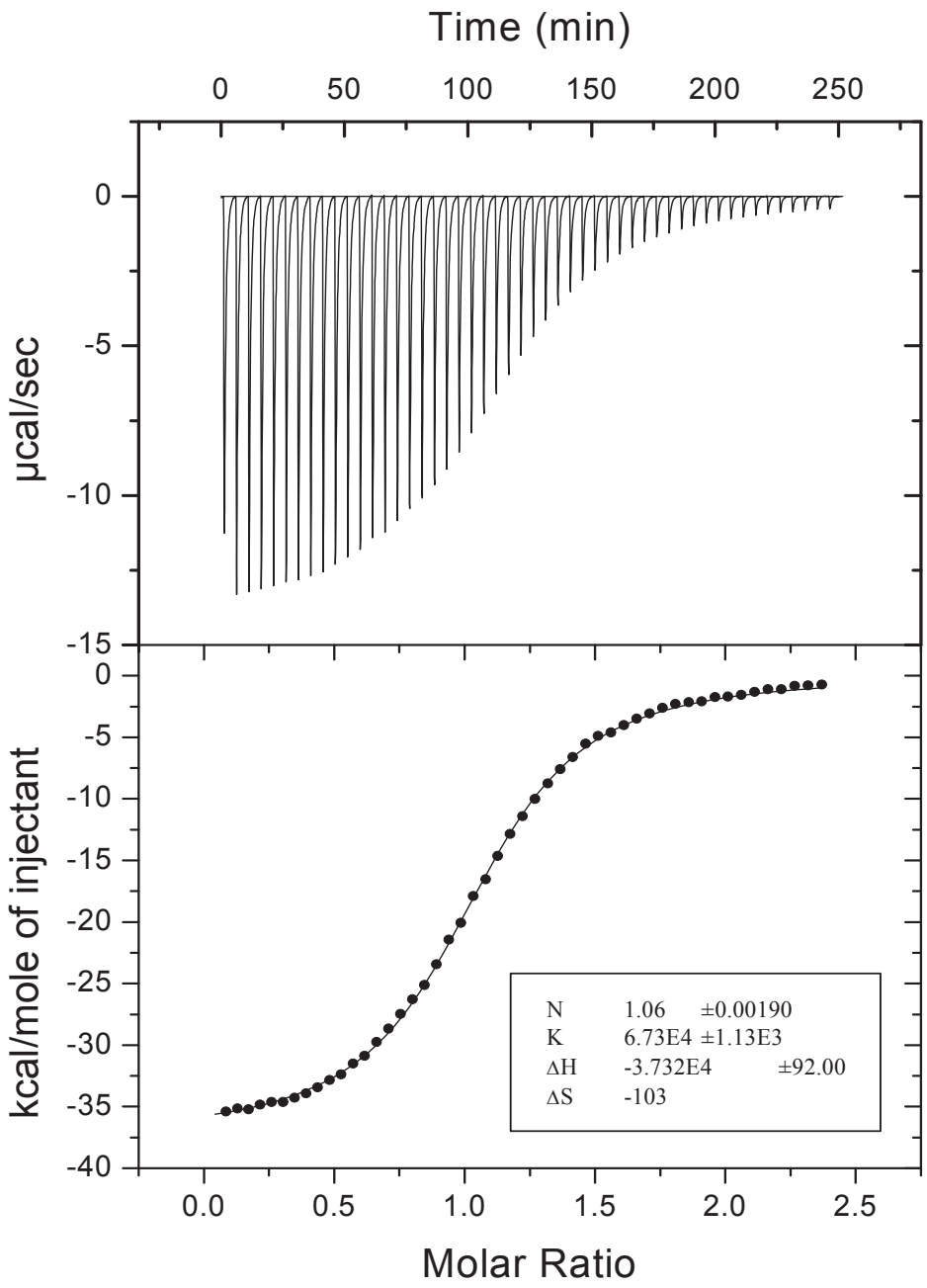
Titration **2a·3** (energy in cal rather than J)



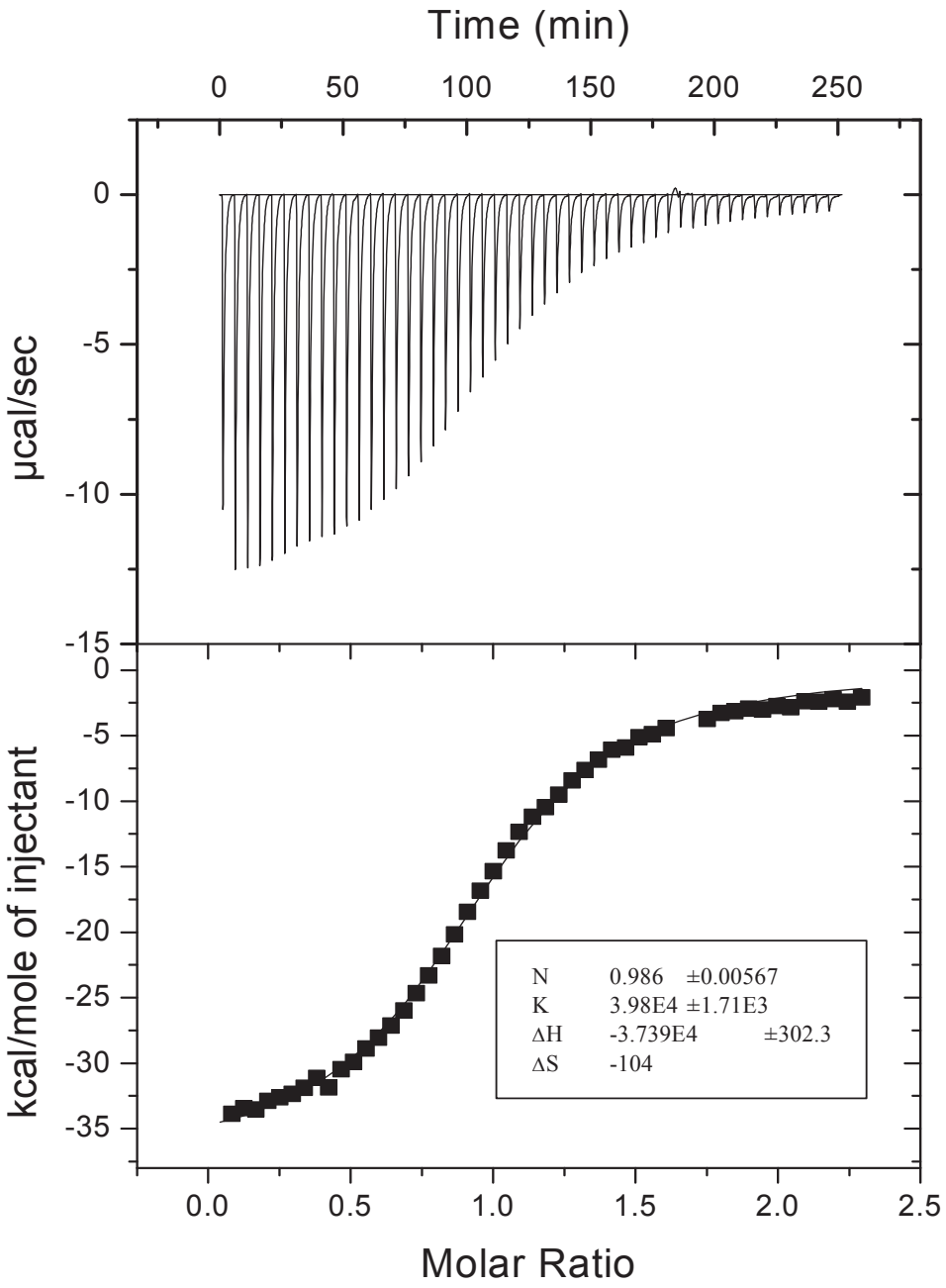
Titration **1b·3** (energy in cal rather than J)



Titration **2b·3** (energy in cal rather than J)



Titration **1c·3** (energy in cal rather than J)



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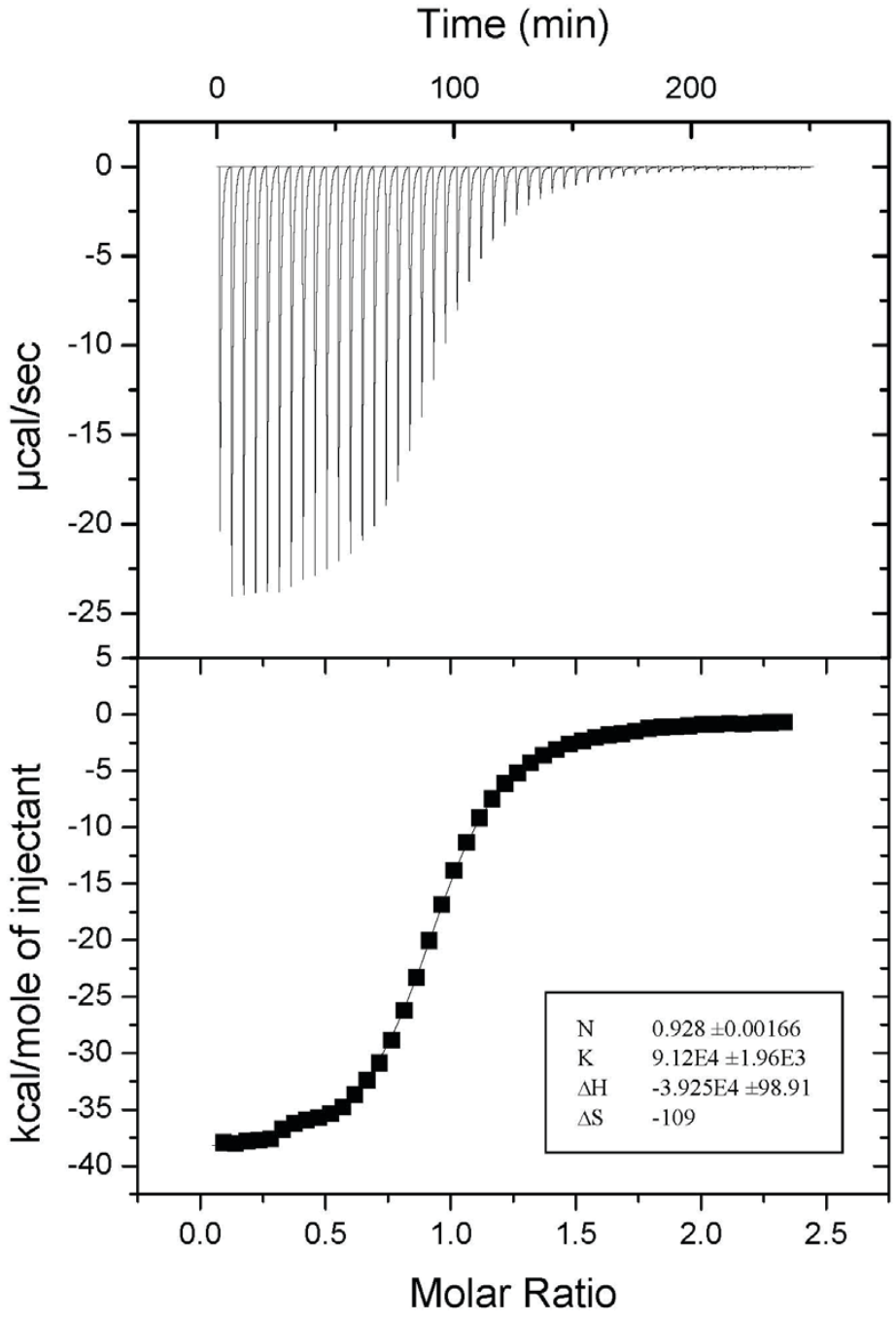
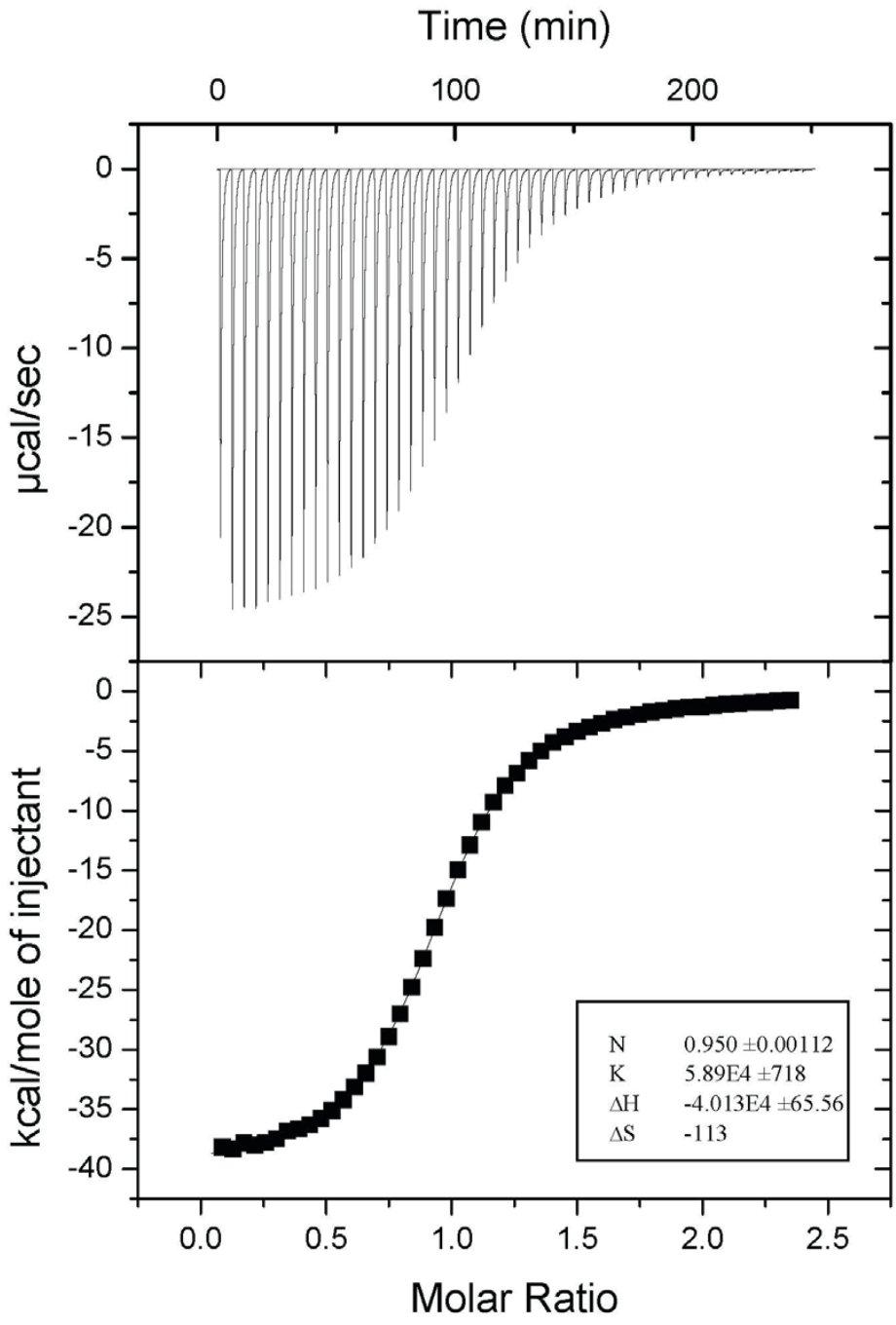


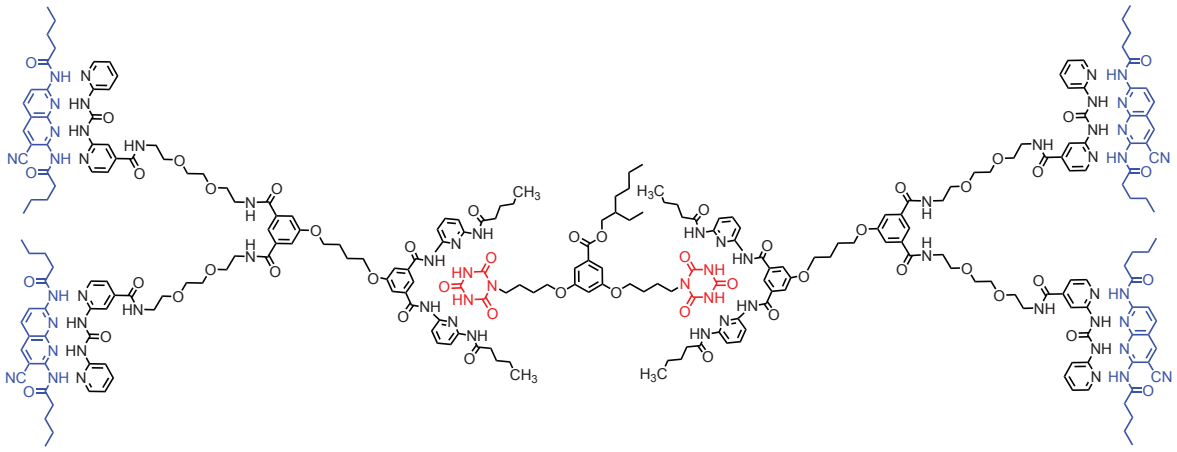
Titration **2d·3** (energy in cal rather than J)



3.4 A Second Generation Supramolecular Dendrimer with a Defined Structure due to Orthogonal Binding

J. Eckelmann, C. Dethlefs, S. Brammer, A. Doğan, A. Uphoff, U. Lüning, eingereicht bei *Chemistry – A European Journal*.

Für den fehlerfreien Aufbau von supramolekularen Dendrimeren sind orthogonale Erkennungsdomänen erforderlich. Erstmals ist es nun gelungen, ein Dendrimer aufzubauen und zu untersuchen, welches über orthogonale Wasserstoffbrücken-Muster in den verschiedenen Sphären verfügt. Grundlegend hierfür ist eine Verzweigungseinheit, die das Wachsen des Dendrimers ermöglicht. Bisherige Versuche scheiterten an der geringen Löslichkeit der Einzelkomponenten. BRAMMER, DOĞAN und UPHOFF erhielten erste Vorstufen, jedoch gelang es erst DETHLEFS 2011, geringe Mengen der Verzweigungseinheit zu isolieren. Für die Synthese konnte nun ein zweiter, erheblich effizienterer und einfacherer Weg entwickelt werden. Neben dem Verzweigungsbaustein wurde ein ditoper Kern benötigt. Abweichend vom bisher verwendeten Barbital wurde hierfür Isocyanursäure verwendet, die eine höhere Bindekonstante zum Hamilton-Rezeptor zeigt. Durch das Einfügen von verzweigten Alkylketten konnte die Löslichkeit in organischen Lösungsmitteln, wie Dichlormethan, ermöglicht werden. Als Endkappen wurden literaturbekannte Naphthyridin-Derivate verwendet, die das passende Wasserstoffbrückenmuster besitzen.



Das Dendrimer und seine Bausteine wurden ausführlich mittels ^{1}H-NMR-Diffusions-Experimenten untersucht. Dabei bestätigten die Experimente die bisher erhaltenen Ergebnisse aus ITC- bzw. NMR-Messungen, sowohl im Bezug auf Bindekonstanten als auch bezogen auf die Orthogonalität. Während die Bindung zwischen Kern- und Verzweigungsbaustein fest ist ($K_{ass} \sim 10^5$ M^{-1}), binden die Endkappen nur mit einer Assoziationskonstante von $K_{ass} \sim 10^3$ M^{-1}. Dieses Verhalten konnte mit temperaturabhängigen NMR-Diffusionsmessungen nachgewiesen werden.

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A Second Generation Supramolecular Dendrimer with a Defined Structure due to Orthogonal Binding[†]

Jens Eckelmann,[a] Christiane Dethlefs,[a] Stefan Brammer,[a] Ahmet Doğan,[a] Andreas Uphoff,[a] and Ulrich Lüning*[a]

Abstract: A second generation supramolecular dendrimer has been prepared by orthogonal multiple hydrogen bonding. In the first (inner) recognition domain, the interaction of one bis-isocyanuric acid **25** with two branching units **21** which carry complementary Hamilton receptors has been exploited. In the second (outer) generation, two ADDA (A = hydrogen bond acceptor, D = donor) receptors of each branching unit **21** have bound complementary DAAD units **4**. The problem of limited solubility of the building blocks has been overcome by introduction of branched ethylhexyl residues and by use of flexible alkylene or oligoethylene glycol linking chains. The orthogonal binding of the two hydrogen bonding pairs has been elucidated by CIS NMR titrations proving that the two pairs – isocyanuric acid with Hamilton receptor, and ADDA with DAAD – bind preferentially. The formation of the supramolecular self assembled 1:2:4 dendrimer with a molecular weight of 5065 g/mol was investigated by diffusion NMR.

Keywords: Supramolecular chemistry• Dendrimers• Self-assembly• Receptors• Diffusion NMR

Introduction

In nature, several types of macromolecules exist, for example polysaccharides, polypeptides, nucleic acids or caoutchouc. While many of them do not possess a well defined molecular weight, proteins for instance do. Until some decades ago, artificial polymers were not accessible with a defined molecular weight, and many attempts have been undertaken to narrow the molecular weight distribution of classical "plastic" material.[1]

Then in 1978, Buhleier, Wehner and Vögtle[2] developed the cascade reaction, and with increasing ability of the analytic tools (MS in particular), well defined branched structures, named arborols or dendrimers were synthesized soon.[3,4,5] Today, thousands of dendrimers have been synthesized with molecular weights similar to traditional polymers but with a distinct monodispers molecular weight.

Their syntheses can be devided into divergent and convergent approaches. The divergent approach starts out from a core, and generation by generation, the dendrimer grows to the outside. Vögtle's cascade reactions[2] were of this type. In contrast, the convergent synthesis[6] connects the building blocks generation by generation starting from the surface of the dendrimer, and dendrons are formed first. Finally, several dendrons are connected to the core.

In these two approaches, irreversible bond forming reactions are used repetitively, with the result, that a defect by an incomplete reaction in one generation will be carried through all other generations to remain in the final product. In a divergent synthesis,

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[†] Multiple Hydrogen Bonds, ##. Part ##-1: ((to be inserted in the proofs))

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the difference between the perfect dendrimer and one in which a little part of the structure is missing is so small that the products can not be separated. In a convergent approach, however, the molecular weights of dendrons and dendrimers differ considerably, thus allowing for an easier isolation of a perfectly monodispers dendrimer.[7]

Besides the kinetically controlled syntheses described above, also reversible reactions can be used to build up a dendrimer by self assembly, also called self organization. The analogy in the peptide world is the formation of quaternary structures of proteins by assembly of subunits, as for instance in hemoglobin.[8] Whole dendrons can be connected by reversible interactions, too.[9,10,11,12] But also in each generation, reversible reactions can be used. In 2005, Hirsch[13] presented a supramolecular dendrimer in which core, branching units and outer-most units (caps) are self assembling by hydrogen bonds. However, in each generation, the same type of supramolecular interaction was used.

The final composition of such a dendrimer can be changed by choosing different ratios of core, branching units and caps. For a trivalent core and doubling branching units, the ratio must be 1:3:6 for the first generation, 1:9:12 for the second, and so on. But due to the fact that the recognition event is the same in each generation, dendrimers of higher generation can be formed if, at the same time, some smaller dendrimers are formed (see Figure 1c and d). Furthermore, even with the same ratio of, for instance, 1:9:12, several isomers are possible (see Figure 1b). Thus a monodispers, structurally well defined dendrimer is not guaranteed by this approach.

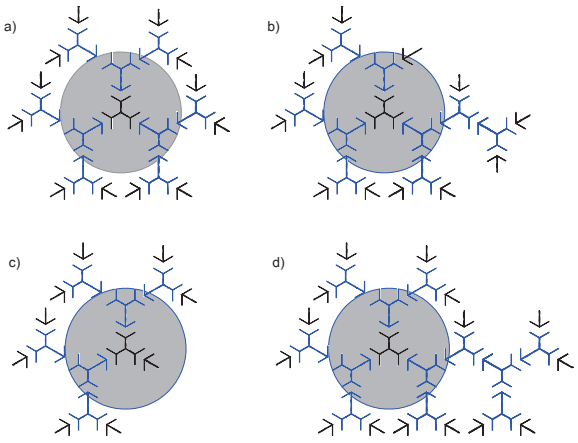


Figure 1: Schematic representation of possible assemblies of dendrimers when a 1:9:12 stoichiometry of core, branching unit and caps and a branching unit with identical host guest pairs for the inner and outer generation is used. The first example of such supramolecular dendrimers used Hamilton receptors in combination with an isocyanuric acid.[13] The gray circles are drawn to facilitate the recognition of the differences between the structures a) – d). a) Desired perfect geometry of the 1:9:12 assembly, b) A 1:9:12 dendrimer will not necessarily assemble in a spheric, highly symmetric fashion, c) and d) larger dendrimers may form at the cost of the formation of smaller dendrimers, i. e. the formation of a 1:12:15 assembly (d) may form if accompanied by a 1:6:9 assembly (c).

The problem described in Figure 1 can be solved if different and orthogonal recognition events are chosen for each generation. Besides hydrogen bonds, also coordinative bond formation[9,10] can be used for the assembly of dendrimers or betains.[11] A combination of coordinative bond formation for the core and hydrogen bonds for the next generation has been shown by Hirsch.[14]

In this investigation, we chose to combine two different hydrogen bonding patterns for the first and second generation recognition domains: The isocyanuric acid/Hamilton[15] receptor pair as used by Hirsch,[13] and a linear quadruple hydrogen bond dimer developed in our group.[16,17,18]

Two problems had to be solved: (i) Do the chosen recognition domains operate orthogonally to one another? (ii) The central task in the realization of such a dendrimer is the synthesis of a respective branching unit which connects one hydrogen bond pattern of one pair with two patterns of the other. This task does not seem too complicated but solubility is a crucial problem when dealing with molecules which are capable of forming numerous hydrogen bonds.

Results and Discussion

To answer the first question, the members of the different recognition domains were titrated with their partners as well as with the recognition domains of the potentially orthogonal system. In chloroform at 298 K, the respective association constants K_{ass} were determined. Table 1 shows that the matching pairs **2·1a** and **4·5** possess association constants K_{ass} of 10^3-10^5 M^{-1}. In contrast, most non-matching pairs interacted with K_{ass} values of less than 10^2 M^{-1}, with the exception of **1a·5** for which K_{ass} = 320 M^{-1} was determined.

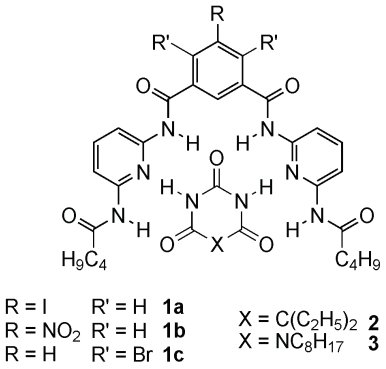


Figure 2: Interaction of different Hamilton receptors with derivatives of barbituric or isocyanuric acid. Association constants K_{ass} were determined by ^{1}H NMR titration or ITC (see Table 1 and Table 3).

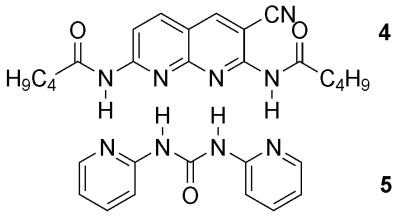


Figure 3: Linear quadruple hydrogen bond dimer DAAD·ADDA (**4·5**).

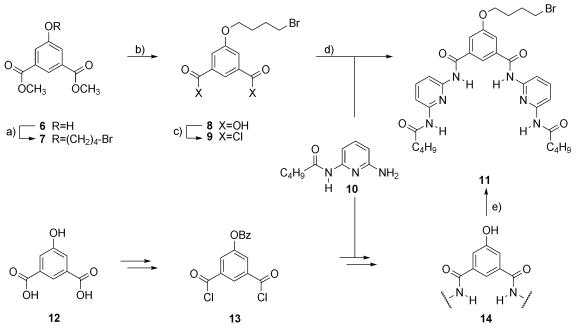
Table 1. Association constants K_{ass} determined by ^{1}H NMR titration in $CDCl_3$ at 298 K. Data are mean values of several titrations, the error (statistic and weighing errors) are estimated to be <+/-20%.

	2 [M^{-1}]	**4** [M^{-1}]	**5** [M^{-1}]
1a	60 000	72	320
4	98	-	2000
5	54	2000	-

With high association constants for the matching pairs and considerably smaller ones for the mis-matches, the self-organization of the desired dendrimer should be possible. A second generation dendrimer based on these two orthogonal recognition domains needs a branching unit which connects one recognition pattern of one pair with two recognition sites of one partner of the orthogonal pair. We choose to connect a Hamilton receptor for the inner with two ADDA units for the outer recognition. Insolubility of intermediates complicated the synthesis[19,20,21] but finally branching unit **21** could be synthesized.[22] As core, we chose a dimer of isocyanuric acid **25**. By introduction of respective substituents, we ensured sufficient solubility also for this core **25**. Scheme 5 summarizes the synthetic access to core **25.** Schemes 1, 2 and 3 describe the route to branching unit **21**.

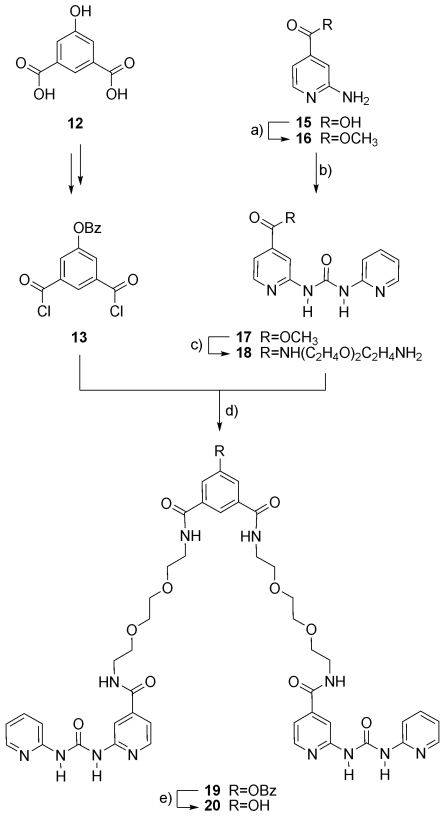
The most challenging task was the synthesis of a branching unit with two different orthogonal binding motifs. Several hydrogen bond acceptor and donor positions lead to poor solubility in aprotic solvents, and unfortunately the overall organic character of the molecules does not produce water solubility either. In order to enhance solubility, alkyl or ethylene glycol chains as well as chiral centers were included.

The branching unit **21** was synthesized in a convergent way. The Hamilton motif (DAD^DAD) on the west side (see Scheme 3) is a further development of a previously published synthesis of related receptors.[23] Here, we can present a different and improved synthesis (Scheme 1).



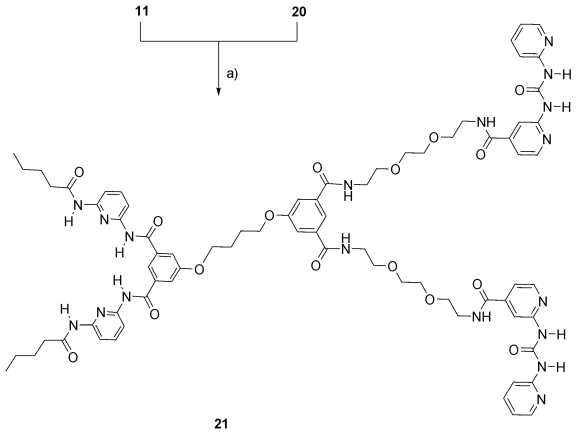
Scheme 1: Synthesis of the branching unit precursor **11**. a) 1,4-Dibromobutane, nBu$_4$NBr, NaH, THF, 70 °C, 4 h; b) LiOH, THF/H$_2$O/MeOH, room temp., 14 h; c) $SOCl_2$, PPh_3, reflux, 60 min; d) Et_3N, CH_2Cl_2, 0 °C → room temp., 12 h. e) 1,4-Dibromobutane, K_2CO_3, DMF, 70 °C, 2 d.

The synthesis starts from 5-hydroxyisophthalic acid dimethylester (**6**) instead[23] of 5-hydroxyisophthalic acid (**12**). Ester **6** was treated with sodium hydride and 1,4-dibromobutane to obtain the alkylated ester **7**. After cleavage of the methyl esters with lithium hydroxide in a mixture of water, tetrahydrofuran and methanol, the isophthalic acid derivative **8** was converted into its acid chloride **9** with thionyl chloride. In the final synthetic step, Hamilton receptor **11** was formed by reaction of the acid chloride **9** with two equivalents of monoacylated[23] diaminopyridine **10**.



Scheme 2: Synthesis of the (ADDA)$_2$ motif. a) H_2SO_4, MeOH, 80 °C, 72 h; b) pyridine-2-carboxylic acid, Et_3N, diphenylphosphoryl azide (DPPA), benzene, reflux, 24 h; c) 1,8-diamino-3,6-dioxaoctane, THF, 60 °C, 24 h; d) Et_3N, THF, room temp., 24 h; e) 1M aq. NaOH, MeOH, room temp., 1 h.

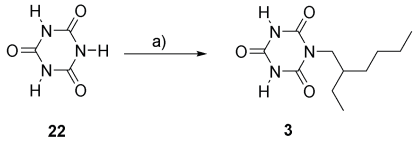
The (ADDA)$_2$ motif on the east side (see Scheme 3) of the branching unit **21** was prepared in 7 steps (Scheme 2). ADDA precursor **17** was synthesized starting from 2-amino-isonicotinic acid (**15**). First, the acid function of **15** was protected as its methyl ester (**16**) in methanol with sulfuric acid. The amino group was then coupled in benzene with pyridine-2-carboxylic acid using diphenylphosphoryl azide and triethylamine. The resulting urea derivative **17** was treated with 1,8-diamino-2,6-dioxaoctane to obtain an ADDA sidearm **18**. 5-Benzoyl isophthaloyl chloride (**13**), prepared from 5-hydroxyisophthalic acid (**12**) and two ADDA sidearms **18** provided the protected (ADDA)$_2$ precursor (**19**). After deprotection with aqueous sodium hydroxide in methanol, the (ADDA)$_2$ building block **20** was ready for a coupling reaction with the Hamilton receptor **11**.



Scheme 3: Synthesis of the branching unit **21**. a) K_2CO_3, DMF, 70 °C, 48 h.

Branching unit **21** was obtained in a Williamson type etherification with potassium carbonate in *N,N*-dimethylformamide in 40 % yield. Due to the ethylene glycol chains and the butyl connection between the isophthalic units, branching unit **21** possessed the desired pleasant solubility for further studies.

First, the interactions with simple partners for the two recognition sites were investigated. The most simple supramolecular aggregate in which all hydrogen bonding domains are binding to a respective partner is shown in Figure 4. The supramolecule consists of a monovalent analogue **3** of the future core unit, a branching unit **21** and two termini **4**. The synthesis of **3** was carried out in a one step procedure starting from isocyanuric acid (**22**) and 2-ethylhexylbromide (Scheme 4).



Scheme 4: Synthesis of model core unit **3**. a) K_2CO_3, 2-ethylhexylbromide, DMSO, 60 °C, 24 h.

The ethylhexyl substitution renders **3** a chiral entity with a branched residue. This results in good solubility in dichloromethane or chloroform. A set of comparative ITC experiments with different Hamilton receptors **1a-c** and isocyanuric acid **3** or barbital (**2**) showed five times higher binding constants K_{ass} for **3** than for **2** (see Table 2).

Table 2. Association constants K_{ass} determined by ITC titration of the Hamilton receptors **1a-c** with barbital (**2**) or isocyanuric acid **3** in chloroform at 298 K. For errors, see supporting information.

	1a [10^3 M^{-1}]	**1b** [10^3 M^{-1}]	**1c** [10^3 M^{-1}]
barbital (**2**)[a]	98	100	40
3	443, 175[b]	648	172

[a] For details see [23], [b] in CH_2Cl_2.

The termini **4** were prepared according to the method developed in our working group and published before.[16]

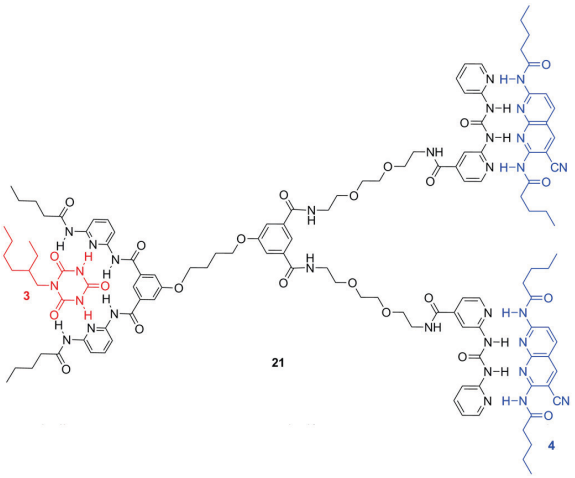


Figure 4: 1:1:2 Supramolecule derived from branching unit **21.**

^{1}H NMR titrations were carried out to prove the orthogonality of each binding domain. Starting from the branching unit **21**, isocyanuric acid **3** was added stepwise. As expected, the NH-protons in the Hamilton binding motif shifted to lower field, while the protons of the ADDA unit showed no significant change. Next, caps **4** were added to the mixture of **3** and **21** and the urea protons shifted to lower field. The self assembly was repeated starting with the branching unit **21** and the end caps **4** followed by addition of the isocyanuric acid **3**. The respective NH protons experienced the same chemically induced shifts. A part of the ^{1}H NMR spectra is shown in Figure 5, for full set of spectra see supporting information.

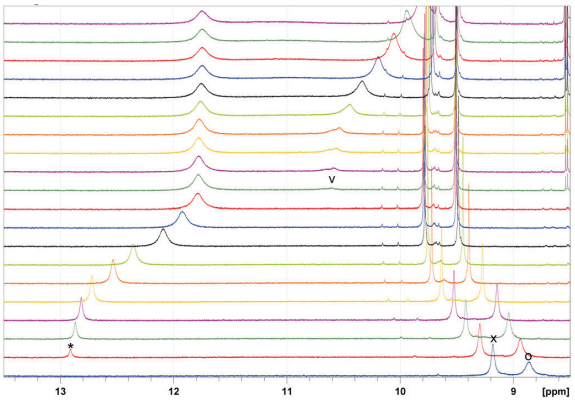
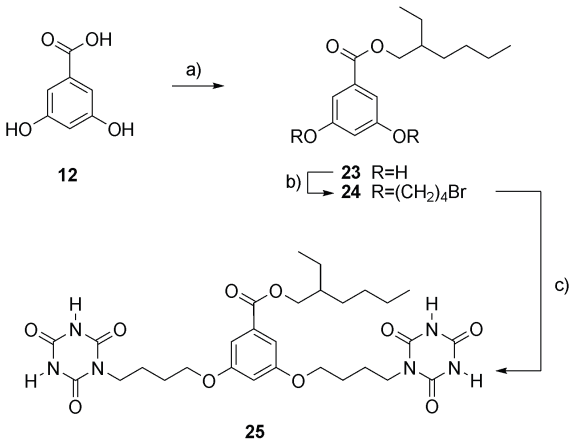


Figure 5: Selected ^{1}H NMR signals for the titration of branching unit **21** (respective NH signals: x, o) with isocyanuric acid **3 (*)** and then with caps **4 (v)**.

The 1:1:2 supramolecule **3** · **21** · 2 **4** proved the concept of orthogonal binding to the branching unit **21**. In order to obtain a dendrimer, a multivalent core had to substitute **3** in the supramolecule. We chose core **25** which consists of two isocyanuric acids and contains a solubility enhancing ethylhexyl group, too (Scheme 5). Starting from 3,5-dihydroxy benzoic acid (**22**), the acid function was reacted with 2-ethylhexan-1-ol and ester **23** was obtained. Besides the enhancement of solubility of the ditopic core **25**, the existence of the carboxylic acid derivative allows for future further modifications. Next, the phenol functions of ester **23** were reacted with 1,4-dibromobutane in a Williamson etherification and dibromide **24** was obtained. Finally, the ditopic core **25** was synthesized by alkylation of two equivalents of isocyanuric acid (**17**) with dibromide **24** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base.



Scheme 5: Synthesis of ditopic core **25**. a) 2-Ethylhexan-1-ol, H_2SO_4, 60 °C, 8 h; b) 1,4-dibromobutane, K_2CO_3, acetone, 60 °C, 24 h; c) isocyanuric acid, DBU, DMF, 70 °C, 24 h.

With the ditopic core **25**, the branching unit **21** and caps **4**, all building blocks for a second generation, supramolecular dendrimer with orthogonal recognition domains existed, and their reaction to form the 1:2:4 supramolecule **25** · 2 **21** · 4 **4** could be investigated (see Figure 2).

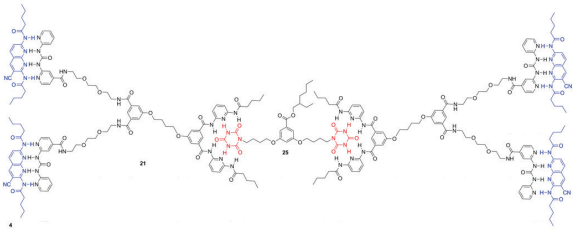


Figure 6: The second generation, supramolecular dendrimer **25** · 2 **21** · 4 **4**. ((for letter size reasons to be printed across two columns))

The self assembly of the supramolecular dendrimer **25** · 2 **21** · 4 **4** was followed by diffusion NMR experiments in dichloromethane. For comparison, these experiments were also carried out for the 1:1:2 supramolecule **3** · **21** · 2 **4.** First, the diffusion constants *D* of all components were determined separately, then they were measured in respective mixtures. The determined diffusion constants *D* are summarized in Table 3.

Table 3. Diffusion constants *D* [10^{-10} m^2s^{-1}] for dendrimeric supramolecules and their components determined in CD_2Cl_2. For errors, see experimental section.

	T	c (**3** or **25**)	*D* (**3**)	*D* (**25**)	*D* (**21**)	*D* (**4**)
as isolated molecules	298 K	–	12.1	5.60[a]	5.09	11.0
3 · **21** (1:1)	298 K	1.1 mM	5.36	–	4.92	-
3 · **21** · 2 **4** (1:1:2)	298 K	1.1 mM	5.25	–	4.80	7.60
25 · 2 **21** (1:2)	298 K	1.7 mM	–	3.85	3.94	–
25 · 2 **21** · 4 **4** (1:2:4)	298 K	1.7 mM	–	3.48	3.75	7.10
25 · 2 **21** · 4 **4** (1:2:4)	298 K	3.8 mM	–	3.13	3.20	6.02
25 · 2 **21** · 4 **4** (1:2:4)	278 K	1.7 mM	–	2.71	2.79	4.91
25 · 2 **21** · 4 **4** (1:2:4)	278 K	3.8 mM	–	2.26	2.30	3.83

[a] Without its binding partner, core **25** was not soluble enough in CD_2Cl_2 for determination of its diffusion constant. Therefore, the experiment was carried out in DMSO-D_6 with 1% of CH_2Cl_2 as internal reference. The diffusion constant of **25** is estimated by taking into account the change of the diffusion constant of CH_2Cl_2 in DMSO-D_6 in comparison to CH_2Cl_2/$CDHCl_2$ in CD_2Cl_2.

For every component of the supramolecular dendrimer, the diffusion constants *D* were determined separately. They reflect the difference in molecular weight of the building blocks **25**, **21** and **4**, although the method does not determine the molecular weight but reflects the differences in solvodynamic radius. When one of the components binds to a partner, the complex becomes larger and, accordingly, it diffuses slower. With an infinite binding constant, the resulting diffusion constants *D* should be indistinguishable regardless of whether the diffusion constant *D* of the supramolecule has been determined using a proton from one component or the other. In reality, a certain fraction of the complex will be dissociated, and therefore the observed diffusion constants *D* will be larger and may differ when determined from protons of different subunits.

The diffusion constants *D* determined from protons of the core **3** or **25** or the branching unit **21** resulted in similar values reflecting the strong binding in a Hamilton receptor. The comparable receptors **1a-c** possess binding constants K_{ass} of ca. 10^5 M^{-1} (see Table 2). In comparison, the binding between the branching unit **21** and the caps **4** is weaker (ca. 10^3 M^{-1})[16] and, consequently, the diffusion constant *D* determined from protons of the caps **4** in the self assembly experiment was larger. For the parent DAAD-ADDA pair, an association constant of $2 \cdot 10^3$ M^{-1} was found at room temperature.[16] Applying this value to the concentrated supramolecular dendrimer solution **25** · 2 **21** · 4 **4** (c = 3.8 M), the degree of dissociation of the fourth DAAD cap **4** was calculated: 30 % of the dendrimer are intact

as **25** · 2 **21** · 4 **4** and close to 70 % carry three caps **4**. In total, more than 80 % of the caps **4** are bound. Taking into account that (i) the exact association constant for the interaction of one ADDA moiety of the branching unit **21** with one DAAD cap **4** is not exactly known and (ii) the diffusion constants are a result of the solvodynamic radii, the determined diffusion constant *D* of $6.02 \cdot 10^{-10}$ $m^2 s^{-1}$ is quite reasonable.

Next, a set of ^{1}H NMR diffusion experiments were carried out at different temperatures. Starting from 298 K, the NMR probe head was cooled to 278 K in steps of 5 K. Every 5 K, a diffusion NMR was recorded (for details see supporting information and experimental section). Based on the stronger binding of **4** and **21** at lower temperatures, only a smaller fraction of the quadruple hydrogen bonding domain is dissociated and consequently the diffusion constants *D* determined from protons of the different subunits **25**, **21** and **4** approach each other. The resulting data is shown in Figure 7 which also shows the influence of dilution on association.

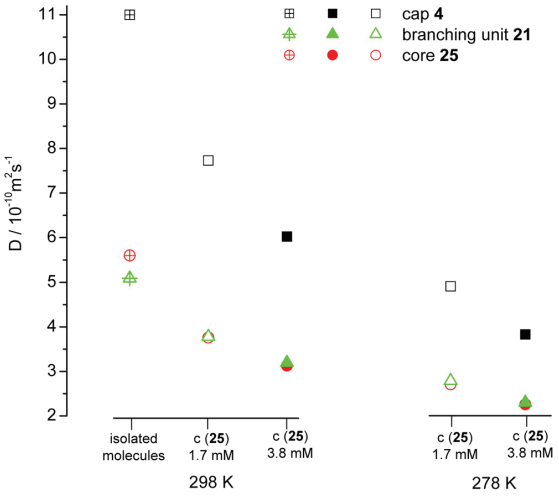


Figure 7. Temperature dependent diffusion NMR experiment with supramolecular complex **25** · 2 **21** · 4 **4** in dichloromethane. The full symbols represent the data points determined for the supramolecule **25** · 2 **21** · 4 **4** at 3.8 mM and the open ones at 1.7 mM while the crossed symbols compare the diffusion constants *D* of the building blocks **25**, **21,** and **4** when measured separately. Please note that due to limited solubility, the diffusion constant *D* for the isolated cap **4** has been determined in DMSO instead of dichloromethane.

Conclusion

Using two orthogonal binding domains, a self assembled dendrimer of second generation **25** · 2 **21** · 4 **4** could be constructed and its formation was investigated by diffusion NMR. The identical (within titration errors of 10 – 20 %) diffusion constants *D* which were determined from protons of the core **25** and the branching units **21** reflect the strong binding between isocyanuric acid and Hamilton receptor. The diffusion constants *D* determined from the caps **4** experience a considerable decrease but even at 278 K do not reach the diffusion constants of the other two building blocks. This indicates that a certain fraction of the dendrimer is dissociated into a 1:2:3 self assembly. At 298 K, the *D* value determined from the caps lies approximately in the middle between the diffusion constant for the free cap **4** and that for the dendrimer **25** · 2 **21** · 4 **4**. An calculation of the degree of dissociation of **25** · 2 **21** · 4 **4** from these values is difficult because the solvation and shape of the two compared structures are unknown. But a *D* value "half way" between the supramolecule and the free cap suggests that free cap **4** and dendrimer **25** · 2 **21** · 4 **4** exist in comparable concentrations in the self-assembling mixture. This is accord with estimations based on a independently determined binding constant for similar parent DAAD and ADDA units. Taking into account that four caps are bound in the dendrimer **25** · 2 **21** · 4 **4**, the observed value for *D* proves that also cap **4** is bound to large extent, certainly above 80 %. This fraction is even higher at lower temperatures.

Future work will now concentrate on (i) an improvement of the bindung constants within each recognition domain and of course (ii) on incorporation of additional orthogonal binding domains in order to build up dendrimers of higher generation than 2.

Experimental Section

General Remarks: NMR spectra were recorded with Bruker AC 200, DRX 500, or AV 600 instruments. Assignments are supported by COSY, HSQC, and HMBC. Even when obtained by DEPT, the type of ^{13}C signal is always listed as singlet, doublet, etc. All chemical shifts are referenced to TMS or to the residual proton or carbon signal of the solvent. All diffusion and titration measurements were carried out with a Bruker AV 600 spectrometer with a triple-resonance cryo probehead with a maximum *z*-gradient strength of 5.67 Gmm^{-1}. As pulse sequence a double stimulated echo with bipolar gradient pulses was chosen. The diffusion time in all these experiments was 100 ms and each gradient pair was applied for 2500 µs. The maximum gradient strength was varied between 5 and 95 % of the gradient strength in 16 or 64 steps. EI/CI mass spectra were recorded with a Finnigan MAT 8200 or MAT 8230. MALDI mass spectra were recorded with a Bruker–Daltonics Biflex III instrument and Cl-CCA (α-cyano-4-chlorocinnamic acid) as matrix. ESI mass spectra were recorded with an Applied Biosystems Mariner Spectrometry Workstation. IR spectra were recorded with a Perkin–Elmer Paragon 1000, Perkin–Elmer Spectrum 100 fitted with an MKII Golden GateTM Single Reflection ATR unit. Elemental analyses were carried out with a Euro EA 3000 Elemental Analyzer from Euro Vector. An addional procedure for the synthesis of compound **7** was published recently by Tian and coworkers.[24] The synthesis of compound **16** starting from **15** was established in our working group from 1999 on. It is based on a synthesis developed by Rowe and coworkers.[25]

^{1}H NMR Diffusion and Titration Experiments: For each guest, a stock solution in CD_2Cl_2 (dry, as purchased) with a concentration of about 200 µM was prepared. A 5 mm NMR tube was filled with **21** (3-5 mg, 2-5 mM) and 600 µL of CD_2Cl_2. The samples were prepared by injecting the stock solution of isocyanuric acid (**3**, 4-8 µL) or DAAD (**4**, 8-20 µL) into the NMR tube with a standard microliter syringe. The ratio of 1:1:2 was controlled by ^{1}H NMR integration. The diffusion analyses were carried out with the aid of Bruker's Topsin 2.1 software. A double stimulated echo with bipolar gradient pairs and longitudinal eddy current delay (dstebpgp3s) was used. The statistical errors were marginal (R > 0.999), the largest errors probably stem from the ratio determination by NMR integration.

Isothermal Titration Calorimetry Experiments were carried out with a VP-ITC microcalorimeter (MicroCal LLC, GE Healthcare) in anhydrous chloroform or dichloromethane. A Hamilton receptor (**1a-1c**, ca. 1.4 mL, 0.3–0.5 mM) was placed in the calorimeter cell. The titration syringe was loaded with barbital (**2**) or isocyanuric acid (3) at a 10 times higher concentration than in the cell. The titrations were usually carried out with 50 injections of 6 µL each with time intervals of 5 min. The solution was stirred at 300 rpm as suggested by the manufacturer. Titrations were carried out at a cell temperature of 298 K (shield: 297 K) and with a reference power of 10 $\mu cal\ s^{-1}$. ITC data analyses were carried out in Origin 7 SR 2 (OriginLab Corp.) with the provided microcal ITC routines. Please note that all energies are listed as $kcal\ mol^{-1}$ rather than $kJ\ mol^{-1}$ by this routine. Each experiment was carried out at least twice. In cases of larger deviations (due to, for instance, changes in room temperature stability), more titrations were carried out. One representative titration curve for the titrations of each host guest pair is shown in the supporting information.

1-(2-Ethylhexyl)-1,3,5-triazinane-2,4,6-trione (3): A solution of isocyanuric acid (5.16 g, 40.0 mmol), 2-ethylhexyl bromide (3.86 g, 3.58 mL, 20.0 mmol), potassium carbonate (2.76 g, 20.0 mmol), and anhydrous DMSO (40 mL) were heated at 60 °C for 24 h. The solution was poured into sat. aq. sodium hydrogen sulfate solution (200 mL)

and extracted trice with diethyl ether (80 mL). The combined org. layers were washed with brine (3 x 100 mL) and finally dried with sodium sulfate. The solvent was concentrated in vacuo to 100 mL. The crude product was precipitated with *n*-hexane and isolated by vacuum filtration. Finally it was washed with *n*-pentane (100 mL) to obtain **3** as a white powder (960 mg, 20 %); m.p. 152 °C; ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 8.74 (br. s, 2 H, N*H*), 3.75 (m_c, 2 H, NCH_2), 1.81 (sept., ^3J=6.3 Hz, 1 H, CH_2CH), 1.38-1.2 (m, 8 H, CH_2), 0.90 (t, ^3J=7.4 Hz , 3 H, CH_3), 0.89 (t, ^3J=7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 149.3 (s, *C*ONHCH$_2$), 147.8 (s, NH*C*ONH), 45.7 (t, NCH$_2$), 37.8 (d, CH_2CH), 30.4 (t, $CHCH_2CH_2$), 28.6 (t, $CH_2CH_2CH_2CH_3$), 23.8 (t, $CHCH_2CH_3$), 23.1 (t, $CH_2CH_2CH_3$), 13.9 (q, $CH_2CH_2CH_3$), 10.3 (q, $CHCH_2CH_3$) ppm. MS (EI, 70 eV): *m/z* (%) = 241 (1) $[M]^+$, 143 (54), 130 (100), 112 (52) $[C_8H_{16}]^+$. MS (CI, isobutane): *m/z* (%) = 242 (100) $[M+H]^+$. IR (ATR): $\tilde{\nu}$ = 3198, 3062 (NH), 2958, 2930, 2869 (aliph. CH), 1666 (C=O), 1452, 1411 (aliph. CH_2, CH_3) cm^{-1}; $C_{11}H_{19}N_3O_3$ (241.14) calcd. C 54.76, H 7.94, N 17.41; found C 54.66, H 7.75, N 17.45.

5-(4-Bromobutoxy)-*N,N*-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (11): Method A: 1,4-Dibromobutane (265 µL, 2.25 mmol) and 5-hydroxy-*N,N*-bis[6-(pentanoylamino)pyrid-2-yl]isophthalamide (**14**, 300 mg, 563 µmol) were dissolved in anhydrous DMF (10 mL) and potassium carbonate (189 mg, 3.37 mmol) was added. The solution was stirred at 70 °C for 2 d. Chloroform (20 mL) and water (20 mL) were added, the solid was removed by filtration and the org. layer was separated. The org. layer was dried with magnesium sulfate and the solvents were removed in vacuo. The residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 3:1, R_f = 0.06) and **11** was obtained as a white solid (139 mg, 37 %); m.p. 96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (br. s, 2 H, N*H*), 7.99 (d, ^3J = 8.1 Hz, 2 H, Py-*H*-5), 7.96-7.93 (m, 3 H, Py-*H*-3, Ar-*H*-2), 7.88 (br. s, 2 H, N*H*), 7.73 (t, ^3J = 8.1 Hz, 2 H, Py-*H*-4), 7.58 (d, ^4J = 1.4 Hz, 2 H, Ar-*H*-4,6), 4.07 (t, ^3J = 6.0 Hz, 2 H, ArOCH_2), 3.49 (t, ^3J = 6.5 Hz, 2 H, CH_2Br), 2.39 (t, ^3J = 7.6 Hz, 4 H, NHCOCH_2), 2.10-2.03 (m, 2 H, CH_2CH$_2$Br), 2.00-1.94 (m, 4 H, ArOCH$_2$CH_2), 1.71 (quint., ^3J = 7.6 Hz, 4 H, NHCOCH$_2$CH_2), 1.41 (sext., ^3J = 7.4 Hz, 4 H, CH_2CH$_3$), 0.95 (t, ^3J = 7.4 Hz, 6 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1 (s, *C*ONHCH$_2$), 164.2 (s, *C*ONHPy), 159.7 (s, Ar-*C*-5), 149.8 (s, Py-*C*-2), 149.2 (s, Py-*C*-6), 140.9 (d, Py-*C*-4), 136.1 (s, Ar-*C*-1,3), 117.4 (d, Ar-*C*-2), 117.1 (d, Ar-*C*-4,6), 110.2 (d, Py-*C*-3), 109.6 (d, Py-*C*-5), 67.7 (t, ArOCH$_2$), 37.5 (t, ArOCH$_2$CH$_2$), 33.1 (t, *C*H$_2$Br), 29.3 (t, NHCO*C*H$_2$) 27.7 (t, *C*H$_2$CH$_2$Br), 27.4 (t, NHCOCH$_2$*C*H$_2$), 22.3 (t, *C*H$_2$CH$_3$), 13.8 (q, *C*H$_3$) ppm. IR (ATR): $\tilde{\nu}$ = 3277 (N-H), 2958 (aliph. C-H), 2939 (aliph. C-H), 2872 (aliph. C-H), 1668 (C=O), 1582 (N-H), 1505 (arom.), 1442 (CH_2), 1293 (C-O-C) cm^{-1}. MS (MALDI, Cl-CCA): *m/z* = 667 $[M+H]^+$, 689 $[M+Na]^+$, 705 $[M+K]^+$. $C_{32}H_{39}BrN_6O_5$ (667.6) calcd. C 57.57, H 5.89, N 12.59; found: C 57.74, H 5.97, N 12.76.

Method B (starting from 8 and 10): 5-(4-Bromobutoxy)-isophthalic acid (**8**, 821 mg, 2.59 mmol) and triphenylphosphine (4.00 mg, 15.3 µmol) were suspended in thionyl chloride (12 mL). The mixture was heated to reflux for 60 min. Excess of thionyl chloride was removed in a stream of nitrogen at 60 °C. The residue **9** was cooled to room temp. **10** (1.00 g, 5.18 mmol) was dissolved in dichloromethane (20 ml) and was added to the residue. The solution was cooled to 0 °C, and triethylamine (3.63 mL, 25.9 mmol) was added dropwise while stirring. Stirring was continued for 12 h and the solution was concentrated under reduced pressure. The crude product was dissolved in dichloromethane (50 mL) and was washed with diluted HCl (0.1 M, 50 mL) and with water (2 x 50 mL). The solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 3:1, R_f = 0.06) and **11** was obtained as a white solid (580 mg, 34 %).

3,5-Dihydroxy-benzoic acid 2-ethyl-hexyl ester (23): To a solution of 2-ethylhexan-1-ol (40.0 mL, 33.2 g, 255 mmol) and 3,5-dihydroxybenzoic acid (**22**, 5.00 g, 32.5 mmol), conc. sulfuric acid (5 mL) was added. After the mixture was stirred for 8 h at 60 °C, it was allowed to cool down over night (10 h). Ice cold water (100 mL) was added slowly and the mixture was carefully neutralized with solid sodium bicarbonate. The mixture was extracted twice with *tert*-butyl methyl ether (100 mL), and the combined organic layer was dried with magnesium sulfate. The solvent was removed under reduced pressure and excess of 2-ethylhexan-1-ol was removed at a rotary evaporator connected to a rotary vane pump (0.1 mbar) to yield a brown oil. The crude product was dissolved in dichloromethane and was filtrated through a short column (20 cm) with silica gel. The column was flushed with dichloromethane (200 ml) to remove remains of 2-ethylhexan-1-ol. Afterwards the product was eluted using dichloromethane/methanol (3:1) and **23** was obtained as a brownish oil (7.64 g, 88 %). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.10 (d, ^4J = 2.3 Hz, 2 H, Ar-2,6-*H*), 7.02 (br. s, 2 H, O*H*), 6.16 (t, ^4J=2.3 Hz, 1 H, Ar-4-*H*), 4.20 (m_c, 2 H, OCH_2), 1.63 (m_c, 1 H, OCH$_2$C*H*), 1.50-1.10 (m, 8 H, 4 CH_2), 0.96-0.82 (2 t, ^3J = 7.3 Hz, ^3J = 7.1 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.3 (s, *C*O), 156.9 (s, Ar-3,5-*C*), 132.2 (s, Ar-1-*C*), 109.0 (d, Ar-2,6-*C*), 107.5 (d, Ar-4-*C*), 68.0 (t, OCH_2), 38.8 (d, CH_2CH), 30,5 (t, $CHCH_2CH_2$), 28.9 (t, *C*H$_2$CH$_2$CH$_3$), 23.8 (t, CHCH_2CH$_3$), 22.9 (t, CH$_2$CH_2CH$_3$), 14.0 (q, CH$_2$CH$_2$CH_3), 11.0 (q, CHCH$_2$CH_3) ppm. MS (EI): *m/z* (%) = 266 (10) $[M]^+$, 154 (100) $[M - C_8H_{17}+H]^+$, 137 (59) $[M - C_8H_{17}O]^+$. MS (CI): *m/z* (%) = 267 (10) $[M + H]^+$, 155 (100) $[M - C_8H_{17}+2H]^{++}$. IR (ATR): $\tilde{\nu}$ = 3352 (O-H), 2959, 2928, 2860 (aliph. C-H), 1688 (C=O), 1599, 1508 (arom.), 1452 (aliph. C-C), 1242, 1154 (C-O-C) cm^{-1}. $C_{15}H_{22}O_4$ (266.33) calcd. C 67.64, H 8.33; $C_{15}H_{22}O_4 \cdot 0.5\ H_2O$ (275.34) calcd. C 65.43, H 8.42; found C 65.48, H 8.53.

3,5-Bis(4-bromobutoxy)-benzoic acid 2-ethyl-hexyl ester (24): 1,4-Dibromobutane (28.1 g, 130 mmol) and **23** (3.50 g, 13.0 mmol) were dissolved in anhydrous acetone (50 mL). Potassium carbonate (5.40 g, 39 mmol) was added and the mixture was stirred for 24 h at 60 °C. The mixture was filtered and the solvent was removed under reduced pressure. Excess 1,4-dibromobutane was removed at a rotary evaporator connected to a rotary vane pump (0.1 mbar) to yield a yellow oil. The crude product was dissolved in cyclohexane (100 mL) and was filtrated through a short column (20 cm) with silica gel. The column was flushed with cyclohexane (200 ml) to remove remains of 1,4-dibromobutane. Afterwards the product was eluted using cyclohexane/ethyl acetate (9:1, R_f = 0.40) and **24** was obtained as a yellow oil (6.06 g, 87 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, ^4J = 2.4 Hz, 2 H, Ar-2,6-*H*), 6.62 (t, ^4J = 2.4 Hz, 1 H, Ar-4-*H*), 4.22 (m_c, 2 H, OCH_2CH), 4.02 (t, ^3J = 6.6 Hz, 4 H, Ar-O-CH_2), 3.49 (t, ^3J = 6.4 Hz, 4 H, CH_2-Br), 2.07 (m_c, 4 H, BrCH$_2$CH_2), 1.96 (m_c, 4 H, Ar-OCH$_2$CH_2), 1.72 (sept, ^3J = 6.1 Hz, 1 H, OCH$_2$C*H*) 1.50-1.28 (m, 8 H, 4 x CH_2), 0.94 (t, ^3J = 7.4 Hz, 3 H, CHCH$_2$CH_3), 0.90 (t, ^3J = 7.0 Hz, 6 H, CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4 (s, *C*=O), 159.9 (s, Ar-3,5-*C*), 132.5 (s, Ar-1-*C*), 107.8 (d, Ar-2,6-*C*), 106.2 (d, Ar-4-*C*), 67.6 (t, COOCH_2), 67.2 (t, ArO*C*H$_2$), 38.9 (d, CH_2CH), 33.3 (t, Br*C*H$_2$), 30.6 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 29.4 (t, BrCH$_2$CH$_2$), 28.9 (t, CH$_2$*C*H$_2$CH$_2$CH$_3$), 27.8 (ArOCH$_2$*C*H$_2$), 24.1 (t, CH*C*H$_2$CH$_3$), 22.9 (t, CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.0 (q, CH$_2$CH$_2$CH$_2$*C*H$_3$), 11.1 (q, CHCH$_2$*C*H$_3$). MS (EI): *m/z* (%) = 536 (5) $[M]^+$, 455 (1) $[M - Br]^+$, 405 (8) $[M - C_8H_{17}O]^+$, 135 (100) $[C_4H_8Br]^+$. MS (CI): *m/z* (%) = 537 (76) $[M+H]^+$, 425 (100) $[M - C_8H_{15}]^+$, 135 (46) $[C_4H_8Br]^+$. IR (ATR): $\tilde{\nu}$ = 2957, 2927, 2872 (aliph. C-H), 1715 (C=O), 1594 (arom.), 1445 (aliph. C-C), 1226, 1160 (C-O-C), 560 (C-Br) cm^{-1}. $C_{23}H_{36}Br_2O_4$ (536.34) calcd. C 51.51, H 6.77; $C_{23}H_{36}Br_2O_4 \cdot 0.3\ C_6H_{12}$ (561.59) calcd. C 53.04, H 7.11; found C 53.17, H 7.03.

3,5-Bis[4-(2,4,6-trioxo-1,3,5-triazinan-1-yl)-butoxy]-benzoic acid 2-ethyl-hexyl ester (25): Isocyanuric acid (1.93 g, 14.9 mmol) and **24** (2.00 g, 3.73 mmol) were dissolved in anhydrous DMF (25 mL). 1,8-Diazabicyclo[5.4.0]undec-7-en (1.14 g, 1.12 mL, 7.46 mmol) was added dropwise and the mixture was stirred for 24 h at 70 °C. Water (100 mL) and *tert*-butyl methyl ether (100 mL) were added and the organic layer was separated. Excess of isocyanuric acid was removed by filtration. The solvent was removed and the crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 10:1, R_f = 0.24) yielding 480 mg (21 %) of **25**. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.39 (br. s, 4 H, N*H*), 7.01 (d, ^4J = 2.2 Hz, 2 H, Ar-2,6-*H*), 6.76 (t, ^4J = 2.2 Hz, 1 H, Ar-4-*H*), 4.18 (d, ^3J = 5.7 Hz, 2 H, OCH_2CH), 4.00 (t, ^3J = 6.0 Hz, 4 H, Ar-OCH_2), 3.69 (t, ^3J = 6.9 Hz, 4 H, CH_2N), 1.80-1.60 (m, 9 H, CH_2CH_2CH_2CH$_2$, CHCH$_2$), 1.38 (quin, ^3J = 7.4 Hz, 2 H, CHCH_2CH$_3$), 1.35-1.23 (m, 6 H, CHCH_2CH_2CH_2), 0.90 (t, ^3J = 7.4 Hz, 3 H, CHCH$_2$CH_3), 0.87 (t, ^3J = 7.0 Hz, 6 H, CH$_2$CH$_2$CH_3) ppm.^{13}C NMR (150 MHz, DMSO-d_6): δ = 165.4 (s, COO), 159.8 (s, Ar-3,5-*C*), 149.9 (s, CH$_2$N*C*O), 148.67 (s, NH*C*ONH) 131.7 (s, Ar-1-*C*), 107.2 (d, Ar-2,6-*C*), 105.9 (d, Ar-4-*C*), 67.6 (t, ArO*C*H$_2$), 66.9 (t, COO*C*H$_2$), 40.1 (t, *C*H$_2$N), 38.2 (d, CH$_2$*C*H), 30.0 (t, *C*H$_2$CH$_2$CH$_2$CH$_3$), 24.1 (t, NCH$_2$*C*H$_2$), 28.4 (t, CH$_2$*C*H$_2$CH$_2$CH$_3$), 25.9 (Ar-OCH$_2$*C*H$_2$), 23.5 (t, CH*C*H$_2$CH$_3$), 22.4 (t, CH$_2$CH$_2$*C*H$_2$CH$_3$), 13.8 (q, CH$_2$CH$_2$CH$_2$*C*H$_3$), 10.1 (q, CHCH$_2$*C*H$_3$). MS (MALDI, Cl-CCA): *m/z* = 633.13 $[M+H]^+$, 655.26 $[M+Na]^+$, 671.28 $[M+K]^+$. MS (ESI): *m/z* = 655.27 $[M+Na]^+$. IR (ATR): $\tilde{\nu}$ = 3208, 3075 (NH, OH), 2960, 2930, 2872 (aliph. C-H), 1675 (CONH), 1595 (arom.), 1453 (aliph. C-C), 1226, 1165 (C-O-C) cm^{-1}. $C_{29}H_{40}N_6O_{10}$ (632.664) calcd. C 55.05, H 6.37, N 13.28; found C 55.03, H 6.49, N 13.32.

***N*-(4-Methoxycarbonylpyrid-2-yl)-*N'*-(pyrid-2-yl) urea 17:** To a suspension of 16 (835 mg, 5.48 mmol), pyridin-2-carboxylic acid (668 mg, 2.56 mmol) and anhydrous triethylamine (751 µL, 5.39 mmol) in anhydrous benzene (24 ml), diphenylphosphoryl azide (1.17 mL, 5.43 mmol) was added. The mixture was stirred under reflux for 24 h and afterwards the residue **17** was filtered and washed with chloroform (935 mg, 62 %); m.p. 205-208 °C. ^{1}H NMR (300 MHz, DMSO): δ = 10.9 (br. s, 1 H, N*H*), 10.2 (br. s, 1 H, N*H*), 8.49 (d, ^3J= 5.1 Hz, 1 H, Py^1-6-*H*), 8.38 (br. s, 1 H, Py^1-3-*H*), 8.31 (ddd, ^3J= 5.0 Hz, ^4J= 1.9 Hz, ^5J= 0.9 Hz, 1 H, Py^2-6-*H*), 7.79 (ddd, ^3J= 8.4 Hz, ^3J= 7.2 Hz, ^4J= 1.9 Hz, 1 H, Py^2-4-*H*), 7.66 (br. s, 1 H, Py^2-3-*H*), 7.49 (dd, ^3J= 5.1 Hz, ^4J= 1.4 Hz, 1 H, Py^1-5-*H*), 7.07 (ddd, ^3J= 7.2 Hz, ^3J= 5.0 Hz, ^4J= 0.9 Hz, 1 H, Py^2-5-*H*), 3.91 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 165.5 (s, *C*OCH$_3$), 153.8 (s, Py^1-2-*C*), 152.8 (s, Py^2-2-*C*), 152.3 (s, NH*C*ONH), 149.3 (d, Py^1-6-*C*), 147.7 (d, Py^2-*C*-6), 139.4 (s, Py^1-4-*C*), 139.1 (d, Py^2-4-*C*), 118.7 (d, Py^2-5-*C*), 117.5 (d, Py^1-5-*C*), 112.9 (d, Py^3-3-*C*), 112.1 (d, Py^1-3-*C*), 53.3 (q, *C*H$_3$). IR (KBr): $\tilde{\nu}$ = 3500, 3300-3021 (N-H, arom. C-H), 1734, 1707 (C=O), 1576, 1560, 1522 (arom.) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 272 (11) $[M]^+$, 241 (4) $[M - OCH_3]^+$, 179 (31) $[M - HN'Py]^+$, 152 (100) $[M - OCNPy]^+$, 121 (51) $[M - OCNPy-OCH_3]^+$. MS (CI, isobutane): *m/z* (%) = 273 (100) $[M+H]^+$, 179 (62) $[M - HN'Py]^+$, 153 (80) $[M - OCNPy]^+$, 121 (73) $[M - OCNPy-OCH_3]^+$. HRMS for $C_{13}H_{12}N_4O_3$ calcd. 272.09094, found 272.09070 (Δ 0.9 ppm); $C_{12}{}^{13}CH_{12}N_4O_3$ calcd. 273.09430, found 273.09400 (Δ 1.1 ppm).

***N*-{4-[*N*-(8-Amino-3,6-dioxaoctyl)-aminocarbonyl]-pyrid-2-yl}-*N'*-(pyrid-2-yl) urea 18:** A suspension of **17** (1.02 g, 3.77 mmol) and 1,8-diamino-3,6-dioxaoctane (11.7 ml, 80.0 mmol) in anhydrous THF was heated under reflux until a transparent liquid formed. Afterwards, the solution was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, the residue was dissolved in chloroform (100 ml) and washed twice with water (100 ml). After extraction of the water layer with chloroform, the combined organic layer was dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue was stirred with diethyl ether (10 ml). After filtration,

18 was obtained as a yellow solid (1.24 g, 85 %). ^{1}H NMR (500 MHz, DMSO-D$_6$): δ = 10.34 (br. s, 2 H, N*H*CON*H*), 8.80 (t, ^3J = 5.7 Hz, 1 H, CON*H*), 8.40 (dd, ^3J = 5.2 Hz, ^5J = 0.7 Hz, 1 H, Py^1-6-*H*), 8.30 (ddd, ^3J = 5.0 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, 1 H, Py^2-6-*H*), 8.16 (br. s, 1 H, Py^1-3-*H*), 7.79 (ddd, ^3J = 8.4 Hz, ^3J = 7.2 Hz, ^4J = 1.9 Hz, 1 H, Py^2-4-*H*), 7.67 (br. d, ^3J = 8.4 Hz, 1 H Py^2-3-*H*), 7.39 (dd, ^3J = 5.2 Hz, ^4J = 1.5 Hz, 1 H, Py^1-5-*H*), 7.06 (ddd, ^3J = 7.2 Hz, ^3J = 5.0 Hz, ^4J = 1.0 Hz, 1 H, Py^2-5-*H*), 3.50-3.47 (m, 8 H, C*H*$_2$OC*H*$_2$C*H*$_2$OC*H*$_2$), 3.35 (t, ^3J = 5.8 Hz, 2 H, C*H*$_2$NH$_2$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 168.4 (s, Py-*C*ONH), 154.5 (s, NH*C*ONH$^-$), 154.3 (s, Py-2-*C*), 153.9 (s, Py^2-2-*C*), 149.2 (d, Py-6-*C*), 147.9 (d, Py^2-6-*C*), 145.9 (s, Py-4-*C*), 140.1 (d, Py^2-4-*C*), 119.6 (d, Py^2-5-*C*), 117.1 (d, Py^2-3-*C*), 114.0 (d, Py-5-*C*), 112.2 (d, Py-3-*C*), 71.4 (t, *C*H$_2$CH$_2$NH$_2$), 70.5 (t, CONHCH$_2$*C*H$_2$), 68.1 (t, OC*H*$_2$*C*H$_2$O), 40.9 (t, CH$_2$*C*H$_2$NH$_2$), 40.8 (t, CONH*C*H$_2$CH$_2$) ppm. IR (ATR): $\tilde{\nu}$ = 3436 (N-H), 1691, 1651 (C=O), 1541, 1474, 1417 (arom.) cm^{-1}. MS (ESI): *m/z* = 411 (5) [M+Na]$^+$, 389 (100) [M+H]$^+$. C$_{18}$H$_{24}$N$_6$O$_2$ (388.4) calcd. C 55.66, H 6.23, N 21.64; C$_{18}$H$_{24}$N$_6$O$_2$ · 1 CH$_3$OH · 0.3 CHCl$_3$ calcd. 49.61, H 6.62, N 17.07; found C 49.54, H 6.71, N 17.44.

5-Benzoyloxy-*N*,*N*′-bis(8-{[2-(pyrid-2-yl-aminocarbonylamino)-pyrid-4-yl]-carbonylamino}-3,6-dioxaoctyl)-isophthalic acid diamide 19: Anhydrous triethylamine (50 mL) and **18** (500 mg, 1.28 mmol) were dissolved in anhydrous THF (50 mL). After the dropwise addition of **13** (207 mg, 644 µmol) dissolved in anhydrous THF (6 mL), the mixture was stirred at room temp. for 24 h. The newly formed solid was filtered off and discarded. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, chloroform/methanol 97:3 to remove educt **18**, then 3:1) yielding **19** as a white solid (206 mg, 31 %); m.p. 134 °C. ^{1}H NMR (500 MHz, DMSO): δ= 10.81 (br. s, 2 H, N*H*CONH), 10.35 (br. s, 2 H, NHCON*H*), 8.76 (t, ^3J = 5.5 Hz, 2 H, PyCON*H*), 8.71 (t, ^3J = 5.5 Hz, 2 H, Ar^{1}CON*H*), 8.39 (d, ^3J = 5.2 Hz, 2 H, Py^1-6-*H*), 8.31-8.29 (m, 3 H, Py^2-6-*H*, Ar^1-2-*H*), 8.17-8.15 (m, 4 H, Py^1-3-*H*, Ar^2-2,6-*H*), 7.92 (d, ^4J = 1.4 Hz, 2 H, Ar^1-4,6-*H*), 7.79-7.75 (m, 3 H, Py^2-4-*H*, Ar^2-4-*H*), 7.69-7.65 (br. s, 2 H, Py^2-3-*H*), 7.63 (m$_c$, 2 H, Ar^2-3,5-*H*), 7.38 (dd, ^3J = 5.2 Hz, ^4J = 1.4 Hz, 2 H, Py^1-5-*H*), 7.05 (ddd, ^3J = 7.2 Hz, ^3J = 6.2 Hz, ^4J = 0.9 Hz, 2 H, Py^2-5-*H*), 3.58-3.54 (m, 16 H, C*H*$_2$O), 3.43 (m$_c$, 8 H, CONHC*H*$_2$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ= 165.0 (s, Ar-*C*ONH), 164.8 (s, Py^1-*C*ONH), 164.5 (s, *C*OAr^2), 152.9 (s, Py^1-2-*C*), 152.3 (s, Py^2-2-*C*), 151.7 (s, NH*C*ONH), 150.4 (s, Ar^1-5-*C*), 147.9 (d, Py^1-6-*C*), 147.2 (d, Py^2-6-*C*), 144.0 (d, Py^1-4-*C*), 138.5 (d, Ar^2-4-*C*), 136.0 (s, Ar^1-1,3-*C*), 134.2 (d, Py^2-4-*C*), 129.8 (d, Ar^2-2,6-*C*), 129.0 (d, Ar^2-3,5-*C*), 128.4 (s, Ar^2-1-*C*), 123.9 (d, Ar^1-2-*C*), 123.3 (d, Ar^1-4,6-*C*), 118.1 (d, Py^2-5-*C*), 115.6 (d, Py^1-5-*C*), 112.4 (d, Py^2-3-*C*), 110.5 (d, Py^1-3-*C*), 69.6 (t, *C*H$_2$O), 68.8 (t, Ar^{1}CONH*C*H$_2$), 68.7 (t, PyCONH*C*H$_2$) ppm. IR (ATR): $\tilde{\nu}$ = 3285 (N-H), 3059 (arom. C-H), 1696 (C=O), 1644 (C=O), 1532 (N-H), 1410 (arom.), 1251 (C-O-C) cm^{-1}. MS (ESI): *m/z* =1049 [M+Na]$^+$, 1027 [M+H]$^+$. C$_{51}$H$_{54}$N$_{12}$O$_{12}$ (1027.1) calcd. C 59.64, H 5.30, N 16.37; C$_{51}$H$_{54}$N$_{12}$O$_{12}$ · 0.5 CHCl$_3$ (1086.7) calcd. C 56.92, H 5.05, N 15.47; found C 56.55, H 5.12, N 15.06.

5-Hydroxy-*N*,*N*′-bis(8-{[2-(pyrid-2-yl-aminocarbonylamino)-pyrid-4-yl]-carbonylamino}-3,6-dioxaoctyl)-isophthalic acid diamide 20: To a suspension of **19** (117 mg, 150 µmol) in methanol (1 mL), aqueous sodium hydroxide solution (1 M, 800 µL) was added resulting in a transparent solution. The mixture was stirred at room temp. for 1 h and afterwards neutralized with hydrochloric acid (2 M). Chloroform (5 ml) was added and the aqueous layer extracted with chloroform (5 ml). The combined organic layer was dried with magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, ethanol, R_f = 0.43) yielding **20** as a white solid (96.0 mg, 69 %); m.p. 123 °C. ^{1}H NMR (500 MHz, DMSO-D$_6$): δ= 10.82 (br. s, 2 H, N*H*CONH), 10.36 (br. s, 2 H, NHCON*H*), 9.93 (br. s, 1 H, Ar-O*H*), 8.77 (t, ^3J = 5.5 Hz, 2 H, PyCON*H*), 8.47 (t, ^3J = 5.5 Hz, 2 H, ArCON*H*), 8.40 (d, ^3J = 5.2 Hz, 2 H, Py^1-6-*H*), 8.30 (m$_c$, 2 H, Py^2-6-*H*), 8.16 (br. s, 2 H, Py^1-3-*H*), 7.78 (m$_c$, 2 H, Py^2-4-*H*), 7.73 (br. s, 1 H, Ar-2-*H*), 7.70-7.65 (m, 2 H, Py^2-3-*H*), 7.39 (dd, ^3J = 5.2 Hz, ^4J = 1.3 Hz, 2 H, Py^1-5-*H*), 7.35 (d, ^4J = 1.3 Hz, 2 H, Ar-4,6-*H*), 7.06 (m$_c$, 2 H, Py^2-5-*H*), 3.59-3.51 (m, 16 H, C*H*$_2$O), 3.47-3.38 (m, 8 H, CONHC*H*$_2$) ppm. ^{13}C NMR (125 MHz, DMSO-D$_6$): δ = 166.0 (s, Ar*C*ONH), 164.9 (Py*C*ONH, Ar-5-*C*), 152.9 (s, Py^1-2-*C*), 152.3 (s, Py^2-2-*C*), 151.7 (NH*C*ONH), 148.0 (d, Py^1-6-*C*), 147.2 (d, Py^2-6-*C*), 144.0 (d, Py^1-4-*C*), 138.5 (s, Ar-1,3-*C*), 135.9 (d, Py^2-4-*C*), 118.1 (d, Py^2-5-*C*), 116.7 (Ar-2,4,6-*C*), 115.5 (d, Py^1-5-*C*), 112.3 (d, Py^2-3-*C*), 110.5 (d, Py^1-3-*C*), 69.5 (t, *C*H$_2$O), 68.8 (s, ArCONHCH$_2$), 68.6 (s, PyCONH*C*H$_2$) ppm. IR (ATR): $\tilde{\nu}$ = 3262 (N-H), 3059 (arom. C-H), 1690 (C=O), 1644 (C=O), 1531 (N-H), 1414 (arom.), 1302 (C-O-C) cm^{-1}. MS (ESI): *m/z* = 945 [M+Na]$^+$, 923 [M+H]$^+$. C$_{44}$H$_{50}$N$_{12}$O$_{11}$ (922.37) calcd. C 57.26, H 5.46, N 18.21; C$_{44}$H$_{50}$N$_{12}$O$_{11}$ · H$_2$O (940.37) calcd. C 56.16, H 5.57, N 17.86; found 56.52, H 5.72, N 17.36.

5-{3,5-Bis[(6-pentanoylamino-pyrid-2-yl-aminocarbonyl)-phenoxy]butoxy}-*N*,*N*′-bis(8-{[2-(pyrid-2-ylaminocarbonylamino)-pyrid-4-yl]-carbonylamino}-3,6-dioxaoctyl)-isophthalic acid diamide 21: To a solution of **20** (340 mg, 364 µmol) and **11** (580 mg, 865 µmol) in anhydrous DMF (15 mL), solid potassium carbonate (119 mg, 2.18 mmol) was added and the mixture was stirred at 70 °C for 48 h. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in chloroform. The crude product was purified by column chromatography (silica gel, chloroform/methanol, 10:1, R_f = 0.21) yielding **21** as a white solid (220 mg, 40 %); m.p. 126 °C. ^{1}H NMR (500 MHz, DMSO-D$_6$): δ= 10.8 (br. s, 2 H, N*H*CONH), 10.5 (br. s, 2 H, Ar^{1}CON*H*), 10.4 (br. s, 2 H, N*H*CONH), 10.1 (br. s, 2 H, Py^{1}N*H*COCH$_2$), 8.81 (t, ^3J = 5.6 Hz, 2 H, PyCON*H*), 8.64 (t, ^3J = 5.6 Hz, 2 H, Ar^{2}CON*H*), 8.44 (d, ^3J = 5.3 Hz, 2 H, Py^2-6-*H*), 8.35 (d, ^3J = 4.9 Hz, 2 H, Py^3-6-*H*), 8.21 (br. s, 2 H, Py^2-3-*H*), 8.17 (br. s, 1 H, Ar^1-2-*H*), 7.97 (br. s, 1 H, Ar^2-2-*H*), 7.90-7.87 (m, 4 H, Py^1-5-*H*, Py^1-3-*H*), 7.85-7.80 (m, 4 H, Py^1-4-*H*, Py^3-4-*H*), 7.77 (d, ^4J = 1.2 Hz, 2 H, Ar^1-4,6-*H*), 7.72 (br. s, 2 H, Py^3-3-*H*), 7.59 (d, ^4J = 1.1 Hz, 2 H, Ar^2-4,6-*H*), 7.43 (dd, ^3J = 5.2 Hz, ^4J = 1.4 Hz, 2 H, Py^2-5-*H*), 7.10 (m$_c$, 2 H, Py^3-5-*H*), 4.27 (br. s, 2 H, Ar^{1}OC*H*$_2$), 4.21 (br. s, 2 H, Ar^{2}OC*H*$_2$), 3.62-3.57 (m, 16 H, CONHCH$_2$C*H*$_2$, CH$_2$OC*H*$_2$C*H*$_2$OCH$_2$), 3.47 (q, ^3J = 5.7 Hz, 8 H, Ar^{2}CONHC*H*$_2$ Py^{2}CONHC*H*$_2$), 2.46 (t, ^3J = 7.4 Hz, 4 H, NHCOC*H*$_2$), 2.01 (br. s, 4 H, Ar^{1}OCH$_2$C*H*$_2$C*H*$_2$CH$_2$OAr^2), 1.62 (quint, ^3J = 7.4 Hz, 4 H, NHCOCH$_2$C*H*$_2$), 1.36 (sext, ^3J = 7.3 Hz, 4 H, C*H*$_2$CH$_3$), 0.94 (t, ^3J = 7.3 Hz, 6 H, C*H*$_3$) ppm. ^{13}C NMR (125 MHz, DMSO-D$_6$): δ= 172.20 (s, Py^{1}NH*C*OCH$_2$), 165.61 (Py^2*C*ONH, Ar^2*C*ONH), 164.91 (s, Ar^1*C*ONH), 158.43 (s, Ar^1-5-*C*), 153.00 (s, Ar^2-5-*C*), 152.37 (s, Py^3-2-*C*, Py^2-2-*C*), 151.79 (s, NH*C*ONH), 150.57 (s, Py^1-6-*C*), 150.06 (s, Py^1-2-*C*), 148.00 (d, Py^2-6-*C*), 147.22 (d, Py^3-6-*C*), 144.00 (s, Py^2-4-*C*), 139.99 (d, Py^1-4-*C*), 138.55 (d, Py^3-4-*C*), 135.88 (s, Ar^2-1,3-*C*), 135.57 (s, Ar^1-1,3-*C*), 119.96 (d, Ar^1-2-*C*), 118.57 (d, Ar^2-2-*C*), 118.18 (d, Py^3-5-*C*), 117.18 (d, Ar^1-4,6-*C*), 115.70 (d, Py^2-5-*C*), 115.55 (d, Ar^2-4,6-*C*), 112.35 (d, Py^3-3-*C*), 110.53 (d, Py^1-3-*C*, Py^2-3-*C*), 109.95 (d, Py^1-5-*C*), 69.55 (CONHCH$_2$C*H*$_2$, CH$_2$OCH$_2$C*H*$_2$OCH$_2$), 68.84 (t, Ar^{2}CONH*C*H$_2$), 68.64 (t, Py^{2}CONH*C*H$_2$), 67.78 (t, Ar^{1}O*C*H$_2$), 67.58 (t, Ar^{2}O*C*H$_2$), 35.80 (t, NHCO*C*H$_2$), 27.12 (t, NHCOCH$_2$*C*H$_2$), 25.29 (Ar^{1}OCH$_2$CH$_2$*C*H$_2$CH$_2$OAr^2), 21.74 (t, *C*H$_2$CH$_3$), 13.71 (q, *C*H$_3$) ppm. MS (MALDI, Cl-CCA): *m/z* = 1547 [M+K]$^+$, 1531 [M+Na]$^+$, 1509 [M+H]$^+$. MS (ESI): *m/z* = 1509.68 [M+H]$^+$, 755.34 [M+2H]$^{2+}$, 766.35 [M+H+Na]$^{2+}$, 774.34 [M+H+K]$^{2+}$. IR (ATR): $\tilde{\nu}$ = 3263 (N-H), 2932 (aliph. C-H), 1652 (C=O), 1519 (N-H), 1444 (arom.), 1300 (C-O-C) cm^{-1}. C$_{76}$H$_{88}$N$_{18}$O$_{16}$ (1509.623) calcd. C 60.47, H 5.88, N 16.70; C$_{76}$H$_{88}$N$_{18}$O$_{16}$ · CHCl$_3$ (1629.001) calcd. 56.77, H 5.51, N 15.48; found C 56.90, H 5.56, N 15.02.

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Entry for the Table of Contents

Supramolecular Dendrimer

*Jens Eckelmann, Christiane Dethlefs, Stefan Brammer, Ahmet Doğan, Andreas Uphoff, and Ulrich Lüning**
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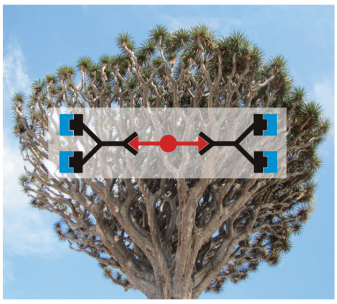
A Second Generation Supramolecular Dendrimer with a Defined Structure due to Orthogonal Binding



A second generation supramolecular dendrimer has been prepared by orthogonal multiple hydrogen bonding. A bis-isocyanuric acid binds to two branching units which contain a Hamilton receptor. Each branching unit binds two cap molecules by a two fold heterodimer formation via quadruple hydrogen bonds. The formation of the 1:2:4 supramolecular dendrimer was investigated by diffusion NMR.

Supplementary information for:

A Second Generation Supramolecular Dendrimer with a Defined Structure due to Orthogonal Binding

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Syntheses of 5-(4-bromobutoxy)-isophthalic acid dimethyl ester (7):

To a solution of 5-hydroxyisophthalic acid dimethyl ester (**6**, 1.99 g, 9.45 mmol), 1,4-dibromobutane (20.4 g, 94.5 mmol), and *n*Bu_4NBr (33 mg, 0.10 mmol) in anhydrous THF (120 mL) was added sodium hydride (60% dispersion in paraffin oil, 377 mg, 9.45 mmol). The heterogeneous mixture was heated to 70 °C for 4 h. TLC control (cyclohexane/ethyl acetate, 2:1; **7**: R_f = 0.45, **6**: R_f = 0.27). The reaction was cooled to room temp. and quenched with sat. aq. NH_4Cl (2 mL). The solvents were removed under reduced pressure and the residue was dissolved in dichloromethane (50 mL), washed with water (50 mL) and brine (50 mL). The solution was dried with magnesium sulfate and all solvents incl. excess of 1,4-dibromobutane were removed under reduced pressure. The residue was extracted three times with cyclohexane (50 ml), **6** was removed by filtration, and pure **7** was obtained as a white solid (2.80 g, 86 %) after the solvent was removed under reduced pressure. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.27 (t, ^4J=1.5 Hz, 1 H, Ar-2-*H*), 7.73 (d, ^4J = 1.5 Hz, 2 H, Ar-4,6-*H*), 4.09 (t, ^3J = 5.9 Hz, 2 H, OCH_2), 3.93 (s, 6 H, C*H*$_3$), 3.50 (t, ^3J = 6.4 Hz, 2 H, C*H*$_2$Br), 2.1-1.9 (m, 4 H, C*H*$_2$) ppm.

Synthesis of 5-(4-bromobutoxy)-isophthalic acid (8):

To a mixture of THF (24 mL), water (8 mL) and methanol (8 mL) were added **7** (2.15 g, 6.23 mmol) and lithium hydroxide hydrate (525 mg, 12.5 mmol). The solution was stirred for 15 h at room temp. THF and methanol were removed under reduced pressure and the solution was acidified with 2 M HCl to p*H* = 1. The product was filtered off, washed with water (50 mL) and cyclohexane (50 mL) to remove remains of **7**. The solid was dried and **8** was obtained as a white powder (1.70 g, 86 %). ^{1}H NMR (500 MHz, DMSO): δ= 13.26 (br. s, 2 H, COO*H*), 8.06 (s, 1 H, Ar-2-*H*), 7.64 (s, 2 H, Ar-4,6-*H*), 4.12 (t, ^3J = 6.7 Hz, 2 H, OC*H*$_2$), 3.61 (t, ^3J = 6.7 Hz, 2 H, C*H*$_2$Br), 1.99 (quin., ^3J = 6.7 Hz, 2 H, OCH_2CH_2) 1.86 (quin, ^3J = 6.7 Hz, 2 H, $BrCH_2CH_2$) ppm. ^{13}C NMR (125 MHz, DMSO): δ= 166.9 (s, *C*OOH), 159.1 (s, Ar-5-*C*), 133.1 (s, Ar-1,3-*C*), 122.7 (d, Ar-2-*C*), 119.5 (d, Ar-4,6-*C*), 67.7 (t, O*C*H$_2$), 35.3 (t, *C*H$_2$Br), 29.4 (t, OCH_2CH_2), 27.7 (t, $BrCH_2CH_2$) ppm. MS (EI, 70 eV): *m/z (%)* = 316 (7) $[M]^{+\cdot}$, 182 (59) $[M - C_4H_8Br + H]^{+\cdot}$, 135 (100) $[C_4H_8Br]^+$. MS (CI, isobutane): *m/z* = 317 (100) $[M+H]^+$, 135 (37) $[C_4H_8Br]^+$, 237 (23) $[M-Br]^+$. IR (ATR): $\tilde{\nu}$ = 3066 (arom. C-H), 2963, 2876 (aliph. C-H) 2560, 2558 (COOH), 1683 (C=O), 1595 (arom.), 1462 (aliph. C-H), 1269 (aryl-OR), 1046 (C-Br) cm^{-1}. $C_{12}H_{13}BrO_5$ (317.13) calcd. C 45.45, H 4.13; $C_{12}H_{13}BrO_5 \cdot 0.2\ C_6H_{12}$ (332.76) calcd. C 47.65, H 4.30; found C 47.78, H 4.39.

Synthesis of 2-aminopyridine-4-carboxylic acid methyl ester (16):

To a suspension of 2-aminopyridine-4-carboxylic acid (**15**, 2.50 g, 18.1 mmol) in methanol (100 mL), conc. sulfuric acid (10 mL) was added. The reaction was heated for 72 h at 80 °C. The solution was cooled down to room temp., diluted with water (60 mL) and solid sodium bicarbonate was added carefully until p*H* = 7-8. The mixture was extracted with ethyl acetate (3 x 60 mL) and the combined organic layers were dried with magnesium sulfate, filtered, and the solvents were removed under reduced pressure to obtain **16** as a yellow to slightly brown solid (2.35 g, 86 %); m.p. 146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (dd, 1 H, ^{3}J = 5.3 Hz, ^{5}J = 0.9 Hz, Py-6-*H*), 7.16 (dd, 1 H, ^{3}J = 5.3 Hz, ^{4}J = 1.4 Hz, Py-5-*H*), 7.08 (dd, 1 H, ^{4}J = 1.4 Hz, ^{5}J =0.9 Hz, Py-3-*H*), 4.68 (br s, 2 H, NH_2), 3.92 (s, 3 H, COOCH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3441, 3299 (N-H), 3177 (arom. C-H), 1725 (C=O), 1628 (N-H), 1551, 1491, 1449 (arom.) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 152 (100) $[M]^{+\cdot}$, 121 (33) $[M -OCH_3]^{+}$, 94 (39) $[M -COOCH_3]^{+\cdot}$.MS (CI, isobutane): *m/z* (%) = 153 (100) $[M+H]^{+}$.

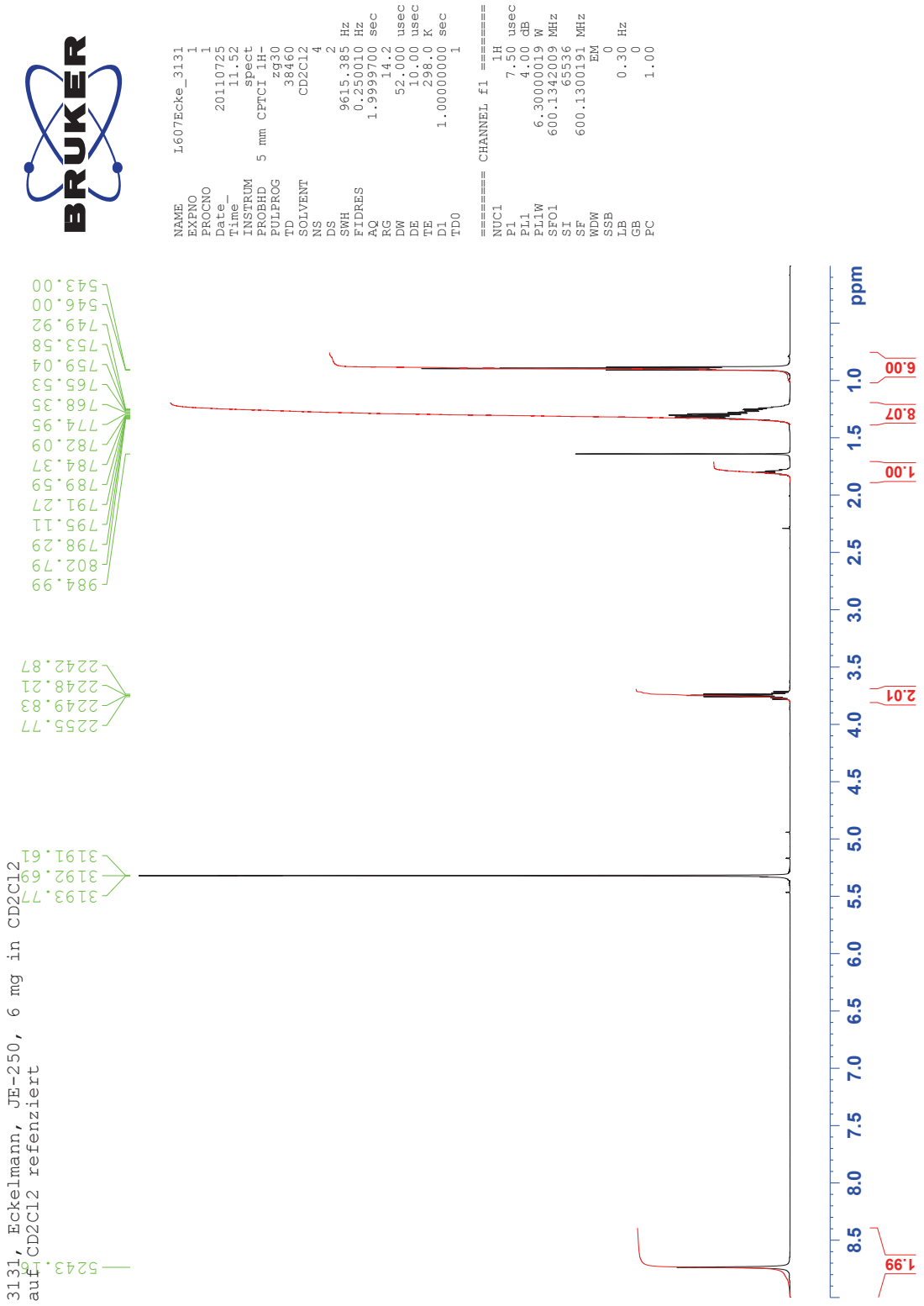


Figure 1: ^{1}H NMR spectrum of **3**.

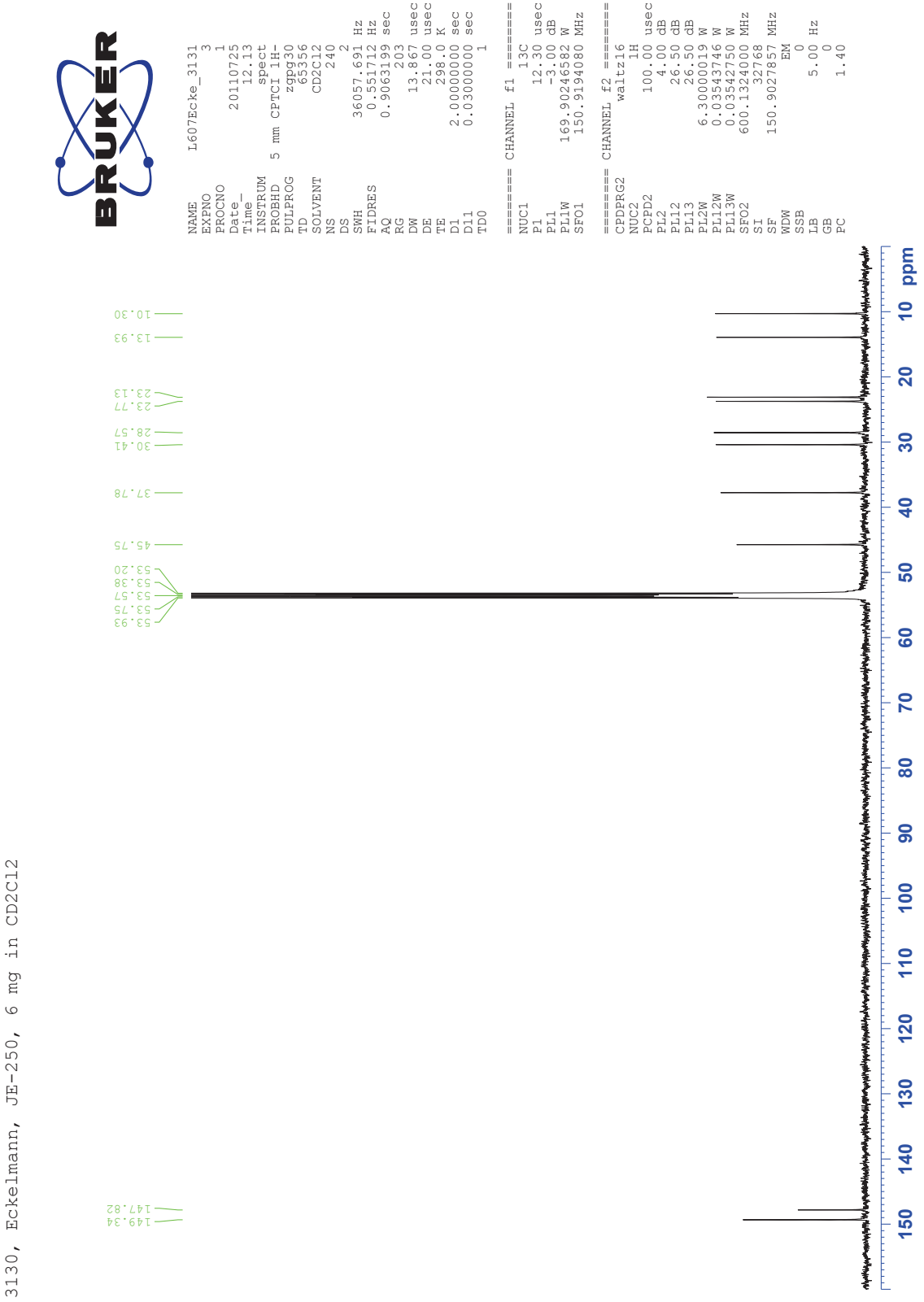


Figure 2: ^{13}C NMR spectrum of **3**

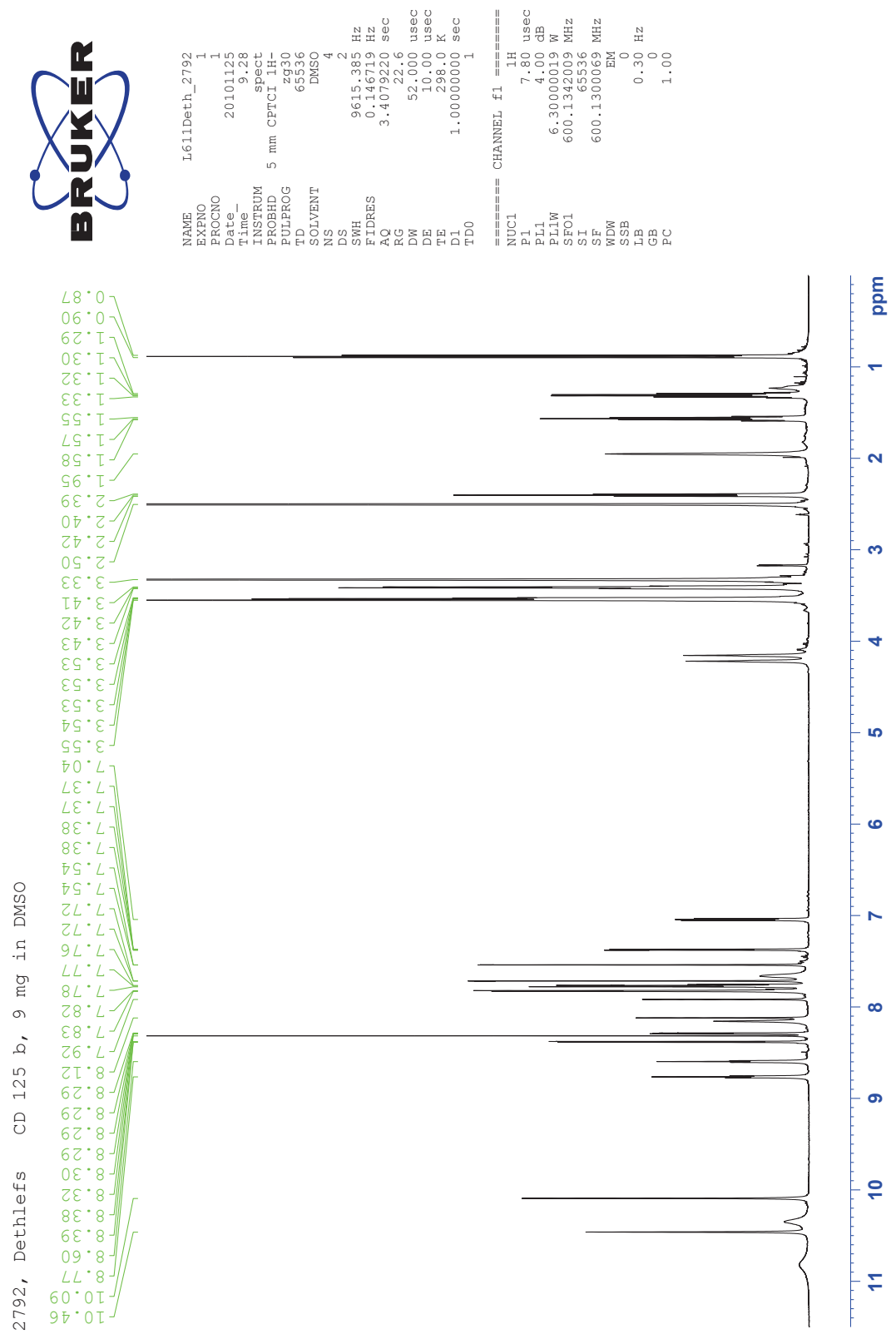


Figure 3: ^{1}H NMR spectrum of **21**.

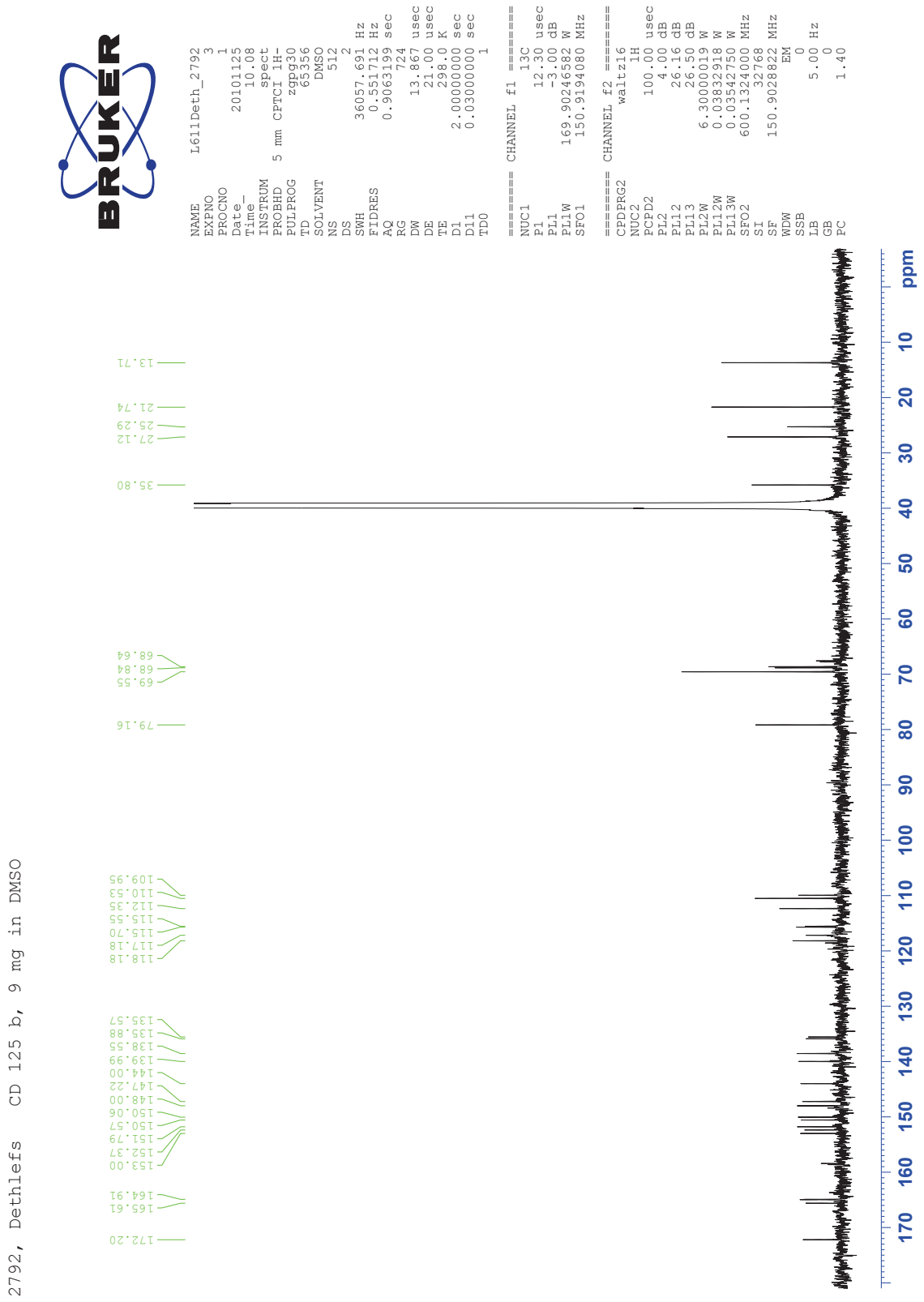


Figure 4: ^{13}C NMR spectrum of **21**.

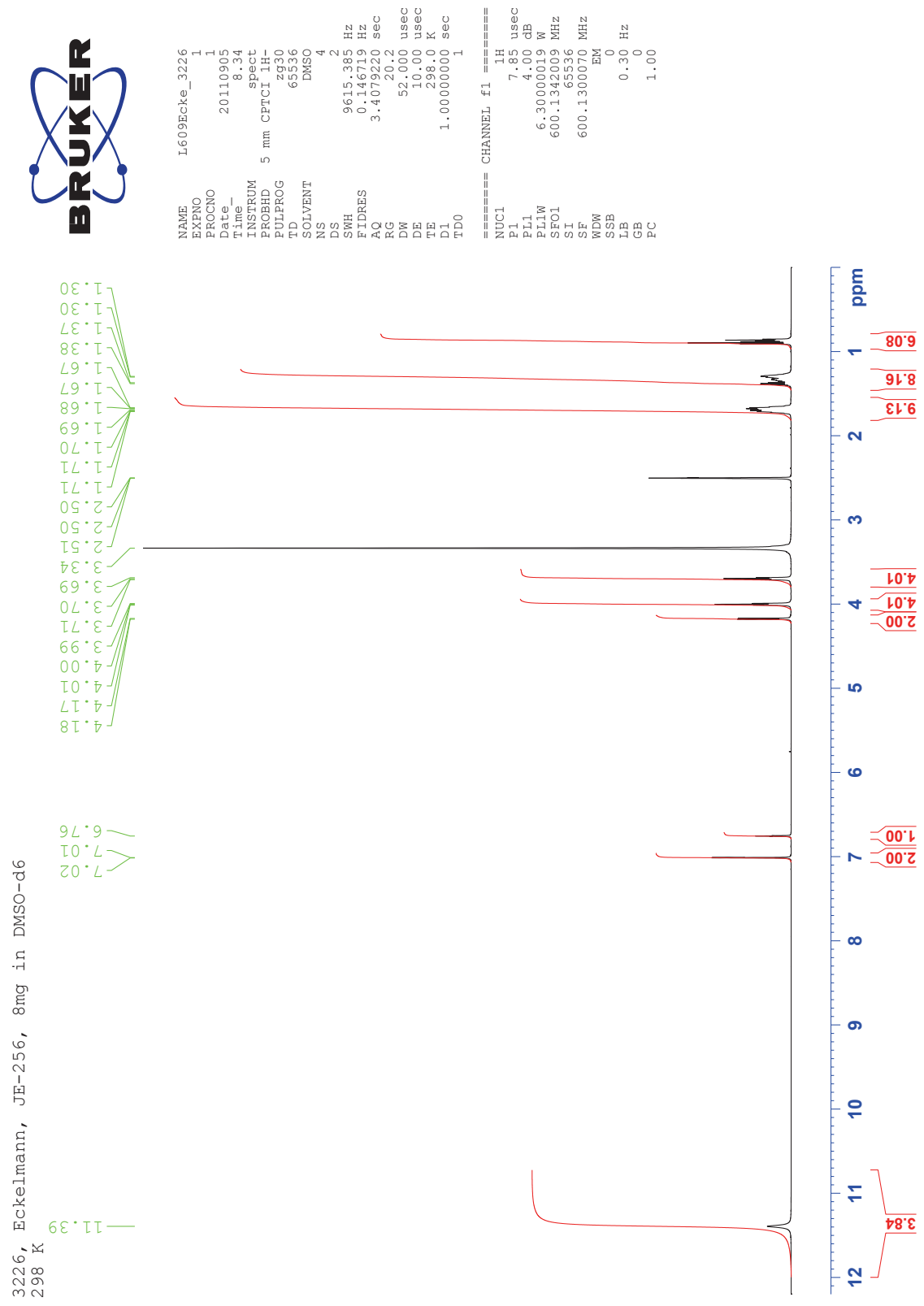


Figure 5: ^{1}H NMR spectrum of **25**.

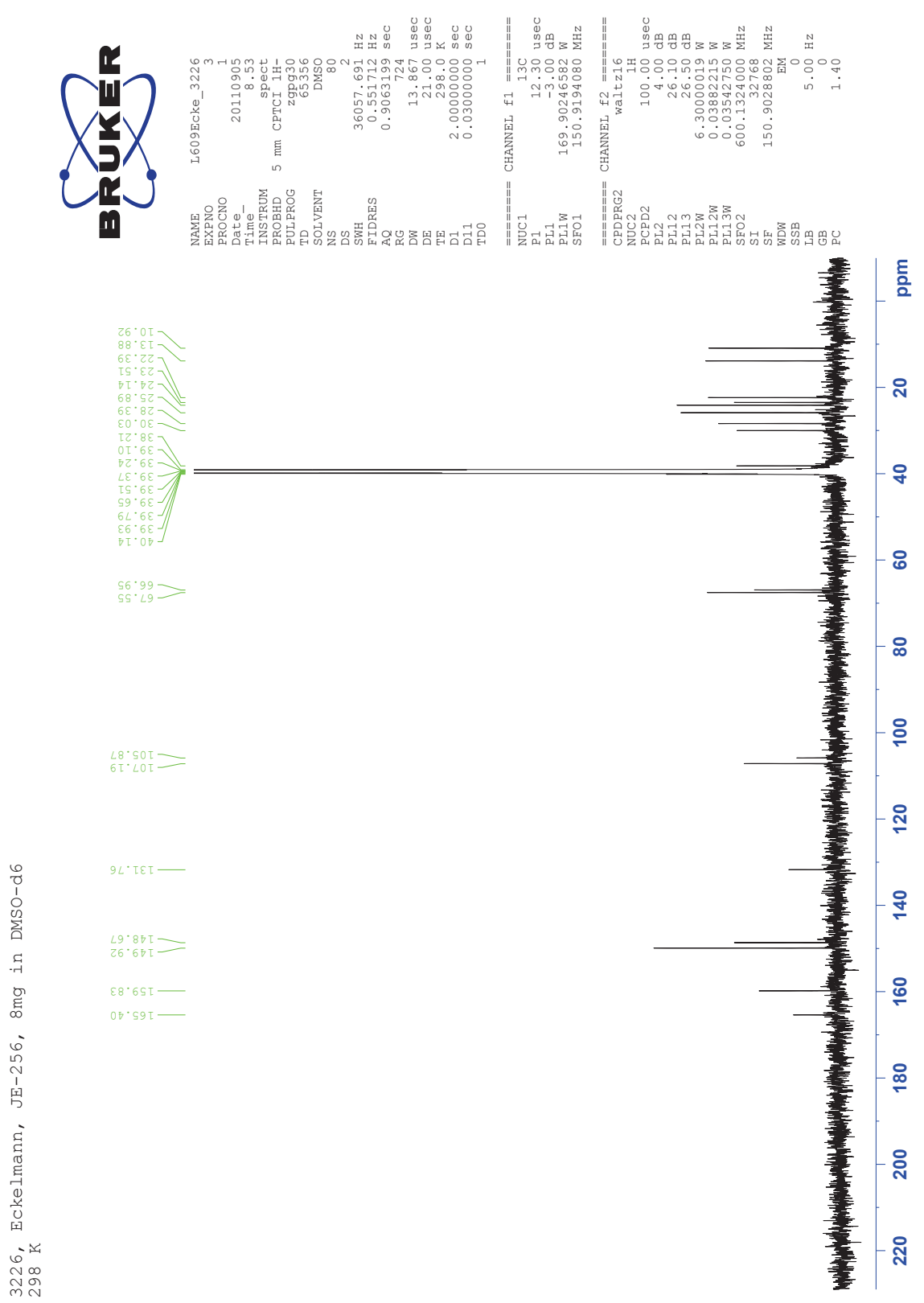


Figure 6: ^{13}C NMR spectrum of **25**.

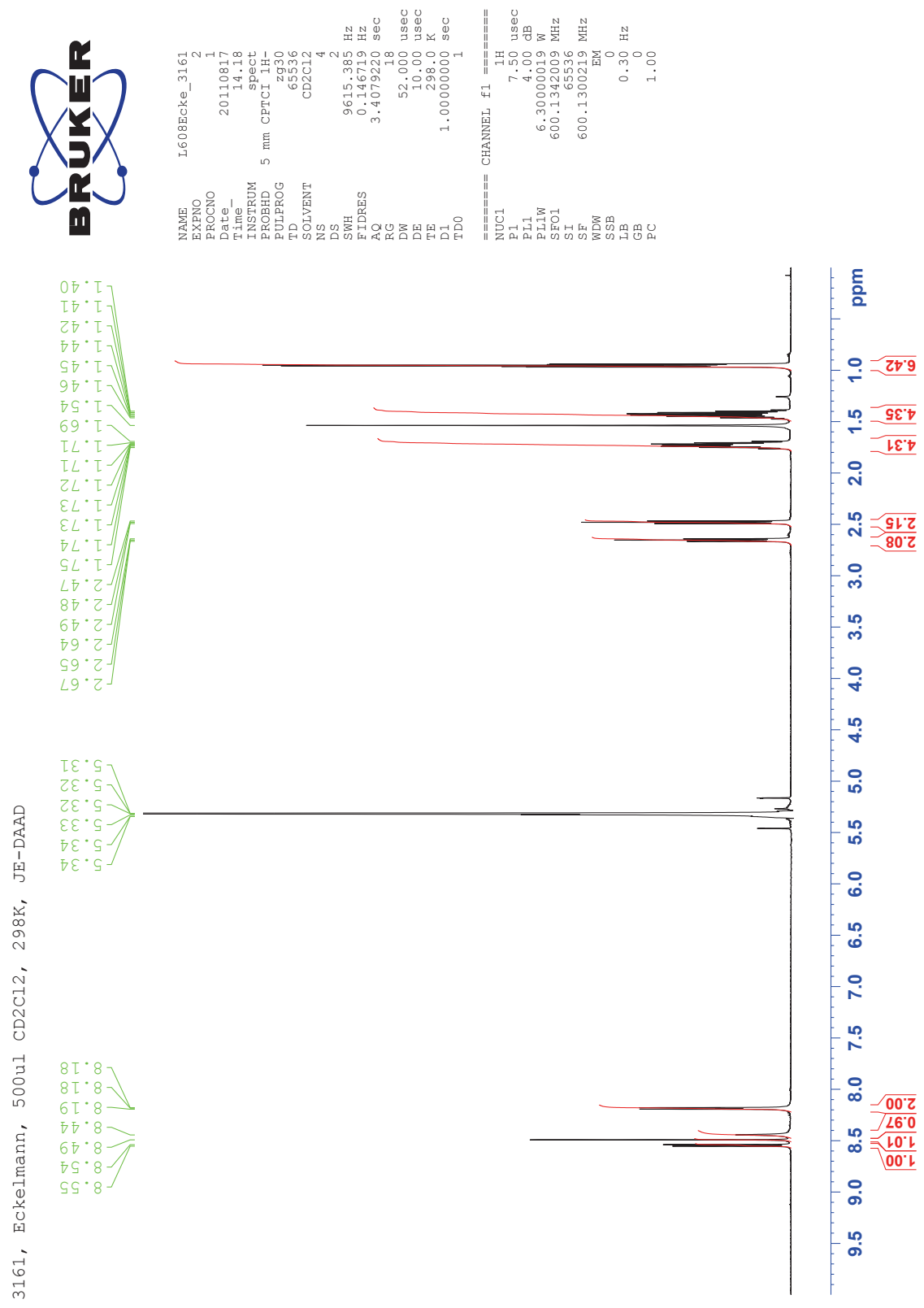


Figure 7: ^{1}H NMR spectrum of **4**.

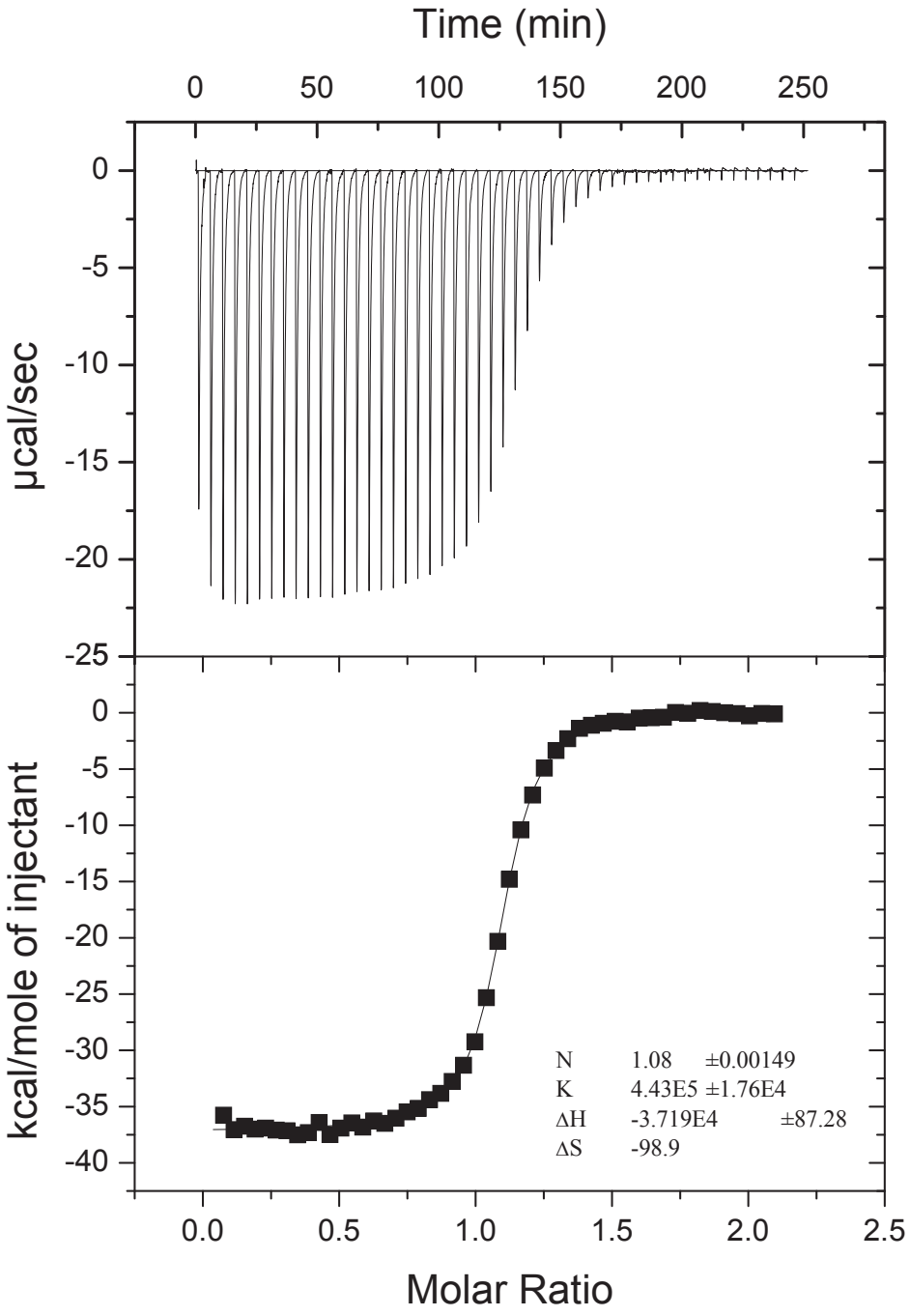


Figure 8: ITC experiment: **3** and Hamilton receptor **1a** (298 K, $CHCl_3$).

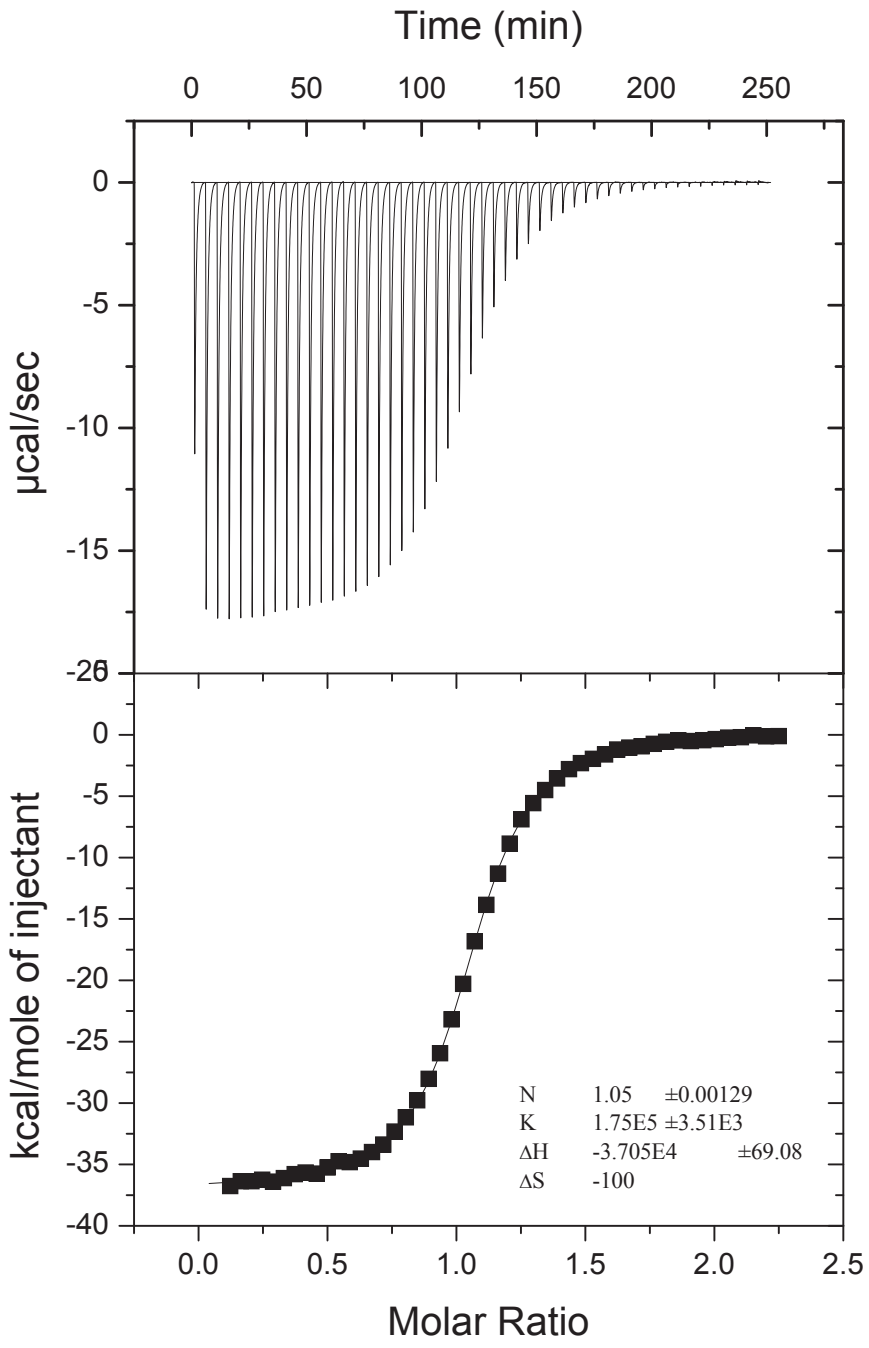


Figure 9: ITC experiment: **3** and Hamilton receptor **1a** (298 K, CH_2Cl_2).

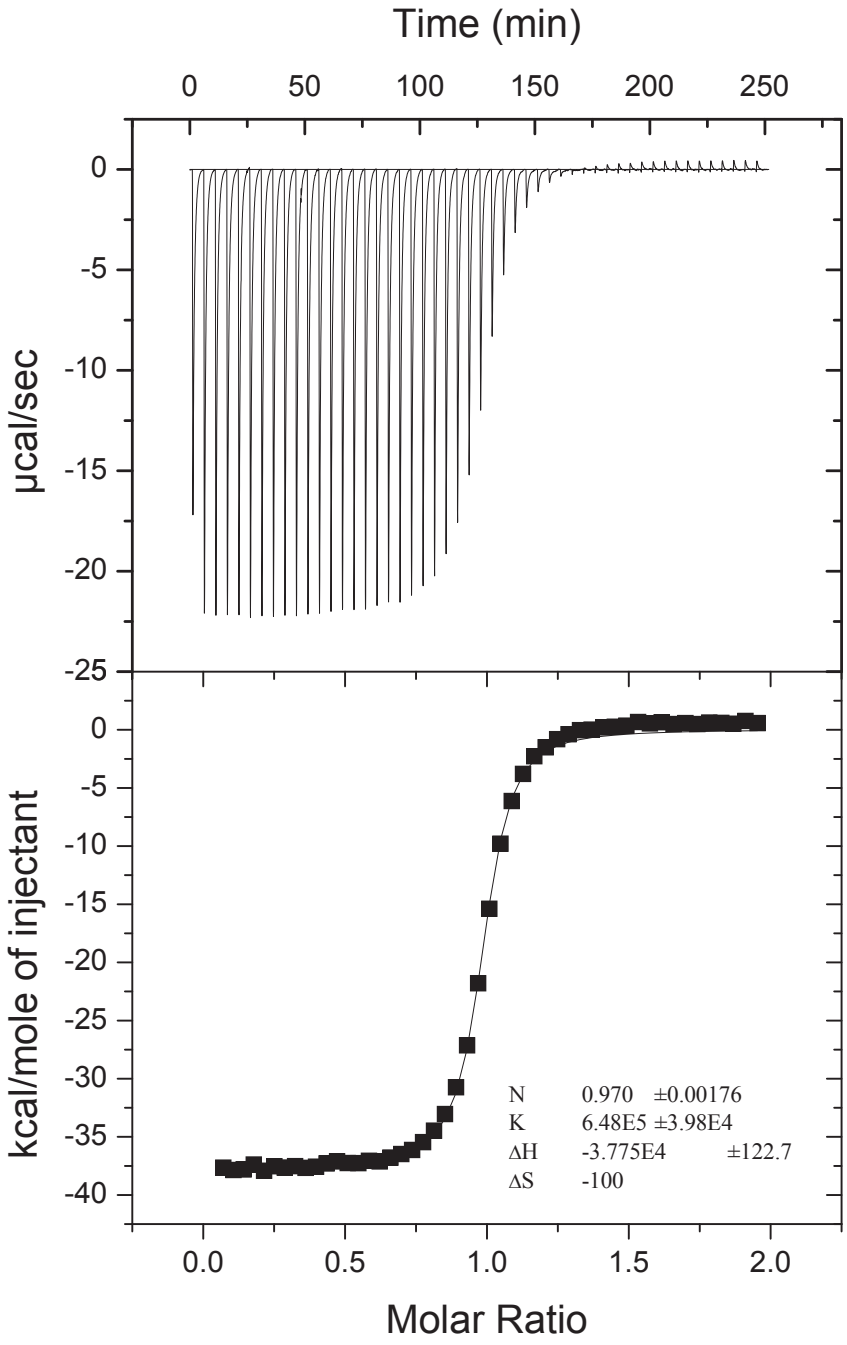


Figure 10: ITC experiment: **3** and Hamilton receptor **1b** (298 K, $CHCl_3$).

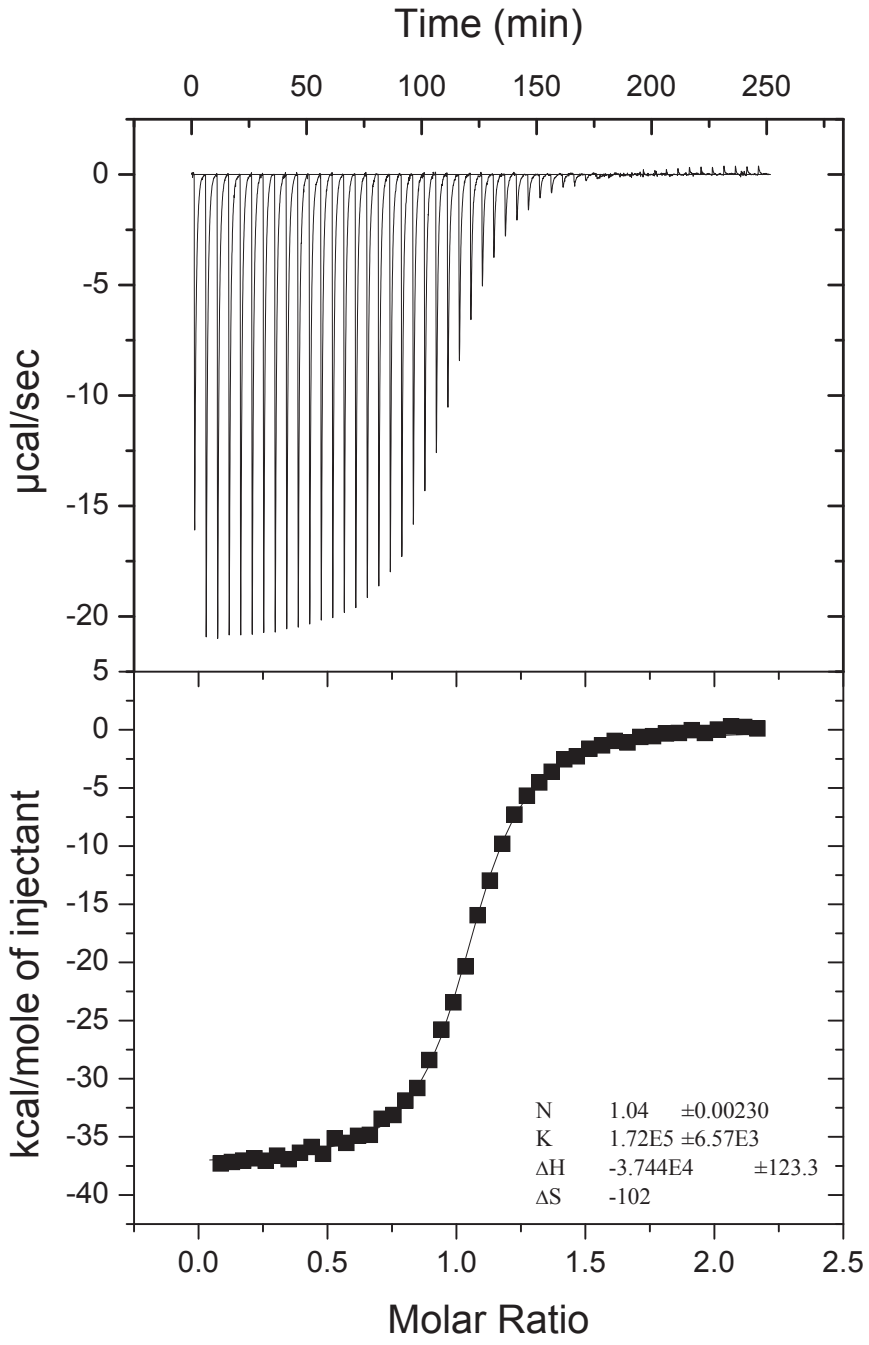


Figure 11: ITC experiment: **3** and Hamilton receptor **1c** (298 K, $CHCl_3$).

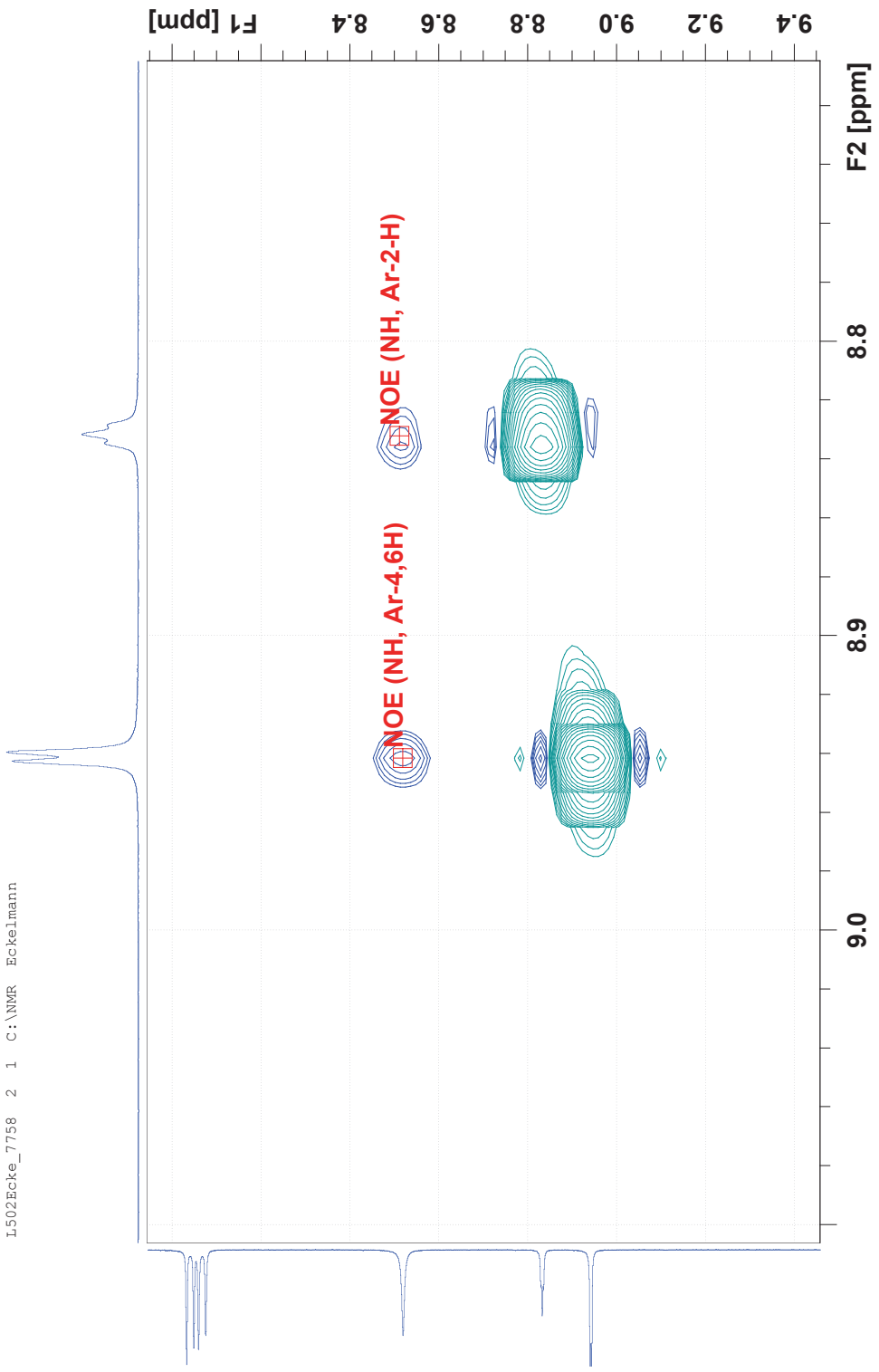


Figure 12: 2D ^{1}H,^{1}H NOESY experiment on Hamilton receptor **1b**. The rotation along the amide–aryl bond allows different conformers. Without a guest there is no preferred conformation and two NOE signals for the NH protons close to the isocyanuric acid appears.

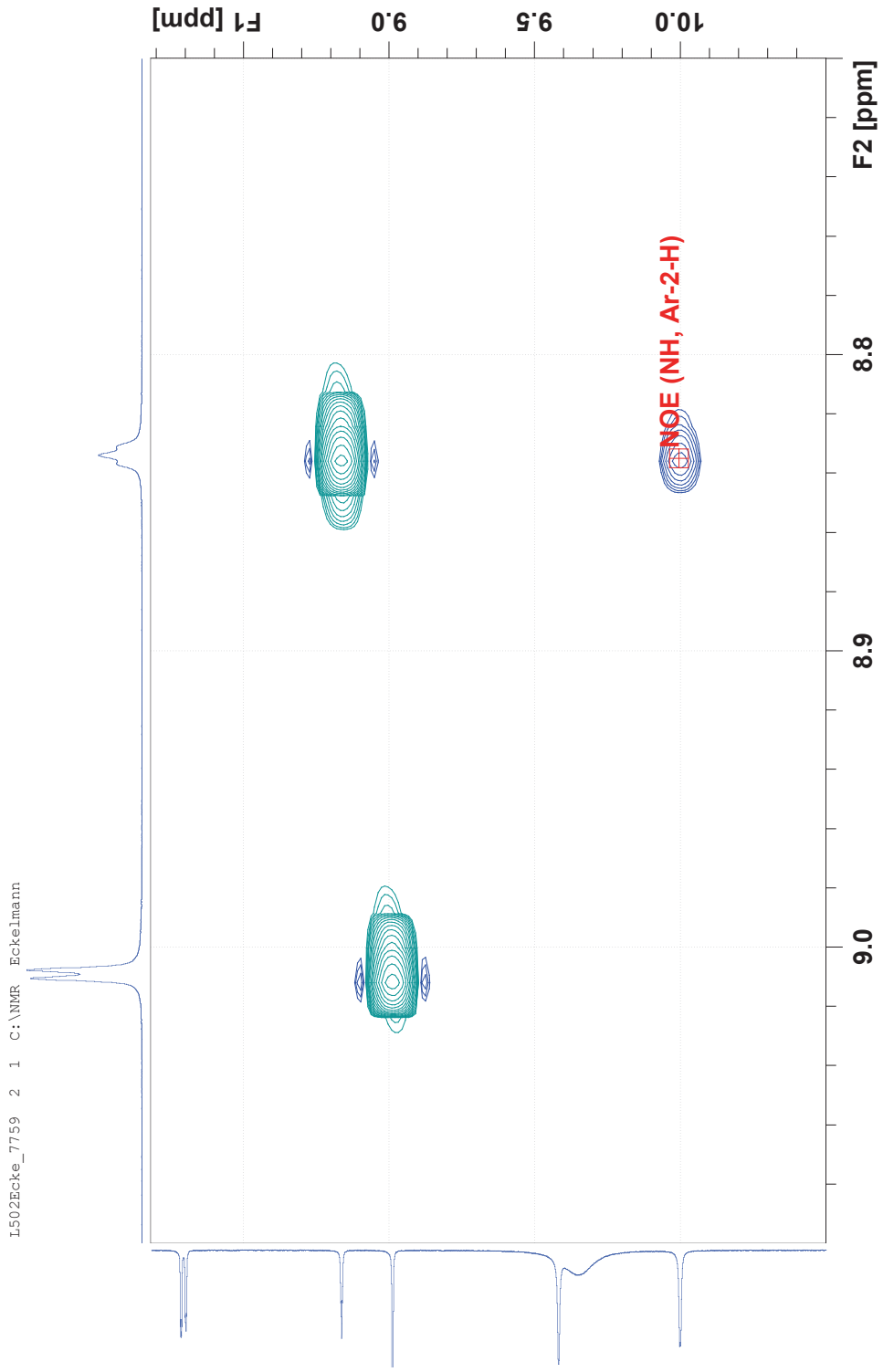


Figure 13: 2D ^{1}H,^{1}H NOESY experiment on Hamilton receptor **1b** after the addition of **2**. The rotation along the amide–aryl is hindered and only one NOE signals appears (cp. figure 12). The V-shaped conformer is favored.

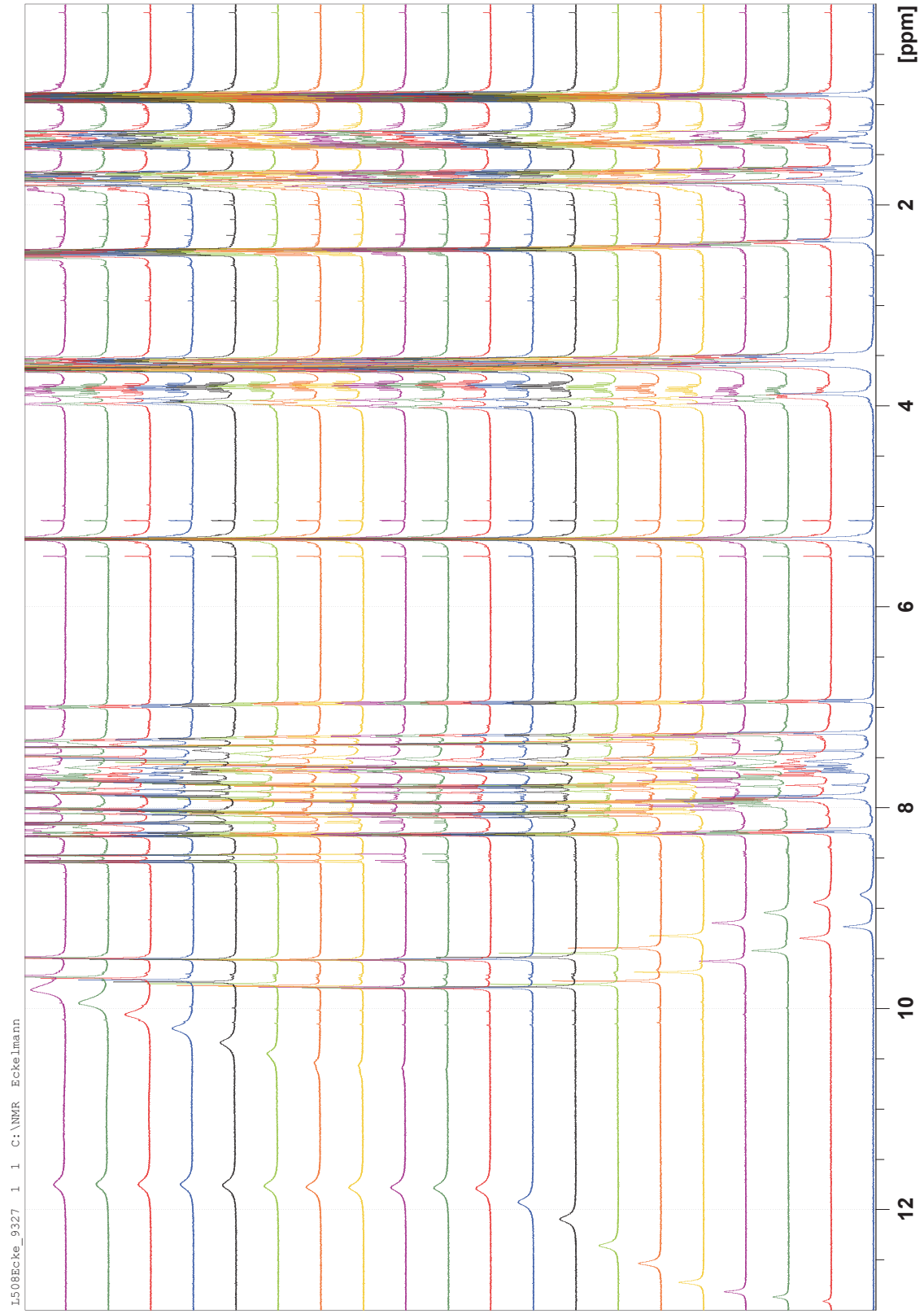


Figure 14: ^{1}H NMR titration (500 MHz) in CH_2Cl_2 at 298 K. 1st spectrum pure **21**, followed by the addition of **3** (9x) and **4** (10x) (bottom up).

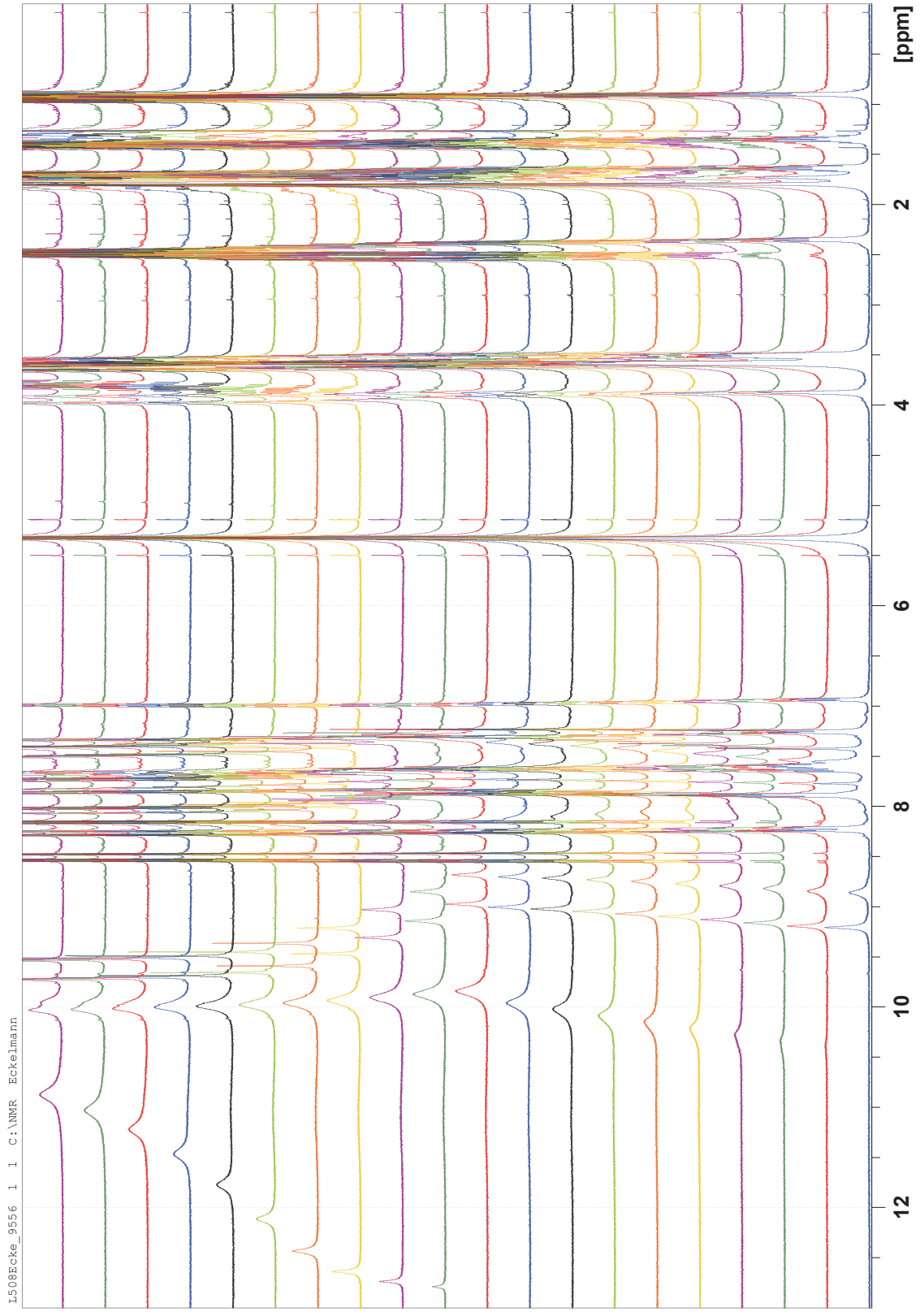


Figure 15: ^{1}H NMR titration (500 MHz) in CH_2Cl_2 at 298 K. 1st spectrum pure **21**, followed by the addition of **4** (9x) and **3** (10x) (bottom up).

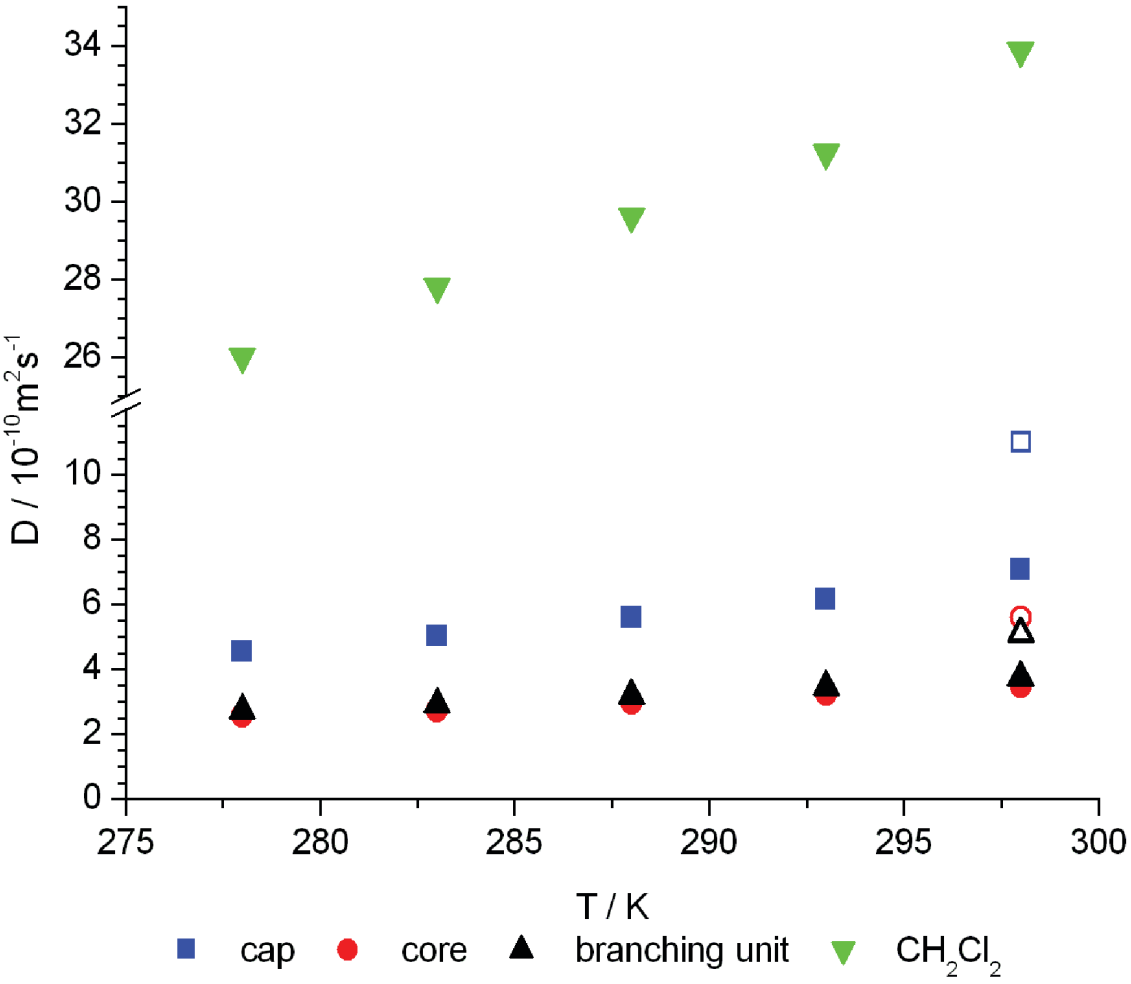


Figure 16: Temperature dependent diffusion NMR experiment.

Diffusion constant *D* [10^{-10} m^2s^{-1}]

T/K	cap **4**	core **25**	b.u. **25**	CH_2Cl_2
298	7.08	3.48	3.75	33.88
293	6.16	3.24	3.45	31.26
288	5.60	2.98	3.20	29.62
283	5.03	2.74	2.93	27.80
278	4.55	2.56	2.75	26.00

Diffusion constants *D* (at 298 K) as isolated molecules:

core **25**: 5.60 10^{-10} m^2s^{-1}

branching unit **21**: 5.09 10^{-10} m^2s^{-1}

cap **4**:11.0 10^{-10} m^2s^{-1}

References:

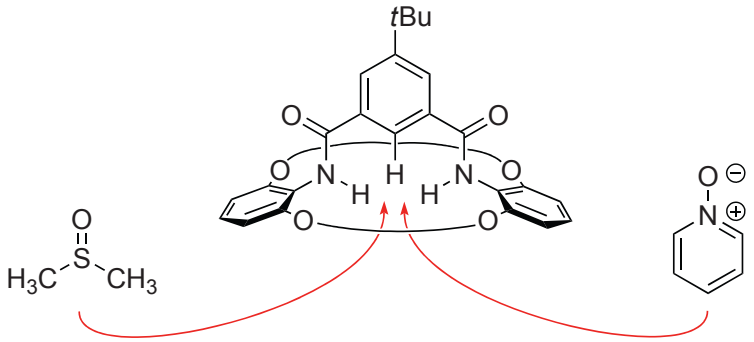
[1] L. Zhu, M. Lu, D. Qu, Q. Wang, H. Tian, *Org. Biomol. Chem.* **2011**, *9*, 4226-4233.

[2] L. W. Deady, O. L. Korytsky, J. E. Rowe, *Aust. J. Chem.* **1982**, *35*, 2025-2034.

3.5 Binding of Group 15 and Group 16 Oxides by a Concave Host Containing an Isophthalamide Unit

J. Eckelmann, V. Saggiomo, S. Fischmann, U. Lüning, *Beilstein J. Org. Chem.* **2012**, *8*, 11-17. DOI:10.3762/bjoc.8.2

In Zusammenarbeit mit SAGGIOMO wurde ein konkaver Bimakrozyklus entwickelt, der nicht nur die Erkennung von Anionen ermöglichen, sondern auch durch seine lampenschirmartige Form eine Selektivität liefern sollte. Ein für dieses Projekt von FISCHMANN synthetisierter Bimakrozyklus wurde im Anschluss untersucht. Hierbei zeigte eine Reihe von NMR-Experimenten, dass der konkave Bimakrozyklus Halogenide nicht gut bindet. Zur Untersuchung der Verbindung konnte für schwach bindende Gäste ein schnelles Screening-Verfahren entwickelt werden. Es ermöglichte, mit nur drei Messpunkten die Stärke der Bindung abzuschätzen. Aus einer Vielzahl von Gästen konnten hiermit gezielt die passenden Gäste ermittelt und genauer untersucht werden.



Mathematische Berechnungen bestätigten die Richtigkeit des Screening-Verfahrens. Weiter konnte gezeigt werden, dass die abgeschätzten Assoziationskonstanten gut mit den durch ^{1}H-NMR-Titrationen erhaltenen Ergebnissen übereinstimmen. Die Halogenide konnten vermutlich durch die vorhandenen Ethersauerstoffatome nicht gut im Bimakrozyklus binden. Das Screening wurde auf ungeladene Gäste erweitert, und es konnte gezeigt werden, dass Dimethylsulfoxid und Pyridin-*N*-oxid besonders gut in dem Bimakrozyklus binden. Es war das zweite Beispiel in der Literatur, bei dem ein Wirt Dimethylsulfoxid in einem organischen Lösungsmittel bindet. Verglichen wurden die Ergebnisse mit einer von FISCHMANN hergestellten Modellverbindung. Diese nicht makrozyklische Verbindung bestätigte die Größenselektivität. Die sterisch nicht anspruchsvolle Modellverbindung bindet – im Gegensatz zum Bimakrozyklus – Triphenylphosphinoxid.

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Binding of group 15 and group 16 oxides by a concave host containing an isophthalamide unit

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Full Research Paper

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Abstract

A bi-macrocycle with an incorporated isophthalamide substructure was synthesized by double amide formation between an isophthaloyl dichloride and two equivalents of a bis(alkenyloxy)aniline, followed by ring-closing metathesis and hydrogenation. In contrast to many related isophthalamides, the concave host exhibits a better binding for oxides, such as DMSO or pyridine-*N*-oxide, than for halide anions. A general method for a quick estimation of the strength of binding derived from only a few data points is presented and gives an estimated K_{ass} of pyridine-*N*-oxide of ca. 40 M^{-1}, NMR titration confirms 25 M^{-1}.

Introduction

In the last decade, isophthalamide derivatives have become attractive neutral hosts as anion receptors [1,2]. Some of these derivatives show a high selectivity for one anion over others [3]. Isophthalamide units have also been incorporated into macrocycles [4,5] or bi-macrocycles for ion-pair and ion-triplet recognition [6-9]. During the last few years, it was also shown that the orientation of the amide bonds of the isophthalamides plays an important role in the effectiveness of anion binding and subsequently in applications such as transmembrane anion transport. Rotation along the amide–aryl bonds leads to *syn/anti*, *syn/syn* and *anti/anti* conformers (*syn* and *anti* defined with respect to the relative orientation of the NH atoms), and only the *syn/syn* conformer of an isophthalamide is capable of simultaneously binding an anion by *both* NH groups. The *syn/syn* conformation can be stabilized by using isophthalamide derivatives capable of intramolecular hydrogen bonding to the CO part of the amide groups [10,11], or by other means of bridging [12]. Due to the preorganization of such molecules, the binding constant for chloride is impressively increased with respect to the non-preorganized isophthalamides. However, an intramolecular hydrogen bond can be easily broken in polar solvents, hence destroying the preorganization and thus decreasing the binding affinities for the anions. Herein we describe the facile synthesis and the binding properties of a concave host **1** with a different type of preorganization. This contains an isophthalamide unit in a bi-macrocyclic structure (Figure 1). Concave hosts and especially concave reagents are best envisioned as having the form of a lamp in a lampshade in

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which the light bulb is the reactive centre [13-15]. The preorganization and the exact shape of the "lampshade" determine the selectivity and the difference in binding of various guests.

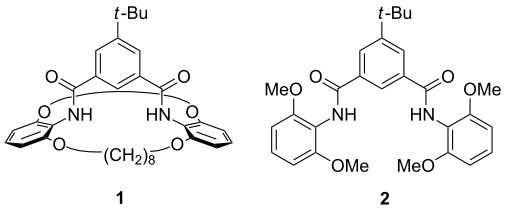


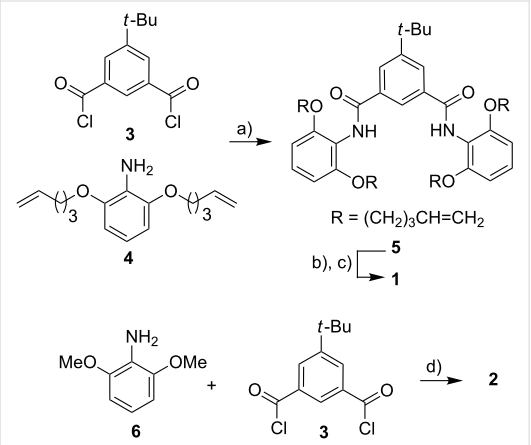
Figure 1: Bi-macrocyclic concave host **1** and its non-macrocyclic model **2**.

Results and Discussion

Synthesis

Besides the desired bi-macrocycle **1**, isophthalamide **2** was synthesized in order to compare the binding properties of a non-macrocyclic host with the concave host **1**. The syntheses of the concave host **1** and its analogue **2** are depicted in Scheme 1.

The preparation of concave host **1** starts with aniline **4**, which was synthesized as previously published [16]. The reaction of two equivalents of this aniline **4** with isophthaloyl dichloride **3** gave the open diamide **5**. This tetraalkene **5** was then converted to bi-macrocycle **1** by ring-closing metathesis followed by catalytic hydrogenation. Model compound **2** was obtained by reacting isophthaloyl dichloride **3** with 2,6-dimethoxyaniline (**6**). The two products **1** and **2** were isolated and characterized. The preorganization of the binding region was investigated by NOESY experiments. While two cross peaks between the NH protons and both types of protons in the central aromatic region were observed in the case of the more flexible compound **2**,



Scheme 1: Synthetic scheme for the syntheses of concave host **1** and non-macrocyclic derivative **2**. a) Et_3N, THF, 16 h, room temp., 61%; b) Grubbs 1st gen. cat., CH_2Cl_2, 24 h, room temp.; c) Pd/C, H_2, MeOH, 24 h, room temp., 77%; d) Et_3N, THF, 18 h, room temp., 97%.

there was only one cross peak of an aromatic proton of the isophthalamide of bi-macrocycle **1** with the NH protons: The *endo*-proton in the 2-position of the isophthalic unit is in close proximity to the NH protons. Thus, the binding region of **1** is preorganized (for details see Supporting Information File 1).

NMR binding studies

Each of the isophthalamides, **1** and **2**, was dissolved in CD_2Cl_2 and ^1H NMR spectra were recorded after addition of five equivalents of different tetrabutylammonium halide salts (TBAHal). The chemically induced shifts (CIS) of the NH and the isophthalamide *endo*-CH protons (i.e., the 2-position of the aromatic ring) were analyzed (Figure 2). Further addition of guests led to larger CIS, but no saturation was observed. The shallow curvature and absence of saturation suggest small

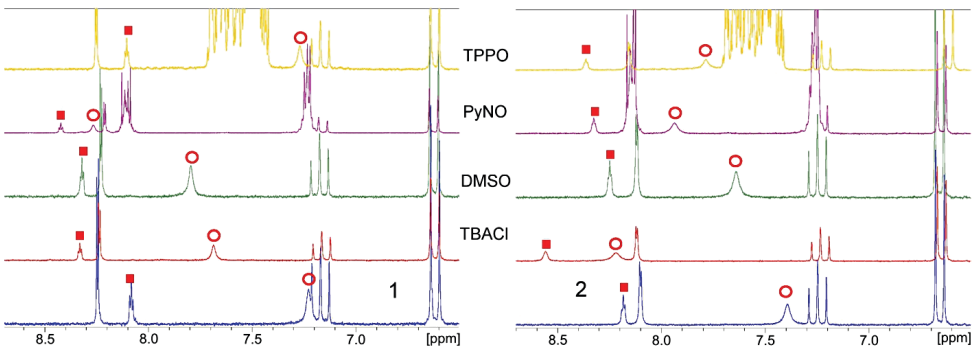


Figure 2: Expansion of a part of the ^1H NMR spectra (200 MHz, 298 K) of pure **1** and **2** in CD_2Cl_2 (bottom) and after addition of TBACl, DMSO, pyridine-*N*-oxide (PyNO), triphenylphosphine oxide (TPPO), from bottom to top, respectively. NH proton (red circles), *endo*-CH proton (red squares).

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binding constants. The different magnitudes of the CIS suggest that concave host **1** binds halides with lower affinity than its acyclic relative **2**, although the magnitude of the CIS need not be correlated with the binding constants.

However, when sulfoxides were added as neutral guests, the relative binding of these guests by **1** and **2** showed drastic differences. Dimethyl sulfoxide (DMSO), methylphenyl sulfoxide (MPSO) and diphenyl sulfoxides (DPSO) induced a shift of the *endo*-CH in the concave host **1** of 0.24 ppm, 0.20 ppm and 0.25 ppm, respectively (for DMSO see Figure 2, left, see also Supporting Information File 1), while the addition of these guests had almost no effect on the *endo*-CH of model compound **2** (for DMSO see Figure 2, right). Although there is almost no CIS observed for the *endo*-CH of model compound **2**, a small shift for the NH protons is observed. However, for DMSO, the CIS of the NH is larger for the concave host **1** than for model compound **2** (0.57 ppm for **1** and 0.25 ppm for **2**), in contrast to the results of the anion-binding experiments (see above). To the best of our knowledge, this is the second host capable of binding DMSO in an organic solvent [17]. In this regard, concave host **1** seems to be selective and a better binder for negatively polarized oxygen atoms when compared to acyclic compound **2**.

Next, element oxides other than sulfoxides were chosen as guests, namely pyridine-*N*-oxide (PyNO) [18,19] and triphenylphosphine oxide (TPPO). PyNO showed the same behaviour as DMSO, i.e., large CIS for concave host **1**, and small CIS for the linear compound (Figure 2, PyNO, *endo*-CH, 0.34 ppm for **1** and 0.14 ppm for **2**). In contrast, with TPPO as guest, model compound **2** showed a larger CIS when compared to concave host **1** (Figure 2, TPPO). This may be explained by the large steric bulk of TPPO, which may be too extreme to allow TPPO to fit nicely inside the cavity of concave host **1** but still allows a binding to the sterically less demanding non-macrocyclic host **2**.

In order to reliably determine small binding constants, a titration up to a large excess of guest has to be carried out but, even then, a limiting value for the CIS often is not reached and thus a second parameter besides K_{ass}, namely the maximum of the observed CIS $\Delta\delta_{max}$, has to be obtained by curve fitting, which adds to the overall error. In our host–guest systems, saturation was not reached even when 20 equivalents of guests were used. An even larger excess of guest changed the polarity of the solvent to such an extent that all signals were affected, not only those involved in the binding [20].

If most guests only bind very moderately, an exact (and tedious) determination of all binding constants K_{ass} is not interesting. It would be sufficient if a quick screening of the binding potentials of the hosts were possible and host–guest pairs with significant association constants were identified. Estimation rather than an exact determination of K_{ass} would be fair enough. Once a good candidate is recognized, a standard determination of the association constant, for example, by NMR titration, can be done.

With $\Delta\delta_{max}$ unknown, the magnitude of the CIS cannot distinguish between weak and strong binding. However, when NMR titrations of different host–guest pairs are carried out with identical concentrations, small and large association constants can be differentiated by the different curvatures of the titration graphs. In a titration curve of strong binding, the curvature is more extreme, and the final value of $\Delta\delta_{max}$ is approached faster than in the case of weak binding. Beyond 1:1 stoichiometry, the CIS values converge more the stronger the binding is.

Can this be a method for the quick estimation of binding constants? We have tested this alternative for hosts **1** and **2**. All measured ^{1}H NMR shifts were normalized to a CIS at high guest concentration, but not at saturation: The CIS from all experiments that used ca. 20 equivalents of a given guest were arbitrarily defined as 100%, and the CIS measured for ca. 5 equivalents of the same guest were divided by that CIS value measured with 20 equivalents. The resulting normalized CIS were plotted against the guest equivalents (Figure 3). With a more strongly binding guest, the titration curve possesses a

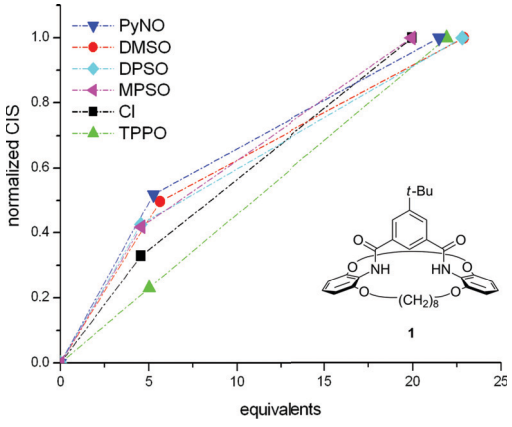

Figure 3: Normalized ^{1}H NMR CIS (see text) for concave host **1** with different anionic and neutral guests. The deviations of the data points at ca. 5 equivalents, from the straight line connecting the origin and the data points at 20 equivalents, describe the strength of binding. The binding strength decreases from top to bottom. The dashed lines have no physical significance but help to demonstrate the deviation from linearity.

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more extreme curvature, and thus, in this normalized form, the data points at 5 equivalents lie further away from the linear line that connects the points corresponding to 0 and 20 equivalents.

The validity of this estimation has been checked with calculated titration curves for different association constants K_{ass} and different maximum CIS (see Supporting Information File 1). For an application on host **1**, see Figure 3; for **2**, see Figure 4. For each host, only those guests that are bound most strongly are listed. For the full data set, see Supporting Information File 1. Data points below the straight line are physically meaningless, and simply reflect the large errors for very weak binding (the method of normalizing the shifts should preferably not be carried out for guests with *very* small CIS).

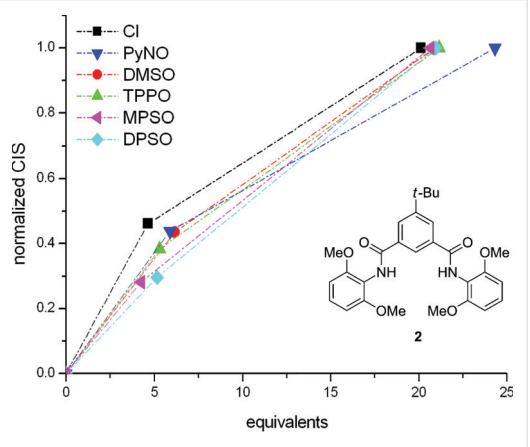

Figure 4: Normalized ^{1}H NMR CIS (see text) for concave host **2** with different anionic and neutral guests. The deviations of the data points at ca. 5 equivalents, from the straight line connecting the origin and the data points at 20 equivalents, describe the strength of binding. The binding strength decreases from top to bottom. The dashed lines have no physical significance but help to demonstrate the deviation from linearity.

In Figures 3 and 4, the relative strengths of binding can be obtained from the vertical deviations of the normalized CIS at ca. 5 equivalents from the straight line connecting the origin and the values at 20 equivalents. The magnitude of the binding decreases from top to bottom.

By using this methodology, it is possible and easy to determine the relative binding strengths of the two hosts **1** and **2** even for weak binding constants and situations where maximal chemically induced shifts $\Delta\delta_{max}$ cannot be determined from only a few measurements. When the two graphs for **1** and **2** with different guests are compared, the different selectivity of the two hosts becomes evident. Concave host **1** shows a better affinity for negatively polarized oxygen atoms than for anions, except in the case of the bulky TPPO. The affinities of concave host **1** lie in the following order: PyNO > DMSO > DPSO = MPSO > Cl^- > TPPO. In contrast, the affinities of the non-macrocyclic analogue **2** are: Cl^- > PyNO = DMSO = TPPO > MPSO = DPSO (see Supporting Information File 1). When the plot was compared with the simulated titration curves (see Supporting Information File 1, page S12), K_{ass} for the best binder to **1**, pyridine-*N*-oxide (PyNO), was estimated to be ca. 40 M^{-1}. A subsequent NMR titration of host **1** with PyNO provided an association constant of 25 M^{-1} (see Supporting Information File 1). Remarkably, chloride ions are only very weakly bound by concave host **1**, and binding constants are moderate anyway. A possible explanation may be a repulsion between the negatively polarized oxygen atoms in the 2- and 6-positions of the bridge heads of **1** and the negatively, or partially negatively charged guests.

Conclusion

1 is a readily synthesized concave host molecule in which the isophthalamide moiety is the central binding unit, and it is preorganized by its incorporation into the bi-macrocyclic structure. This concave host, although it does not exhibit strong binding, is selective for negatively polarized oxygen atoms and selects them according to the steric bulk of the guests. These initial experiments now open the way for the synthesis of new modified concave hosts based on isophthalamide units with improved binding selectivity and/or for organocatalysis [21]. Concave host **1** can also be applied as a carrier in transport experiments. When applied to chloride-loaded liposomes [22], it showed twice as much transmembrane chloride transport with respect to acyclic compound **2** (see Supporting Information File 1). Even if the chloride binding is lower for concave host **1**, the transport through a bilayer membrane is faster. Additional transport experiments are under investigation.

Experimental

General remarks

All reagents were obtained from commercial sources and used without additional purification unless otherwise indicated. 5-*tert*-Butylisophthaloyl dichloride (**3**) was prepared from 5-*tert*-butylisophthalic acid and thionyl chloride according to Vögtle et al. [23]. 2,6-Bis(pent-4-enyloxy)aniline (**4**) was prepared from 2-nitroresorcine according to Winkelmann et al. [16]. 2,6-Dimethoxyaniline (**6**) was synthesized from 2-nitroresorcine according to Mechoulam and Srebnik [24] and was finally reduced to 2,6-dimethoxyaniline (**6**) according to Franck and Kauffmann [25]. THF was freshly distilled from lithium aluminium hydride (triphenylmethane as indicator). All reactions were carried out in an atmosphere of nitrogen. NMR spectra were recorded with Bruker AC 200, DRX 500 or AV 600 instruments. Assignments are supported by COSY, HSQC

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and HMBC. All chemical shifts are referenced to TMS or residual solvent peaks. Mass spectra were recorded with Finnigan MAT 8200 or MAT 8230. ESI mass spectra were recorded with an Applied Biosystems Mariner Spectrometry Workstation. IR spectra were recorded with Perkin-Elmer Spectrum 100 spectrometer, equipped with an ATR unit. Elemental analyses were carried out with a EuroEA 3000 Elemental Analyzer from Euro Vector. MALDI-TOF spectra were recorded with Bruker-Daltonics Biflex III. 4-Chloro-α-cyanocinnamic acid (Cl-CCA) was used as the matrix.

^{1}H NMR experiments

Each NMR tube was filled with 600 µL of a stock solution (5 mg/mL) of **1** or **2** in CD_2Cl_2, and subsequently ca. 5, and later ca. 20 equivalents of the respective guest were added. The exact amount was recalculated from the integrals by using Bruker Topspin® 2.1. All experiments were carried out on a Bruker AC 200 NMR equipped with an autosampler at 300 K. The spectra are referenced to the residual solvent peak.

Synthesis of 25^5-*tert*-Butyl-2,11,13,22-tetraoxa-23,27-diaza-1,12 (1,3,2)-25 (1,3)-tribenzenabicyclo[10.10.5]heptacosaphan-24,26-dione (**1**)

A solution of 25^5-*tert*-Butyl-2,11,13,22-tetraoxa-23,27-diaza-1,12(1,3,2)-25(1,3)-tribenzenabicyclo[10.10.5]heptacosaphan-6,17-dien-24,26-dione (186 mg, 284 µmol), Pd/C (10%, 150 mg) and methanol (30 mL) was stirred under an atmosphere of hydrogen for 24 h. The mixture was filtered through a syringe filter (0.450 µm) to remove all Pd/C, and the solvent was removed under reduced pressure to obtain **1** as a white solid (144 mg, 219 µmol, 77%); mp 225 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H, 25^{4,6}-H), 8.06 (s, 1H, 25^2-H), 7.24 (br. s, 2H, NH), 7.14 (t, ^3J = 8.4 Hz, 2H, 1^5,12^5-H), 6.59 (d, ^3J = 8.4 Hz, 4H, 1^{4,6},12^{4,6}-H), 4.19 (ddd, ^2J = ca. 9 Hz, ^3J = ca. 9 Hz, ^3J = ca. 2 Hz, 4H, OCH_aH$_b$), 3.85 (ddd, ^2J = 9.7 Hz, ^3J = 9.7 Hz, ^3J = 2.1 Hz, 4H, OCH$_a$$H_b$), 1.79 (m$_c$, 4H, OCH$_2CH_aH_b$), 1.62 (m$_c$, 4H, OCH$_2CH_a$$H_b$), 1.43 (s, 9H, CH_3), 1.32 (m$_c$, 8H, CH_2), 1.25 (m$_c$, 8H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4 (s, *C*=O), 154.0 (s, 1^{1,3},12^{1,3}-C), 153.3 (s, 25^5-C), 134.8 (s, 25^{1,3}-C), 129.6 (d, 25^{4,6}-C), 127.1 (d, 1^5,12^5-C), 121.1 (d, 25^2-C), 115.6 (s, 1^2,12^2-C), 105.4 (d, 1^{4,6}, 12^{4,6}-C), 69.2 (t, OCH_2), 35.3 (s, *C*(CH$_3$)$_3$), 31.2 (q, CH_3), 30.6 (t, OCH$_2$*C*H$_2$), 29.7 (t, O(CH$_2$)$_3$*C*H$_2$), 27.4 (t, O(CH$_2$)$_2$*C*H$_2$); IR (ATR) $\tilde{\nu}$: 3430 (w, NH), 2930, 2848 (2 w, aliph. CH), 1683 (m, C=O), 1589 (w, arom. C=C), 1509 (m, arom. C=C),1392 (s, CH_3) cm^{-1}. EIMS (70 eV): *m/z* (% relative intensity) 656 (100) [M]$^{+\bullet}$; CIMS (isobutane): *m/z* (% relative intensity) 657 (30) [M + H]$^+$; ESIMS ($CHCl_3$): *m/z* (% relative intensity) 679 (100) [M + Na]$^+$, 657 (75) [M + H]$^+$; MS (MALDI-TOF, Cl-CCA): *m/z* 695 [M + K]$^+$, 679 [M + Na]$^+$, 656 [M]$^+$; HRMS calcd for $C_{40}H_{52}N_2O_6$ 656.38251; found: 656.38257 (Δ = −0.1 ppm); calcd for $C_{39}{}^{13}CH_{52}N_2O_6$ 657.38586; found: 657.38597 (Δ = −0.2 ppm); Anal. calcd for $C_{40}H_{52}N_2O_6$: C, 73.14; H, 7.98; N, 4.26; found: C, 73.04; H, 8.04; N, 4.39.

Synthesis of 5-*tert*-Butyl-*N,N'*-bis(2,6-dimethoxyphenyl)-isophthalamide (**2**)

A solution of 5-*tert*-butylisophthaloyl dichloride (**3**, 550 mg, 2.12 mmol) in tetrahydrofuran (5.00 mL) was added dropwise over 45 min to a stirred solution of 2,6-dimethoxyaniline (**6**) (650 mg, 4.24 mmol) and triethylamine (2.35 mL, 1.72 g, 17.0 mmol) in tetrahydrofuran (20 mL). The solution was stirred for 24 h. The solvent and excess of triethylamine was evaporated under reduced pressure. The residue was dissolved in chloroform (25 mL) and water (25 mL). The water phase was extracted once with chloroform (25 mL), the combined organic layer was dried with magnesium sulfate and evaporated under reduced pressure to yield a yellow solid, which was purified by column chromatography (silica gel, dichloromethane/methanol, 40:1, R_f = 0.11) to give **2** as a white solid (1.02 g, 2.07 mmol, 97%); mp 122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H, Ar^1-2-H), 8.14 (s, 2H, Ar^1-4,6-H), 7.43 (br. s, 2H, NH), 7.21 (t, ^3J = 8.4 Hz, 2H, Ar^2-4-H), 6.62 (d, ^3J = 8.4 Hz, 4H, Ar^2-3,5-H), 3.84 (s, 12H, OCH_3), 1.38 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8 (C=O), 155.1 (Ar^2-2,6-C), 152.4 (Ar^1-5-C), 134.7 (Ar^1-1,3-C), 128.2 (Ar^1-4,6-C), 127.6 (Ar^2-4-C), 123.4 (Ar^1-2-C), 114.6 (Ar^2-1-C), 104.4 (Ar^2-3,5-C), 56.0 (OCH_3), 35.1 (*C*(CH$_3$)$_3$), 31.3 (q, CH_3); IR (ATR) $\tilde{\nu}$: 3387 (w, NH), 3231 (w, arom. CH), 2947 (m, aliph. CH), 1663 (m, C=O), 1593 (m, arom. C=C), 1519 (s, arom. C=C) cm^{-1}; EIMS (70 eV): *m/z* (% relative intensity) 492 (83) [M]$^{+\bullet}$, 340 (100) [M − $C_8H_{10}NO_2$]$^+$; CIMS (isobutane): *m/z* (% relative intensity) 493 (100) [M + H]$^+$. Anal. calcd for $C_{28}H_{32}N_2O_6$·0.1CH_2Cl_2: C, 67.36; H, 6.48; N, 5.59; found: C, 67.42; H, 6.53; N, 5.74.

Synthesis of *N,N'*-Bis(2,6-bis[pent-4-enyloxy]-phenyl)-5-*tert*-butyl-isophthalamide (**5**)

In 20 mL anhydrous tetrahydrofuran, 2,6-bis(pent-4-enyloxy)aniline (4, 1.95 g, 7.46 mmol) and anhydrous triethylamine (4.14 mL, 3.02 g, 29.7 mmol) were dissolved. A solution of 5-*tert*-butylisophthaloyl dichloride (**3**) (970 mg, 3.75 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise. The solution was stirred for 16 h at room temperature. The solvent and excess of triethylamine were evaporated under reduced pressure and the residue was dissolved in chloroform (25 mL) and water (25 mL). The aqueous phase was extracted with chloroform (25 mL). The organic layers were collected, dried with magnesium sulfate and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography (silica, cyclohexane/ethyl acetate, 1:1, R_f = 0.34) as a

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white solid (1.63 g, 2.30 mmol, 61%); mp 136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H, Ar^1-2-H), 8.08 (s, 2H, Ar^1-4,6-H), 7.28 (br. s, 2H, NH), 7.16 (t, ^3J = 8.4 Hz, 2H, Ar^2-4-H), 6.59 (d, ^3J = 8.4 Hz, 4H, Ar^2-3,5-H), 5.78 (ddt, ^3J = 16.9 Hz, ^3J = 10.2 Hz, ^3J = 6.6 Hz, 4H, C*H*=CH_2), 4.97 (m_c, 4H, H_Z), 4.91 (m_c, 4H, H_E), 4.01 (t, ^3J = 6.5 Hz, 8H, OCH_2), 2.16 (m_c, 8H, CH_2CH=CH_2), 1.85 (m_c, 8H, OCH_2CH_2), 1.38 (s, 9 H, CH_3).^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1 (s, C=O), 154.8 (s, Ar^2-2,6-C), 152.3 (s, Ar^1-5-C), 137.6 (d, *C*H=CH_2), 135.4 (s, Ar^1-1,3-C), 127.6 (d, Ar^1-4,6-C), 127.6 (d, Ar^2-4-C) 123.3 (d, Ar^1-2-C), 115.1 (t, CH=*C*H_2), 106.2 (s, Ar^2-1-C), 105.4 (d, Ar^2-3,5-C), 68.1 (t, OCH_2), 35.1 (s, *C*$(CH_3)_3$), 31.2 (q, CH_3), 30.1 (t, *C*H_2CH=CH_2), 28.4 (t, OCH_2CH_2); IR (ATR) $\tilde{\nu}$: 3207 (br. w, NH), 3076 (w, arom. CH), 2946 (m, aliph. CH), 1669 (m, C=O), 1647 (m, aliph. C=C), 1589 (m, arom. C=C), 1520 (s, arom. C=C) cm^{-1}; EIMS (70 eV): *m/z* (% relative intensity) 709 (49) $[M]^{+\bullet}$, 708 (100) $[M - H]^+$; CIMS (isobutane): *m/z* (% relative intensity) 710 (25) $[M + H]^+$, 709 (59) $[M]^{+\bullet}$, 708 (100) $[M - H]^+$; ESIMS ($CHCl_3$): *m/z* (% relative intensity) 732 (25) $[M + Na]^+$; HRMS: calcd for $C_{44}H_{56}N_2O_6$: 708.41382; found: 708.41390 (Δ = −0.1 ppm); calcd for $C_{43}{}^{13}CH_{56}N_2O_6$: 709.41718; found: 709.41706 (Δ = 0.2 ppm). Anal. calcd for $C_{44}H_{56}N_2O_6{\cdot}0.3C_6H_{12}{\cdot}0.3C_4H_8O_2$: C, 74.18; H, 8.24; N, 3.66; found: C, 73.95; H, 7.93; N, 4.04.

Synthesis of 25^5-*tert*-Butyl-2,11,13,22-tetraoxa-23,27-diaza-1,12(1,3,2)-25(1,3)-tribenzenabicyclo[10.10.5]heptacosaphan-6,17-dien-24,26-dione

Anhydrous dichloromethane (800 mL) was added to a mixture of *N,N′*-bis-(2,6-bis[pent-4-enyloxy]-phenyl)-5-*tert*-butyl-isophthalamide (**5**, 1.00 g, 1.41 mmol) and Grubbs Catalyst 1st gen. (162 mg, 141 µmol). The solution was stirred for 24 h at room temperature. The reaction was quenched with ethyl vinyl ether (2 mL) and the mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude product was filtered over silica gel (1 cm, dichloromethane/methanol, 40:1). The solvent was removed and cyclohexane/ethyl acetate (150 mL, 1:1, v/v) was added to crystallize the product. The product was filtered off and washed with ethyl acetate (10 mL) to obtain a white solid (186 mg, 284 µmol, 20%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 2H, $25^{4,6}$-H), 7.98 (s, 1H, 25^2-H), 7.20 (br. s, 2H, NH), 7.15 (t, ^3J = 8.3 Hz, 2H, 1^5,12^5-H), 6.61 (d, ^3J = 8.3 Hz, 4H, $1^{4,6}$,$12^{4,6}$-H), 5.36–5.27 (m, 4H, C*H*=C*H*), 4.22–3.82 (m, 8H, OCH_2), 2.20–1.60 (m, 16H, CH_2), 1.42 (s, 9H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2 (s, $1^{1,3}$,$12^{1,3}$-C), 153.8 (s, 25^5-C), 134.6 (s, $25^{1,3}$-C), 130.3 (s, *C*H=*C*H), 129.6 (d, $25^{4,6}$-C), 127.0 (d, 1^5,12^5-C), 121.7 (d, 25^2-C), 116.1 (s, 1^2,12^2-C), 105.4 (d, $1^{4,6}$,$12^{4,6}$-C), 69.5 (t, OCH_2), 35.3 (s, *C*$(CH_3)_3$), 31.2 (q, CH_3), 30.7 (t, OCH_2CH_2), 24.9 (t, $O(CH_2)_2CH_2$); The C=O signal was too weak to be detected in this ^{13}C spectrum. MS (MALDI-TOF, Cl-CCA): *m/z* 676 $[M + Na]^+$, 654 $[M + H]^+$.

Supporting Information

NMR spectra and product analyses for **1** and **2** are available in the Supporting Information as well as details of the NMR CIS titrations, the evaluation of the normalized CIS method, ^{1}H,^{1}H NOESY experiments, and the transport experiments.

Supporting Information File 1

Product analyses and experimental data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-2-S1.pdf]

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Supporting Information

for

Binding of group 15 and group 16 oxides by a concave host containing an isophthalamide unit

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Product analyses and experimental data

Contents

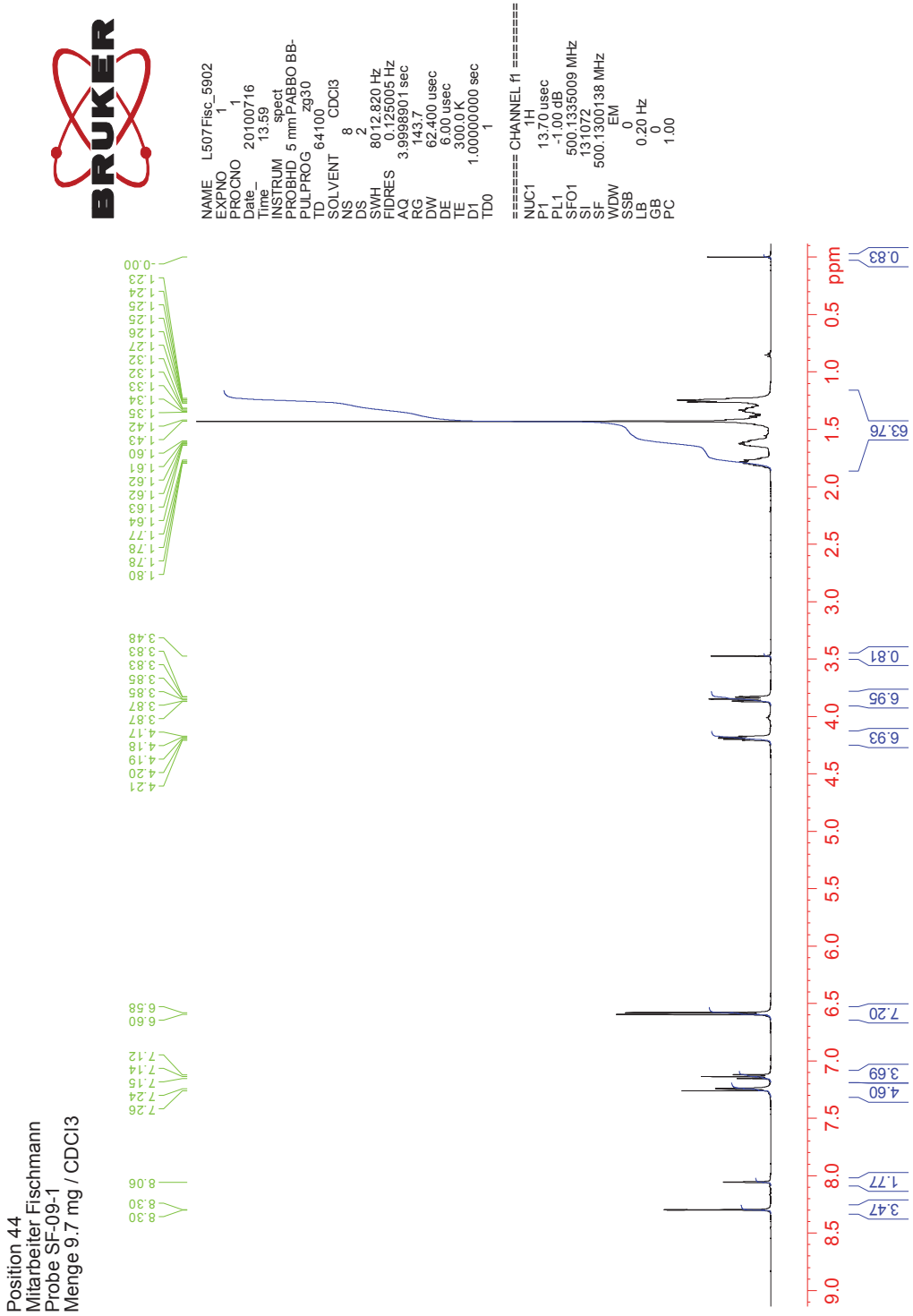


Figure S1: ^{1}H NMR (500 MHz, 300 K, $CDCl_3$) of **1.**

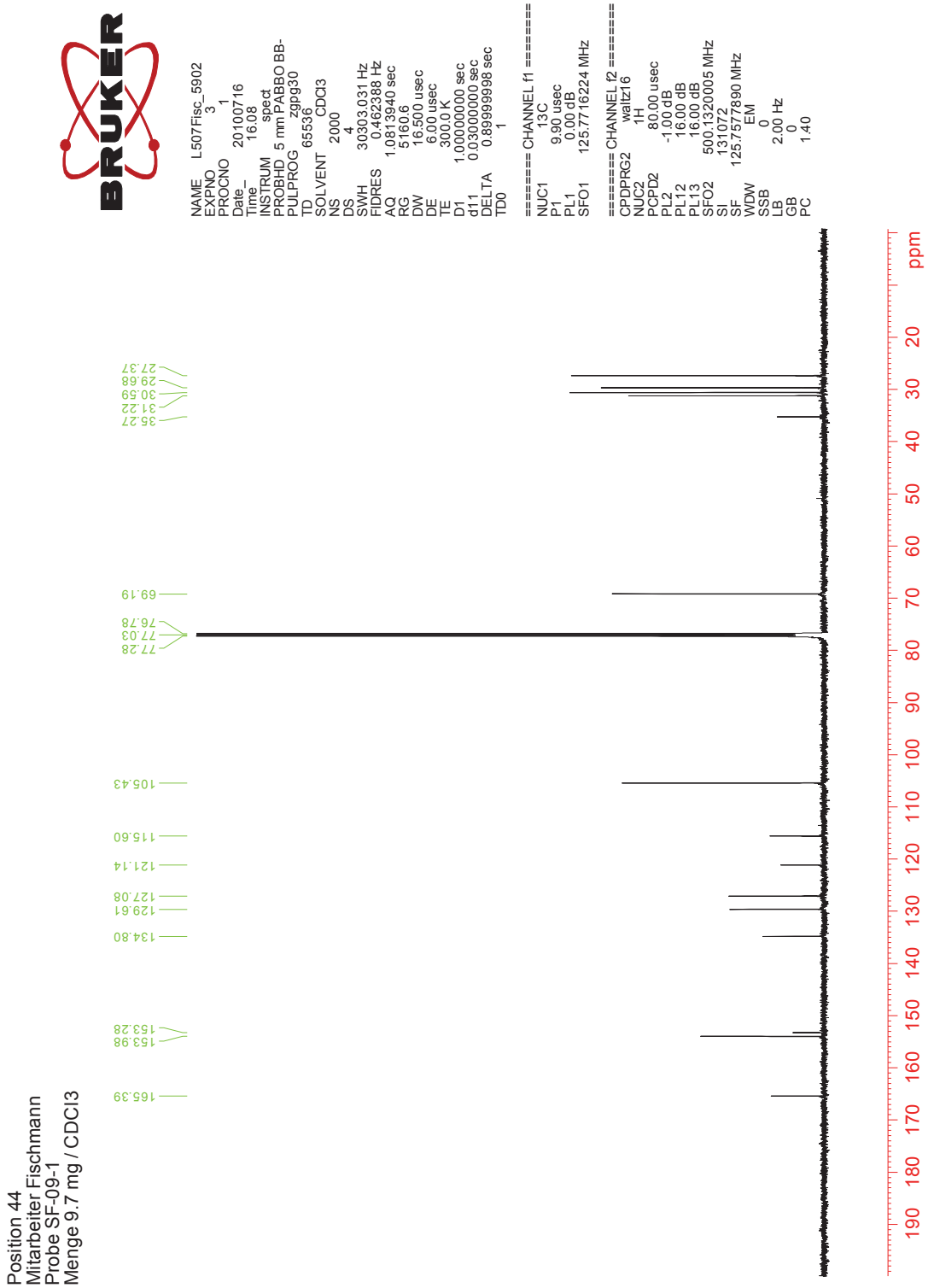


Figure S2: ^{13}C NMR (125 MHz, 300 K, $CDCl_3$) of **1.**

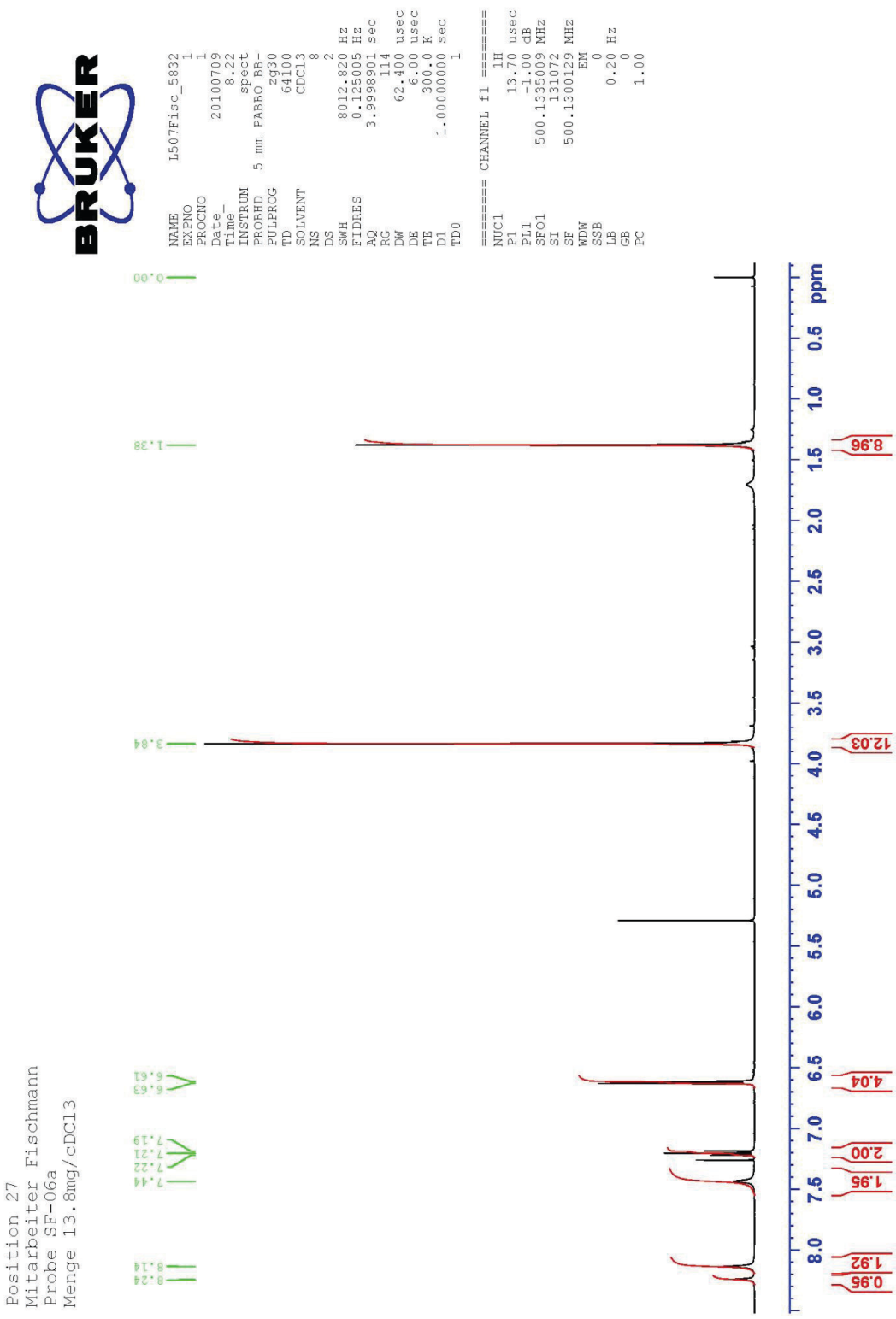


Figure S3: ^{1}H NMR (500 MHz, 300 K, $CDCl_3$) of **2.**

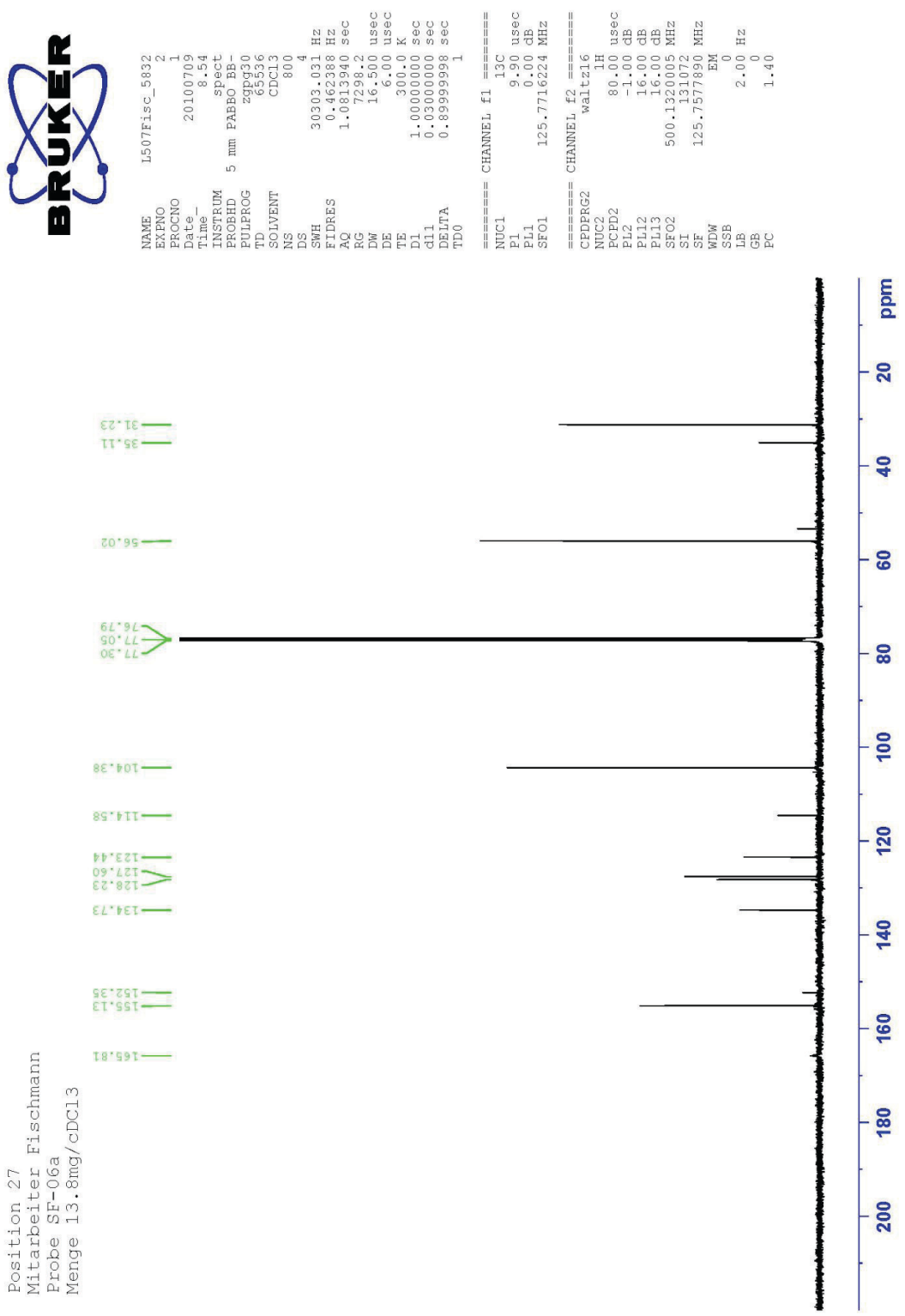


Figure S4: ^{13}C NMR (125 MHz, 300 K, $CDCl_3$) of **2.**

NMR-Experiments

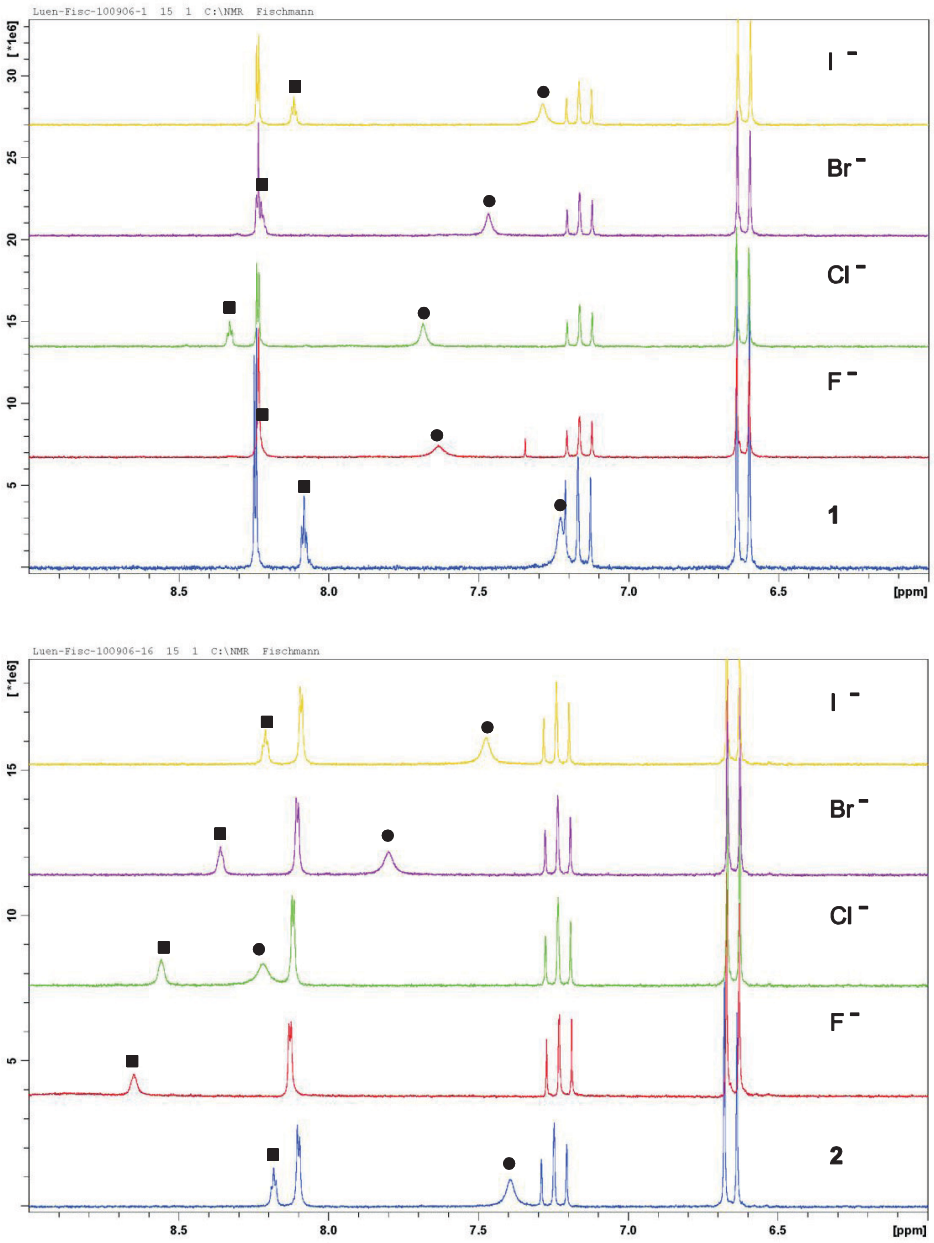


Figure S5: Binding studies with different tetrabutylammonium halides (5 equivalents; top: bi-macrocycle **1**, bottom: isophthalamide **2**). The guests were added in solid form and the exact amount was calculated from the ^{1}H NMR integration.

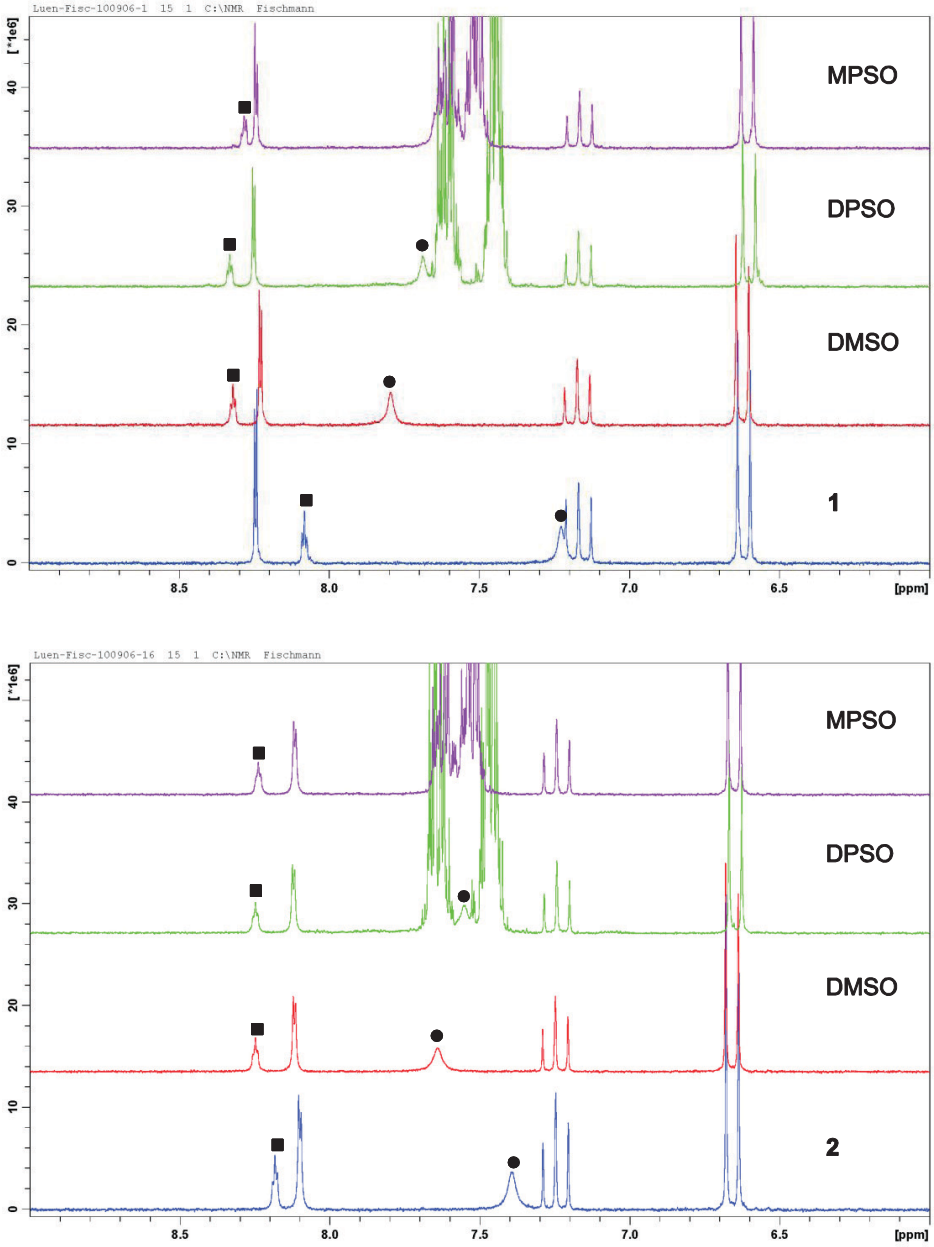


Figure S6: Binding studies with different sulfoxides (5 equivalents; top: bi-macrocycle **1**, bottom: isophthalamide **2**, MPSO = methylphenyl sulfoxide, DPSO = diphenyl sulfoxide, DMSO = dimethyl sulfoxide). The guests were added undiluted and the exact amount was calculated from the ^{1}H NMR integration.

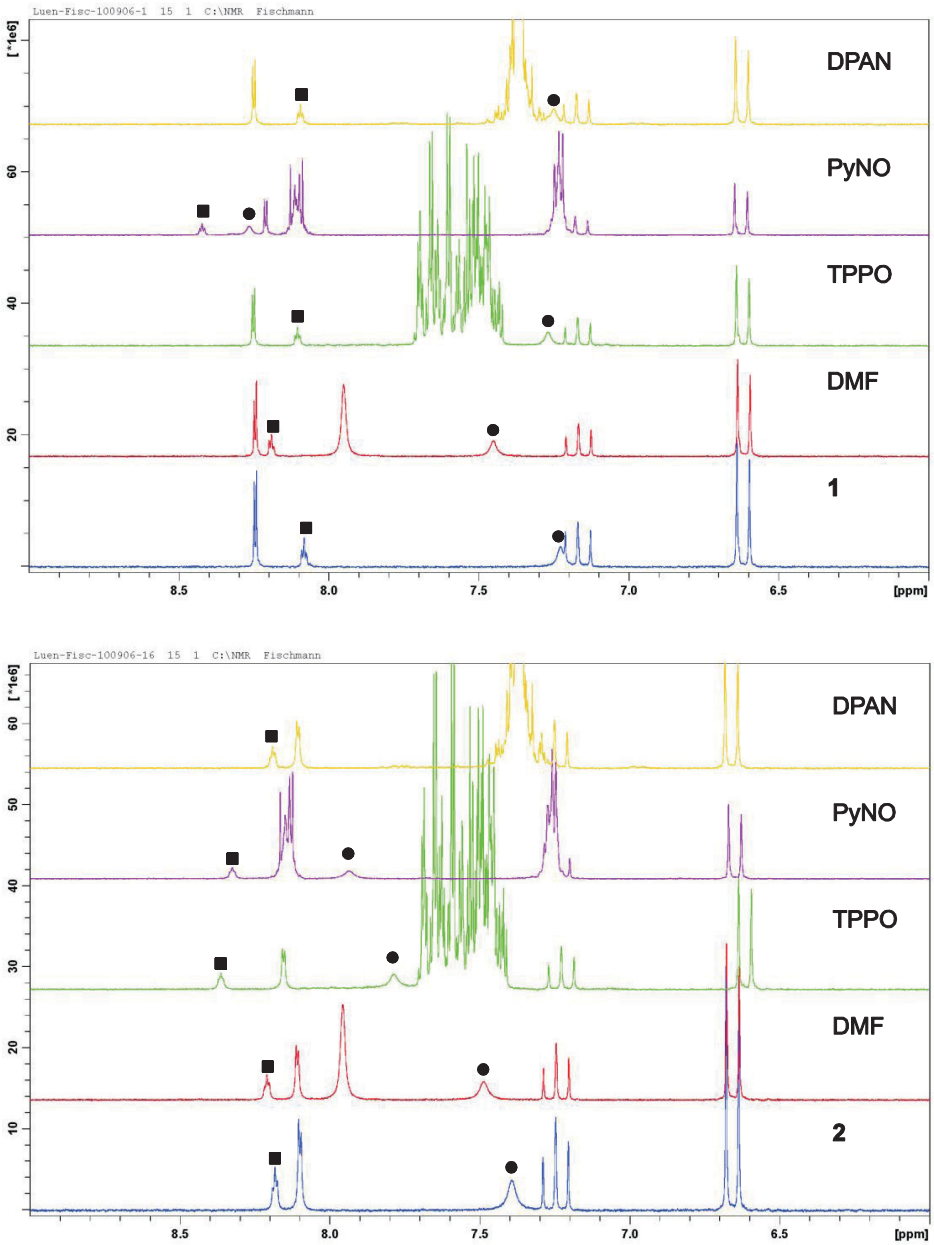


Figure S7: Binding studies with different guests (5 equivalents; top: bi-macrocycle **1**, bottom: isophthalamide **2**, DPAN = diphenylacetonitrile, PyNO = pyridine-*N*-oxide, TPPO = triphenylphosphine oxide, DMF = *N,N*-dimethylformamide). The guests were added undiluted and the exact amount was calculated from the ^{1}H NMR integration.

Normalized CIS of 1

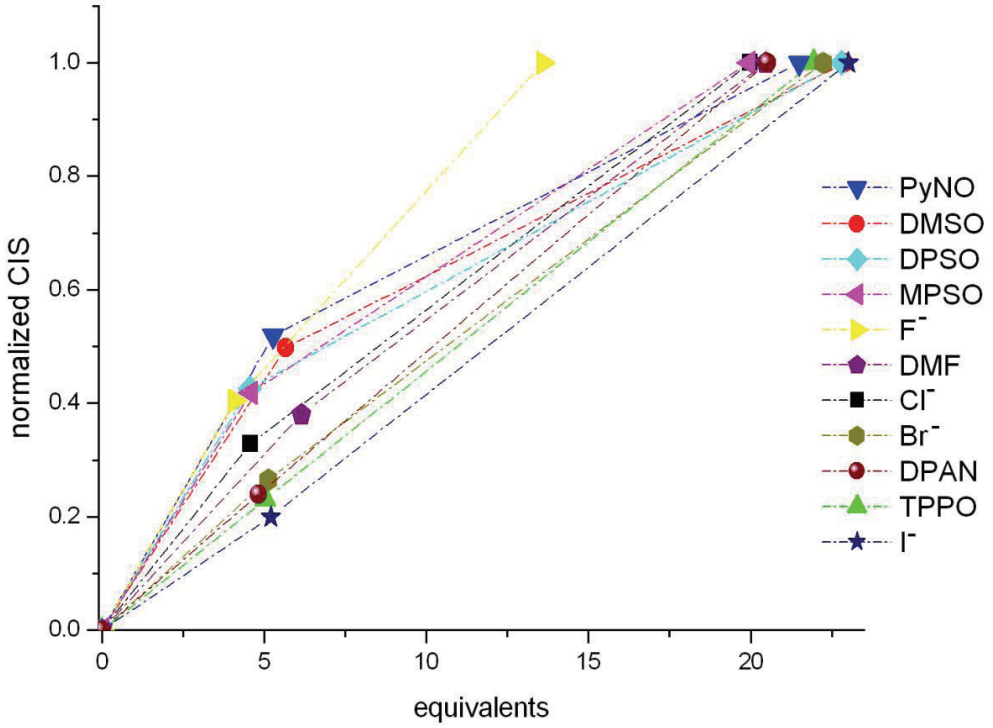


Figure S8: Normalized CIS of **1** (isophthalamide *endo*-CH proton).

Normalized CIS of 2

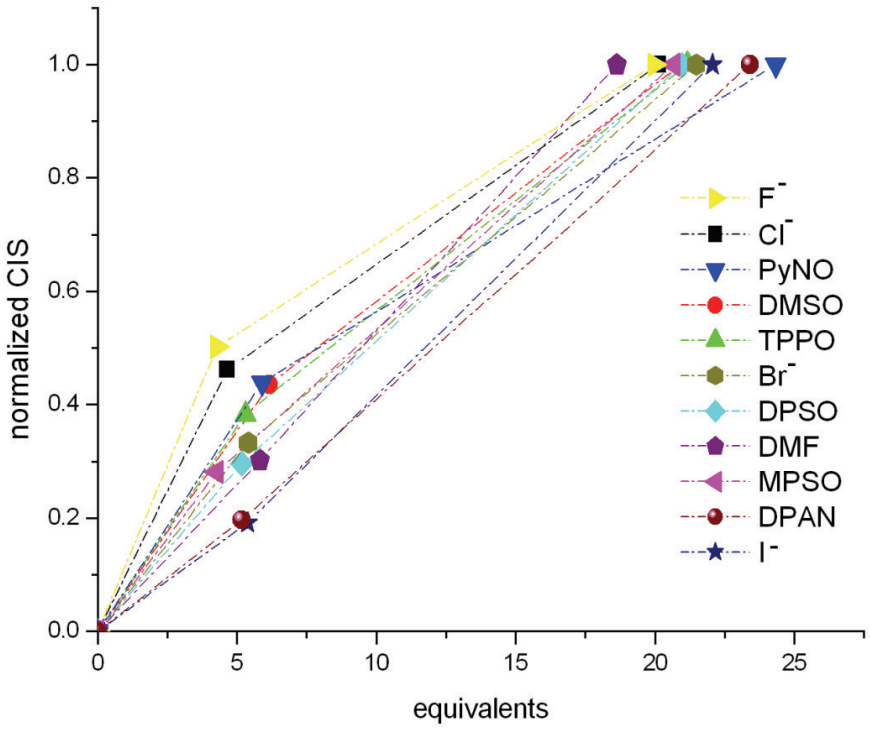


Figure S9: Normalized CIS of **2** (isophthalamide *endo* CH proton).

Evaluation of the Normalized CIS Method

To prove that normalized CIS is a valid method to estimate the binding strength, six different titration curves were simulated. Association constants between K_{ass} = 2 and K_{ass} = 100 were chosen. Host concentration was fixed at 0.003 mol L^{-1}.

Equations used:

$H := 0.003$

$G := 0, 0.0001 .. 0.06$

$\Delta\delta_{max} := 1$

K = association constant (M^{-1})
G = concentration guest (M)
H = concentration host (M)
$\Delta\delta_{max}$ =shift(G_{sat}) - shift (G_0) (ppm)

$K := 2$

$$K_2(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

$K := 5$

$$K_5(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

$K := 10$

$$K_{10}(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

$K := 20$

$$K_{20}(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

$K := 50$

$$K_{50}(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

$K := 100$

$$K_{100}(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

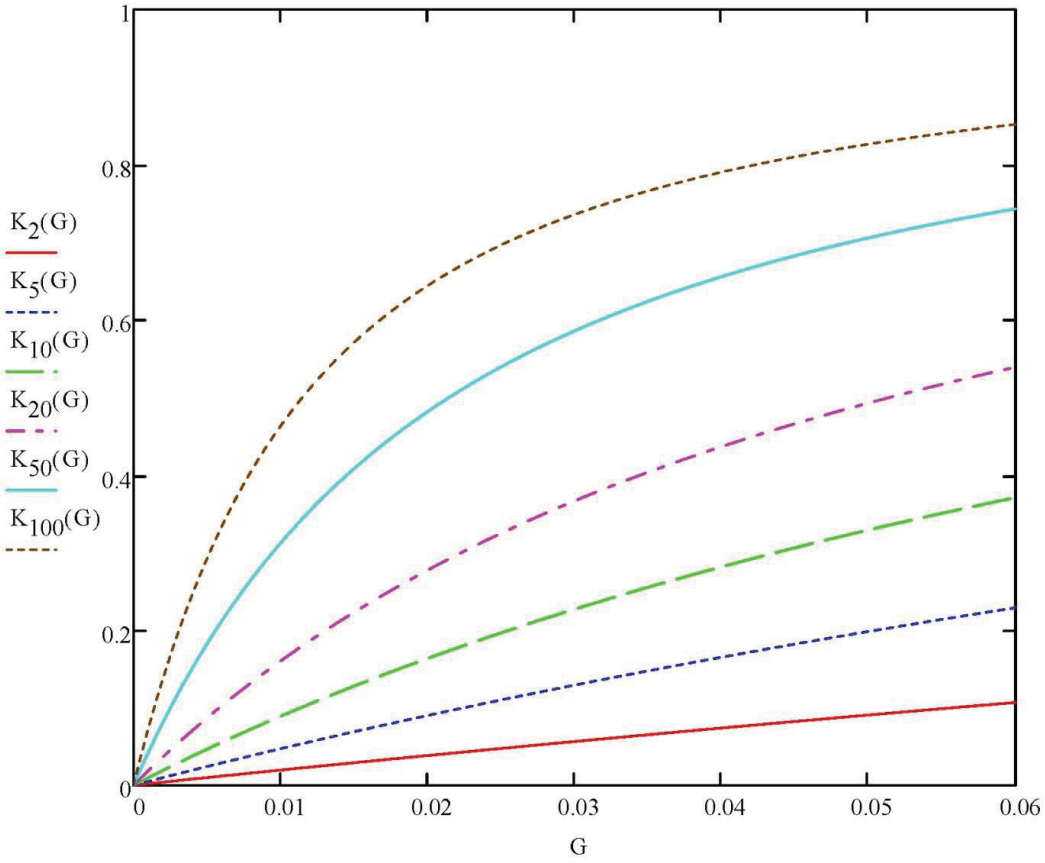


Figure S10: Calculated titration curves for K_{ass} = 2 up to K_{ass} = 100. The change in CIS ($\Delta\delta$, in ppm) is plotted against the concentration of the guest (G, in M^{-1}).

In the normalizing procedure, the CIS at 5 eq. was divided by the CIS at 20 eq. and the CIS at 20 eq. was divided by itself.

$$eq := \begin{pmatrix} 0 \\ 5 \\ 20 \end{pmatrix}$$

$$K_{2n} := \begin{bmatrix} 0 \\ \left(\frac{K_2(5\cdot H)}{K_2(20\cdot H)}\right) \\ 1 \end{bmatrix} \quad K_{5n} := \begin{bmatrix} 0 \\ \left(\frac{K_5(5\cdot H)}{K_5(20\cdot H)}\right) \\ 1 \end{bmatrix} \quad K_{10n} := \begin{bmatrix} 0 \\ \left(\frac{K_{10}(5\cdot H)}{K_{10}(20\cdot H)}\right) \\ 1 \end{bmatrix}$$

$$K_{20n} := \begin{bmatrix} 0 \\ \left(\frac{K_{20}(5\cdot H)}{K_{20}(20\cdot H)}\right) \\ 1 \end{bmatrix} \quad K_{50n} := \begin{bmatrix} 0 \\ \left(\frac{K_{50}(5\cdot H)}{K_{50}(20\cdot H)}\right) \\ 1 \end{bmatrix} \quad K_{100n} := \begin{bmatrix} 0 \\ \left(\frac{K_{100}(5\cdot H)}{K_{100}(20\cdot H)}\right) \\ 1 \end{bmatrix}$$

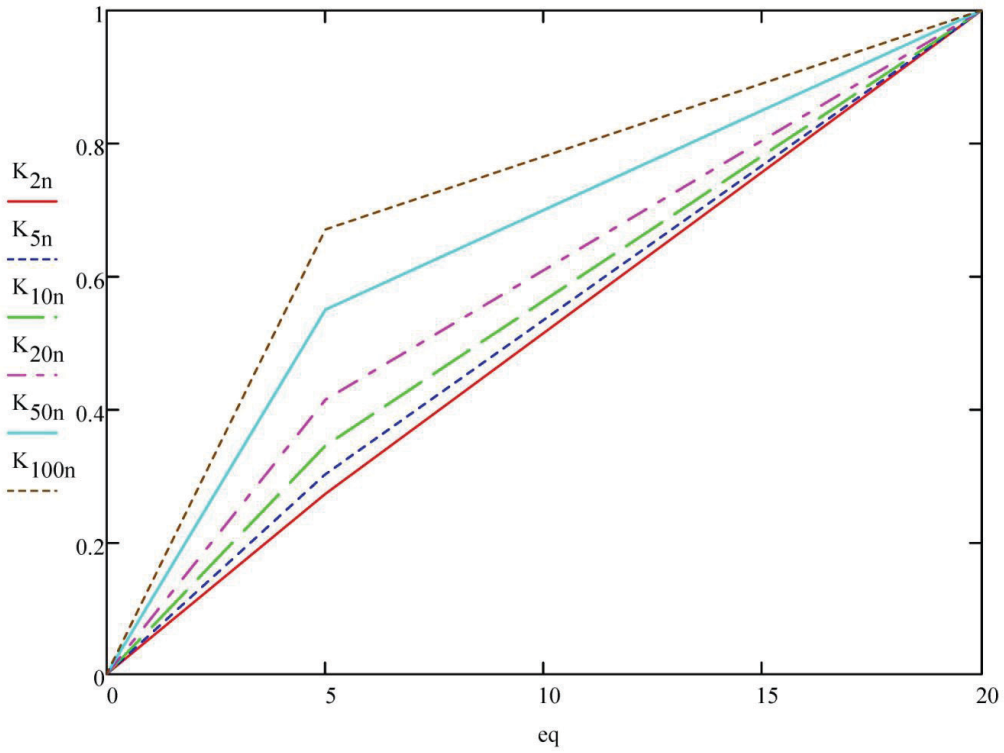


Figure S11: The resulting graph shows the simple correlation between the association constant and the deviation from the diagonal (0,0 → 20,1). The normalized change in CIS ($\Delta\delta_n$, in ppm) is plotted against the number of equivalents of the guest.

In a second test, different titration curves with different $\Delta\delta_{max}$ (0.3, 1, 3 ppm) were simulated at a constant K_{ass} = 20.

$K := 20$

$H := 0.003 \qquad G := 0, 0.0001 .. 0.06$

K = association constant (M^{-1})
G = concentration guest (M^{-1})
H = concentration host (M^{-1})
$\Delta\delta_{max}$ =shift(G_{sat}) - shift (G_0) (ppm)

$\Delta\delta_{max} := 0.3$

$$\Delta\delta_{0.3}(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

$\Delta\delta_{max} := 1$

$$\Delta\delta_{1}(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

$\Delta\delta_{max} := 3$

$$\Delta\delta_{3}(G) := \left[\left[\frac{\Delta\delta_{max}}{(2\cdot H)}\right]\cdot\left[\left[G + H + \left(\frac{1}{K}\right)\right] - \left[\left[(G - H)^2\right] + \left(2\cdot\frac{G}{K}\right) + \left(2\cdot\frac{H}{K}\right) + \left[\frac{1}{(K)^2}\right]\right]^{0.5}\right]\right]$$

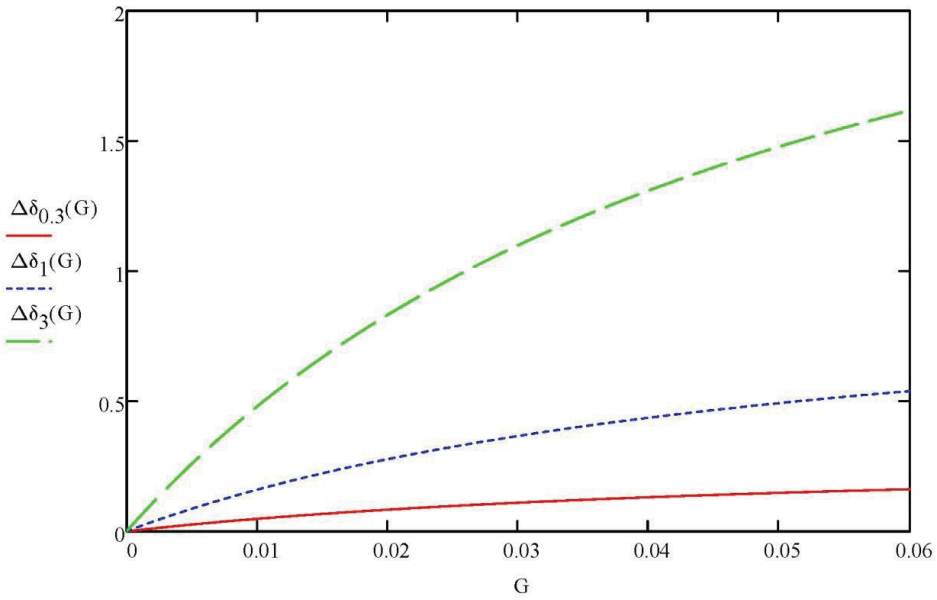


Figure S12: Calculated titration curves for different $\Delta\delta_{max}$ (0.3, 1, 3 ppm) at a constant association constant of 20 M^{-1}. The change in CIS ($\Delta\delta$, in ppm) is plotted against the concentration of the guest (G, in mol L^{-1}).

In the normalized procedure, the CIS at 5 eq. was divided by the CIS at 20 eq. and the CIS at 20 eq. was divided by itself.

$$q := \begin{pmatrix} 0 \\ 5 \\ 20 \end{pmatrix} \qquad \Delta\delta_{0.3n} := \begin{bmatrix} 0 \\ \left(\frac{\Delta\delta_{0.3}(5\cdot H)}{\Delta\delta_{0.3}(20\cdot H)}\right) \\ 1 \end{bmatrix} \quad \Delta\delta_{1n} := \begin{bmatrix} 0 \\ \left(\frac{\Delta\delta_{1}(5\cdot H)}{\Delta\delta_{1}(20\cdot H)}\right) \\ 1 \end{bmatrix} \quad \Delta\delta_{3n} := \begin{bmatrix} 0 \\ \left(\frac{\Delta\delta_{3}(5\cdot H)}{\Delta\delta_{3}(20\cdot H)}\right) \\ 1 \end{bmatrix}$$

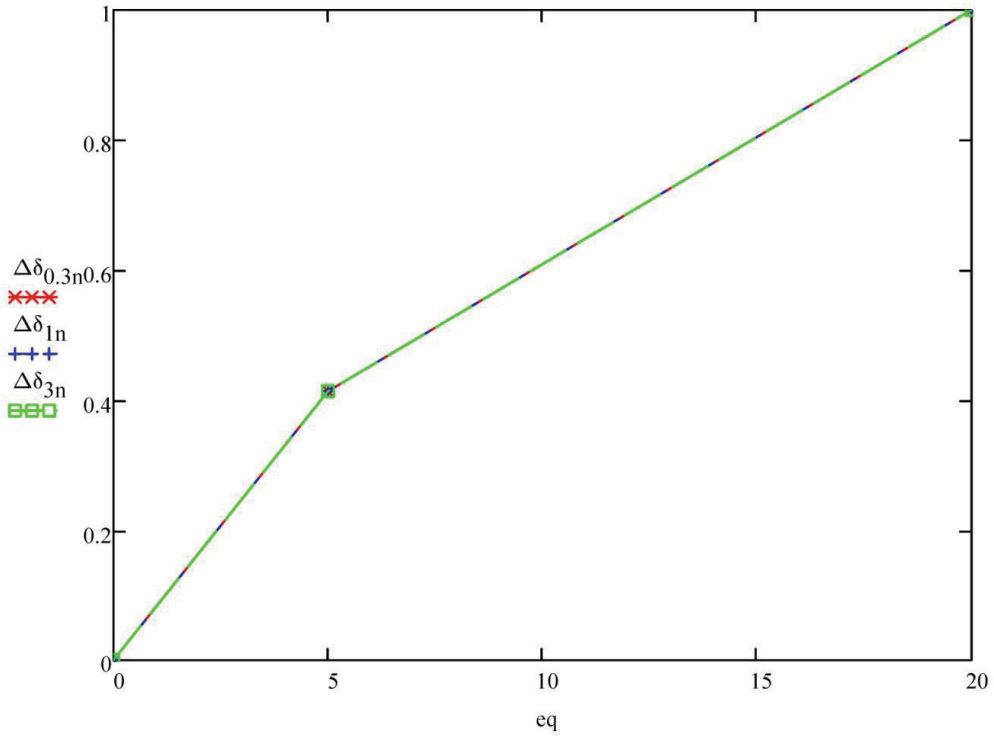
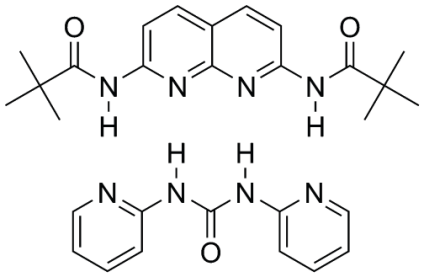


Figure S13: The resulting graph shows that the normalizing CIS method is not influenced by the maximum CIS of a titration experiment ($\Delta\delta_{max}$).

In an additional test, all six different association constants were permuted with these three different $\Delta\delta_{max}$ with results analogous to those already presented.

A cross-check of the normalized CIS method was carried out for a ^{1}H NMR titration with a small binding constant of K_{ass}= 37 M^{-1}, published in the literature [1,2].



By the normalizing CIS method employing only two points, an approximate association constant of K_{ass} = ca. 40 M^{-1} was determined.

All calculations were carried out by using Mathcad® 15.0 (Parametric Technology Corporation).

^{1}H NMR titration of 1 with pyridine-*N*-oxide

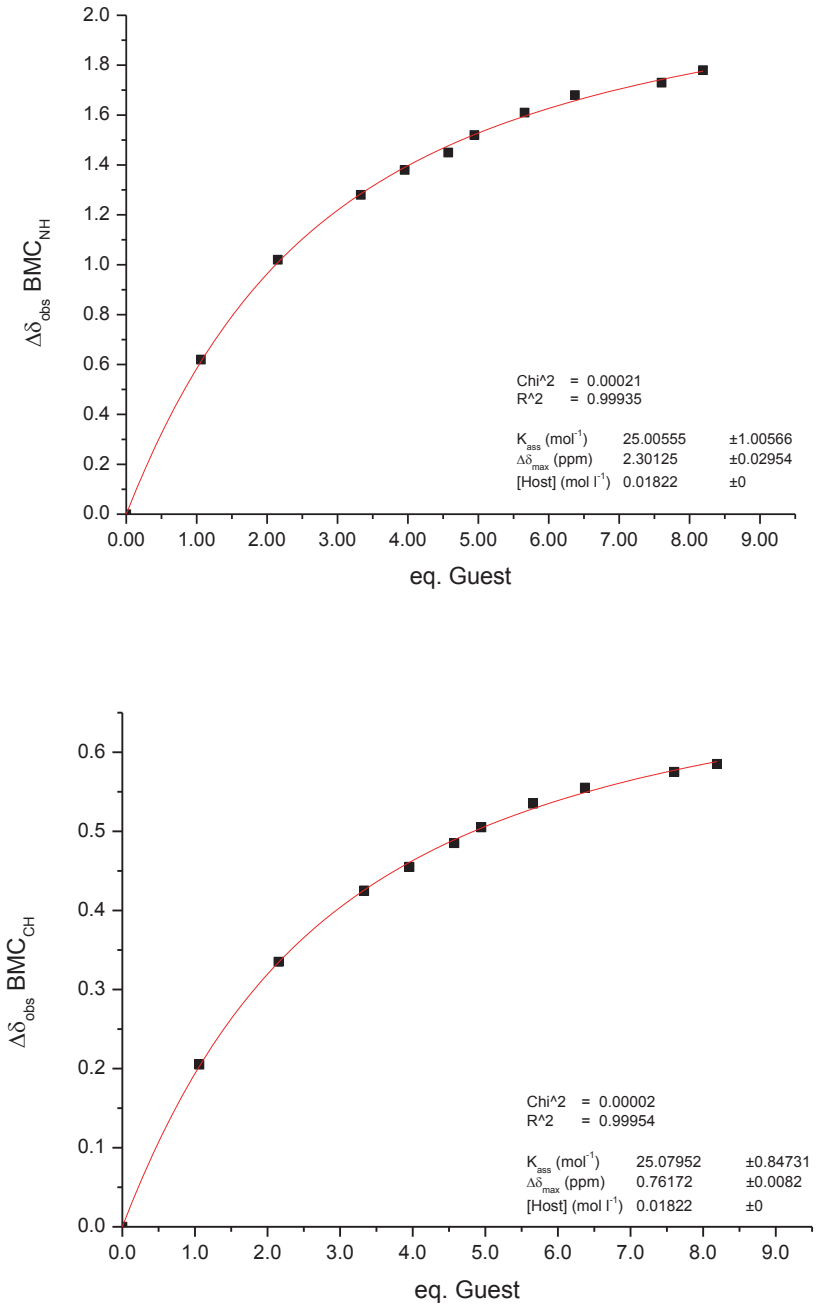


Figure S14: NMR titration of **1** and pyridine-*N*-oxide (500 MHz, 298 K, CD_2Cl_2). To a solution of **1** (7.72 mg in 600 µL CD_2Cl_2) was added pyridine-*N*-oxide (in CD_2Cl_2) in ten steps. Two signals were observed: amide NH (top) and the *endo*-CH (bottom), both resulting in K_{ass} = 25 mol^{-1} L.

^{1}H,^{1}H NOESY experiments

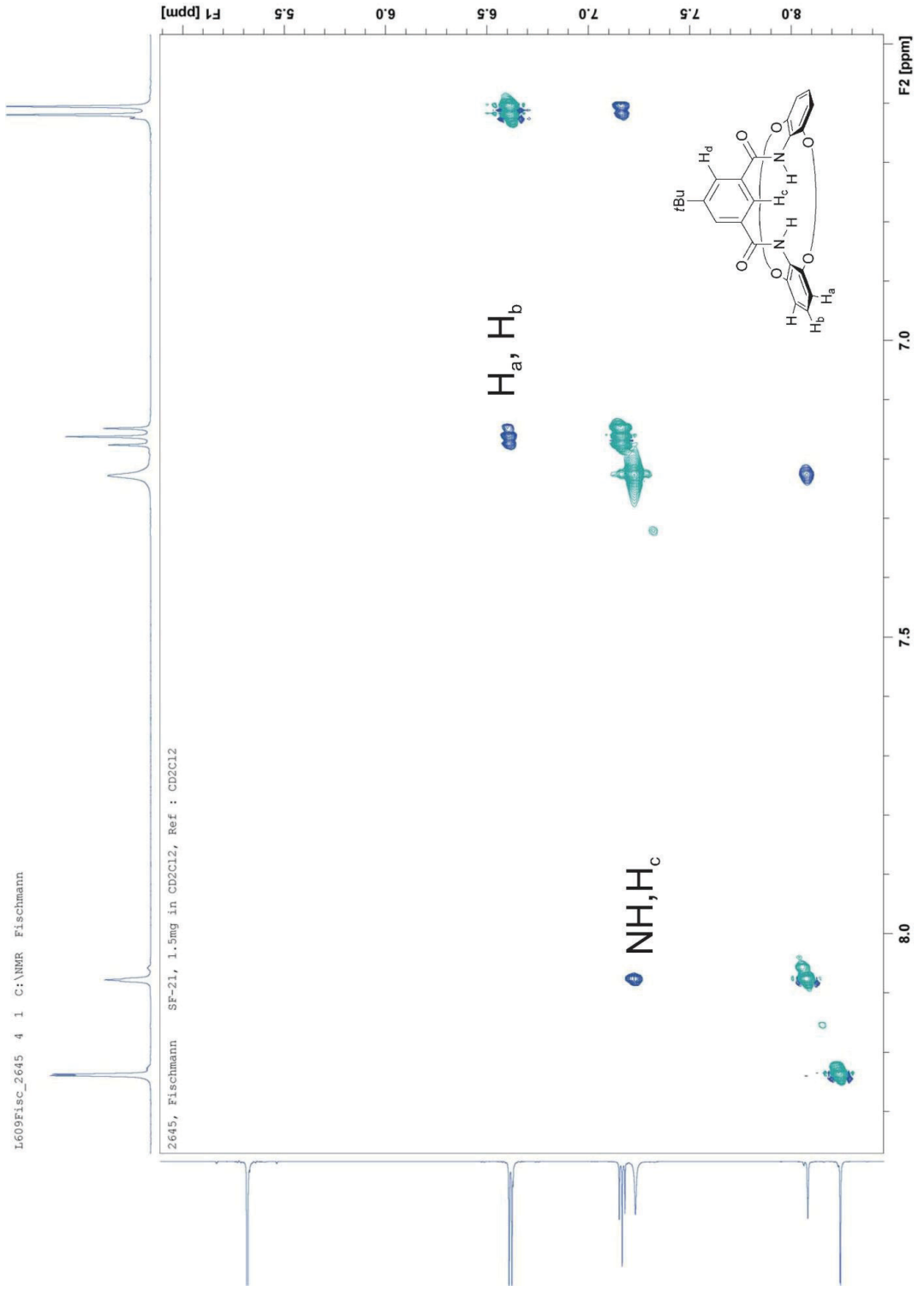


Figure S15: Bi-macrocycle **1**. NOESY experiment, selected signals (600 MHz, 298 K, CD_2Cl_2).

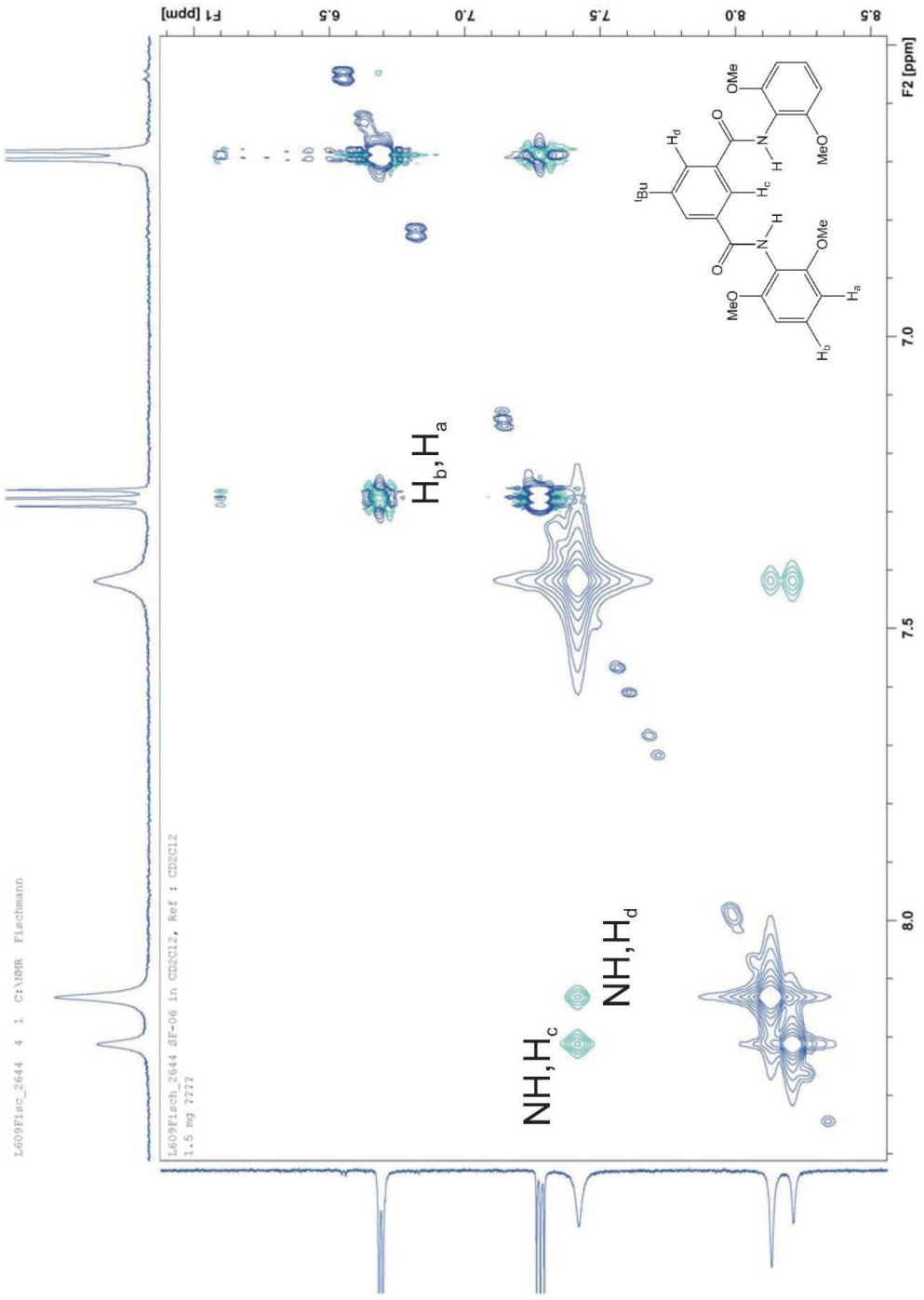


Figure S16: Isophthalamide **2**. NOESY experiment, selected signals (600 MHz, 298 K, CD_2Cl_2).

Transport experiments

Preparation of phospholipid vesicles: The solvent of a solution of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC, Genzyme) in chloroform (20 mg/mL) was evaporated to leave a lipid film. This was then dried under vacuum for 12 h. The lipid film was rehydrated with a solution of sodium chloride (476 mM of NaCl, 10 mM of phosphate buffer, pH = 7.2) and shaken by vortex. The suspension was then subjected to nine freeze–thaw cycles and 29 extrusions through a 200 nm polycarbonate Nucleopore membrane by using a LiposoFast Basic extruder (Avestin) to obtain unilamellar vesicles with a mean diameter of 200 nm. Finally, the suspension was dialysed against a $NaNO_3$ solution (476 mM $NaNO_3$ and 10 mM phosphate buffer, pH = 7.2) to remove unencapsulated NaCl.

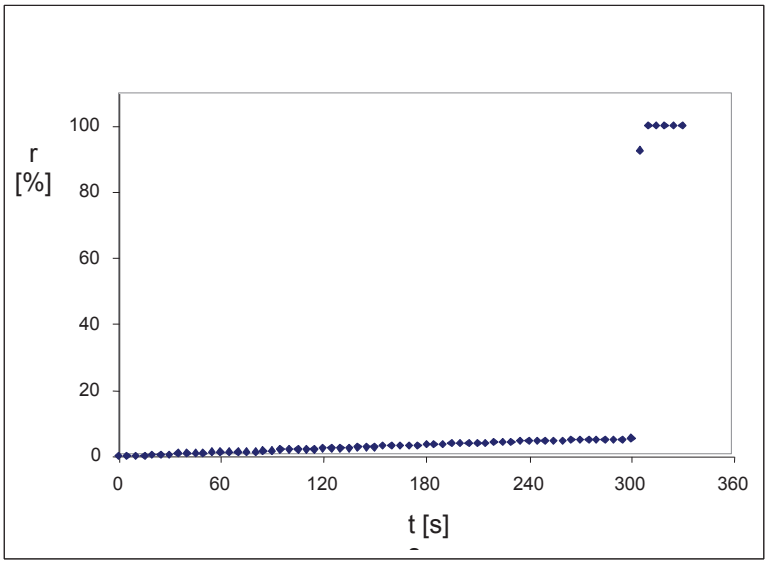


Figure S17: Chloride efflux upon addition of **2** (50 µM, 10 mol % carrier to lipid) to vesicles composed of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC). The vesicles contained NaCl (476 mM NaCl and 10 mM phosphate buffer, pH 7.2) and were immersed in $NaNO_3$ (476 mM $NaNO_3$ and 10 mM phosphate buffer, pH 7.2). Once the electrode reading was stable the carrier was added and the chloride efflux was monitored for 5 min. At the end of the experiment, the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent a 100% release and used as such.

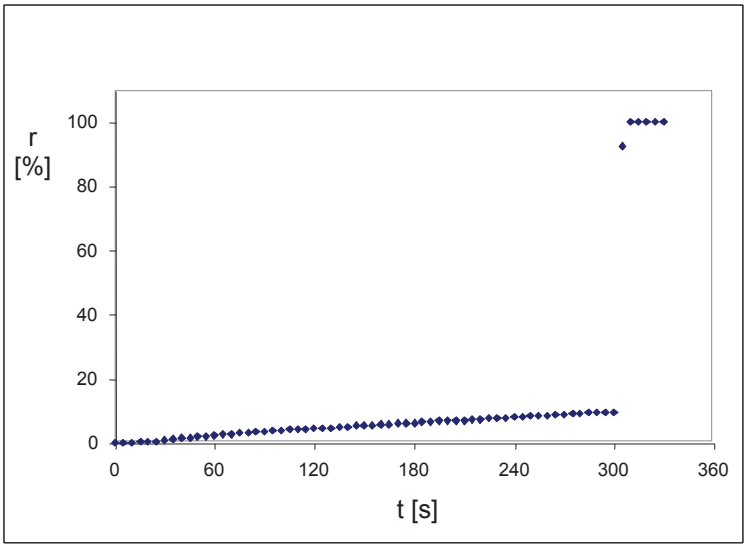


Figure S18: Chloride efflux upon addition of **1** (50 µM, 10 mol-% carrier to lipid) to vesicles composed of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC). The vesicles contained NaCl (476 mM NaCl and 10 mM phosphate buffer, pH 7.2) and were immersed in $NaNO_3$ (476 mM $NaNO_3$ and 10 mM phosphate buffer, pH 7.2). Once the electrode reading was stable the carrier was added and the chloride efflux was monitored for 5 min. At the end of the experiment, the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent a 100% release and used as such.

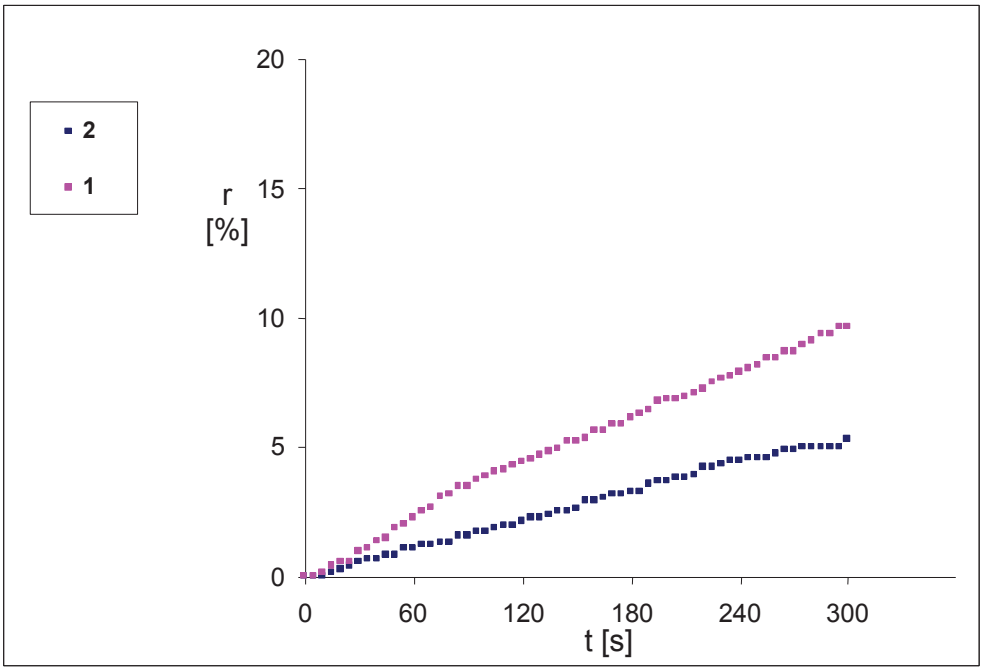


Figure S19: Comparison between chloride effluxes from chloride loaded liposomes promoted by the isophthalamides **1** and **2**.

References

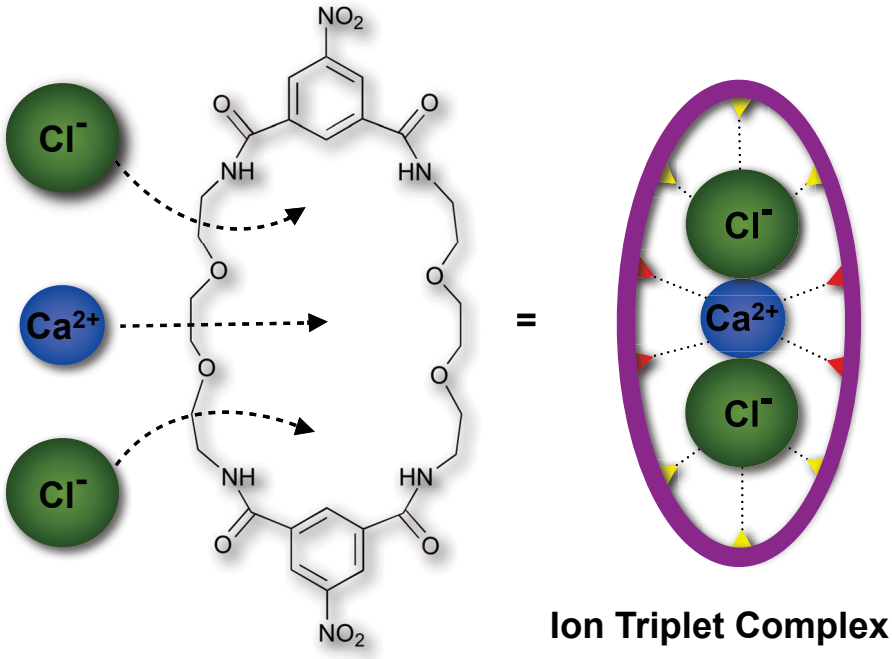
1. Kühl, C.; Lüning, U. *Tetrahedron Lett.* **1998,** *39,* 5735–5738. doi:10.1016/S0040-4039(98)01200-3

2. Kühl, C. Ph.D. Thesis; Christian-Albrechts-Universität zu Kiel, 1998.

3.6 The First Supramolecular Ion Triplet Complex

J. Eckelmann, V. Saggiomo, F. D. Sönnichsen, U. Lüning, *New J. Chem.* **2010**, *34*, 1247-1250. DOI: 10.1039/C0NJ00160K

Ausgehend von 5-Nitroisophthalsäurechlorid und 1,8-Diamino-3,6-dioxaoctan konnte ein [2+2]-Makrozyklus erhalten werden. Das Isophthalsäuregerüst fand bereits in den Hamilton-Rezeptoren zur Erkennung von Barbituraten und Isocyanursäuren Anwendung. Zur Herstellung dieses Makrozyklus wurde von dem in der Literatur üblichen Zweikomponenten-Verdünnungsprinzip abgewichen und mit konzentrierten Lösungen gearbeitet. Hierbei konnten neben dem [2+2]- auch weitere Makrozyklen ([1+1], [3+3], [4+4]) beobachtet werden.



Der [2+2]-Makrozyklus zeichnete sich durch seine besondere Struktur aus. Neben den zwei Isophthalamidköpfen, welche die Erkennung von Anionen ermöglichen, besaß dieser auch zwei Ethylenglykolketten, die in Kronenethern für ihre Kationenbindung bekannt sind. Es wurde überprüft, welche Alkali- bzw. Erdalkalichloride der Makrozyklus in Chloroform binden bzw. aus dem Feststoff aufnehmen kann. Hierbei wurden in Zusammenarbeit mit SAGGIOMO ^{1}H-NMR-Experimente durchgeführt. Dabei zeigte der Makrozyklus eine Selektivität von LiCl gegenüber NaCl und KCl, bzw. von $CaCl_2$ gegenüber $MgCl_2$ und $BaCl_2$. Dieser tritope Makrozyklus konnte Calciumchlorid als Ionentriplett in organischen Lösungen binden und dieses war, nach unserem besten Wissen, der erste supramolekulare Ionentriplett-Komplex. NOESY- und ESI-MS-Experimente, die in Zusammenarbeit mit SÖNNICHSEN durchgeführt wurden, konnten diesen Ionentriplett-Komplex bestätigen.

LETTER www.rsc.org/njc | New Journal of Chemistry

The first supramolecular ion triplet complex†‡

Jens Eckelmann, Vittorio Saggiomo, Frank D. Sönnichsen and Ulrich Lüning*

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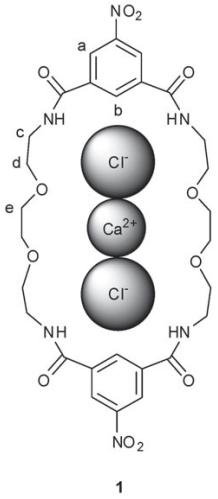
DOI: 10.1039/c0nj00160k

A neutral tritopic macrocycle 1 was obtained by condensation of a diacid dichloride 2 with a diamine 3. 1 contains three binding sites: two for anions by hydrogen bonding and one for cations by ether oxygen atoms. The selective binding of LiCl and $CaCl_2$ has been studied by NMR and MS techniques. 1 is the first host to form a supramolecular complex with an ion triplet: 1·$CaCl_2$.

In supramolecular chemistry, macrocycles have always been widely used to complex different organic and inorganic guests.[1] For a long time, chemists focused their attention on the complexation of cations and anions, with the latter task being more challenging due to the large size, different shapes and the high polarisability of anions.[2] Nowadays, the importance of targeting ion-pairs of salts as guests is growing.[3] In this field, ditopic hosts are usually synthesized as neutral compounds, in which the ditopic nature of the receptor allows to bind both cation and anion in adjacent binding units in close contact.[4] With the matching cation for the contact pair formation in the host–guest complex, it is possible to enhance the binding of a particular anion or *vice versa*.[5]

Although this field is growing and many different ditopic molecules have been synthesized in the last five years, there is still a lack of hosts for complexing alkaline earth metal halides. In order to reach this goal, chemists must move from ditopic hosts to tritopic hosts. In these, two binding units for anions and one for a cation comprise the sites needed for the complexation of an alkaline earth metal halide as ion triplet.[6,7] In this work, we present the neutral tritopic host **1** that is capable to bind an alkaline earth metal salt, and binds calcium dichloride as an ion triplet with high selectivity. To the best of our knowledge, the formation of complex **1**·$CaCl_2$ is the first description of a supramolecular ion triplet complex for alkaline earth metal salts (Fig. 1).[8]

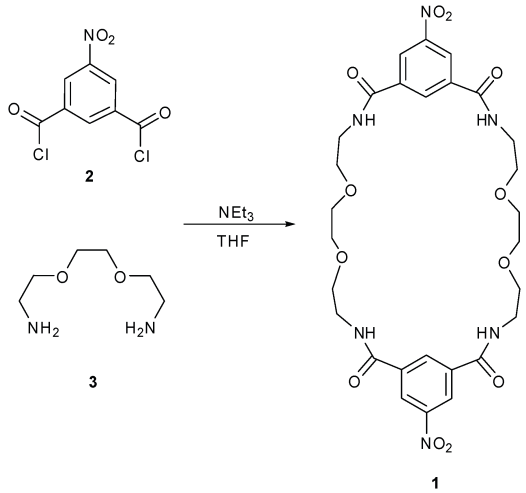
The synthesis of macrocycle **1** is straightforward and starts from two building blocks: diacid dichloride **2** and diamine **3** (see Scheme 1). In order to obtain and study macrocycles of different sizes, we used a combinatorial approach which gave the [2 + 2]-macrocycle **1** (Fig. 1), together with [1 + 1]-, [3 + 3]-, and [4 + 4]-macrocycles and linear products which are not described here. After a simple one-step condensation of diacid dichloride **2** and diamine **3** in the presence of triethylamine, the [2 + 2]-macrocycle **1** could be isolated from the resulting mixture by chromatography (Scheme 1).



1

Fig. 1 Calcium dichloride complex with macrocycle **1** and hydrogen labeling scheme. For structural studies, see ESI.‡

Macrocycle **1** displays three binding sites (tritopic macrocycle): four NH amides in two different isophthalamide residues, well known to complex anions,[9] and four oxygen atoms in the diethylene glycol part able to complex cations.



Scheme 1 Synthetic scheme for the formation of macrocycle **1**.

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† Dedicated to Prof. Dr Bernd Giese on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Experimental and spectroscopic details of **1**. NMR and MS complexation studies, and calculations. See DOI: 10.1039/c0nj00160k

Additionally it has two nitro groups that can be further modified, *e.g.* by reduction. The neutral macrocycle **1** possesses D_{2h} symmetry giving rise to a simple ^{1}H-NMR spectrum: two triplets for the NH and H_d protons, a doublet for H_a, a broad singlet for the H_b and a singlet for the H_e protons.

The easily interpretable and clean ^{1}H-NMR spectra were used to investigate the capability of this tritopic macrocycle **1** to bind salts as contact ions, and to detect their extraction from solid into an organic solvent. A stock solution (2.5 mM) of **1** in $CDCl_3$ with 5% of DMSO-d_6 was allowed to stand over an excess of powdered alkaline and alkaline earth metal chlorides in different NMR tubes. After 12 h, ^{1}H-NMR spectra were recorded and analyzed for differences in chemically induced shifts (CIS) between the free macrocycle **1** and the complexes (Fig. 2).

When comparing the solutions containing the alkaline chlorides LiCl, NaCl and KCl, the NMR spectra clearly show that macrocycle **1** is capable of binding lithium chloride selectively over other alkaline metal chlorides, as the ^{1}H-NMR spectra do not show any change when sodium chloride or potassium chloride is used. In the case of lithium chloride, a significant CIS of NH (−0.88 ppm) and H_b (−0.65 ppm) was detected (Fig. 2, LiCl). The large downfield shift of almost 1 ppm of the amide proton is indicative of the formation of hydrogen bonds to the chloride anion (NH···Cl) in the presence of DMSO.[10] A small difference in the chemical shifts of H_a (−0.08 ppm), not involved in the binding, was also detected. In the diethylene glycol chains, upfield CIS for H_e (+0.04 ppm) and downfield CIS for H_d (−0.05 ppm) were observed. Due to the key importance of lithium salts as drug in different diseases,[11] it is an interesting goal to develop lithium receptors and sensors.[12] The challenge is to bind it selectively over competing ions such as sodium. Macrocycle **1** achieves this task in an organic solvent complexing selectively LiCl as contact ion pair over NaCl.

Additionally, alkaline earth metal dichlorides ($MgCl_2$, $CaCl_2$, $BaCl_2$) were screened applying the same methodology. Indeed, macrocycle **1** is able to form an ion triplet complex **1**·$CaCl_2$, but remarkably only with the calcium salt. The distinct differences in CIS for $MgCl_2$, $CaCl_2$ and $BaCl_2$ show a strong selectivity of macrocycle **1** for calcium dichloride over magnesium and barium dichloride. Although in the presence of magnesium and barium dichloride the NH signal shows a modest CIS (−0.14 and −0.24 ppm, respectively), a prominent NH downfield shift (−0.90 ppm) is observed only when calcium dichloride is used (Fig. 2, $CaCl_2$). The calcium dichloride complex (**1**·$CaCl_2$) shows proton shifts similar to the lithium chloride complex (**1**·LiCl). Only H_e is shifted more upfield (+0.06 ppm) with respect to **1**·LiCl which reflects a different side chain orientation. Due to different sizes of magnesium, calcium and barium, macrocycle **1** is able to complex selectively calcium dichloride as a *contact ion-triplet*. To the best of our knowledge, this is the first neutral macrocycle that binds an alkaline earth metal dihalide as contact ion-triplet.[13]

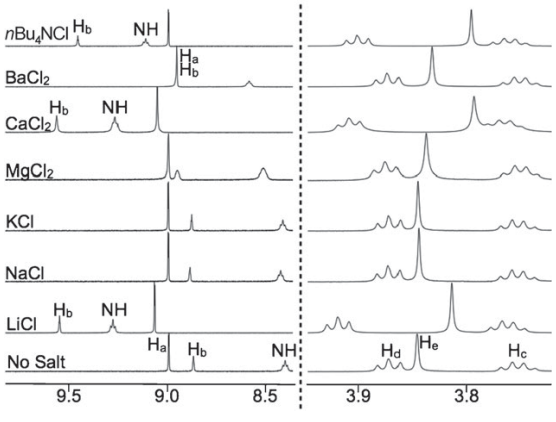

Fig. 2 Expanded sections of ^{1}H-NMR spectra (500 MHz, 298 K, $CDCl_3$/DMSO-d_6 95 : 5) of **1** in the presence of different salts. For proton assignments see Fig. 1.

Mass analyses confirm the strong complexing ability of macrocycle **1** for LiCl and $CaCl_2$ (see ESI‡). When ESI-MS spectra (negative ion mode) were recorded directly from the NMR solutions with either lithium chloride or calcium dichloride, it was possible to detect a single peak as **1** + Cl^- (m/z = 681.20). The ESI-MS scan of **1**·$CaCl_2$ in the positive mode showed two peaks attributable to complex **1**·$CaCl_2$: (**1** + Ca^{2+})/2 (m/z = 343.10) and **1** + $CaCl^+$ (m/z = 721.14). On the other hand, the ESI spectra of the lithium chloride complex **1**·LiCl showed only the protonated peak **1** + H^+, but for this complex the MALDI-TOF spectrum revealed **1** + Li^+ (m/z = 653.31).

To obtain further insight into the complexation of the salts by macrocycle **1**, detailed NOESY experiments were carried out.[14] A stock solution of **1** in $CDCl_3$ (*ca.* 2.5 mM) with 7% of DMSO-d_6[15] was used to record 2D-NOESY spectra in three different NMR tubes: in the absence of salt, in the presence of excess of powdered lithium chloride, and in the presence of excess of powdered calcium dichloride.

Table 1 compiles the proton–proton distances as calculated from the NOESY measurements. When the obtained distances for the free macrocycle **1** are compared to those in the complexes, significant differences are apparent. In pure macrocycle **1**, the average proton–proton distances of H_a–NH and H_b–NH were found to be quite similar. The NH proton is at the same average distance from H_a and H_b, indicating that the benzene ring is capable of rotating around the Ar–CO bond. Thus in about half of the population, NH is close to H_a, and in the other half, NH is close to H_b, resulting in almost identical average distances of 2.6 Å (H_b–NH) and 2.7 Å (H_a–NH) in the free macrocycle.

Table 1 Average proton–proton distances[16] (Å) in macrocycle **1** based on NOESY experiments. For proton labels see Fig. 1

	1	**1**·LiCl	**1**·$CaCl_2$
H_b–NH	2.6	2.85	2.5
H_a–NH	2.7	4.5	4.1
NH–H_c	3.1	3.3	2.95
NH–H_d	3.5	3.85	3.4
H_b–H_c	4.3	4.8	4.3
H_b–H_d	4.0	5.0	4.7
H_a–H_c	4.1	4.6	4.1
H_a–H_d	3.9	—	—

The distances H_a–NH and H_b–NH respond differently to the addition of salts, *i.e.* the binding of chloride anions by hydrogen bonding, as they become different in both the **1**·LiCl and **1**·$CaCl_2$ complexes. The average proton–proton distance between NH and H_a increased considerably, thus on average H_a moved away from NH, while at the same time the apparent NH–H_b distance is shortened. Both facts can be explained by the binding of the NH protons to the chloride anions. In fact, the complex must have been rigidified upon complexation and the two protons (NH and H_a) are now further away from one another, while at the same time H_b spends more time in close proximity to the NH proton. It is interesting to note that also the distances between H_b and H_d increase upon complexation from 4 Å to 5 Å (**1**·LiCl) and 4.7 Å (**1**·$CaCl_2$), respectively.

Finally, we carried out first orientational experiments to quantify the formation of the supramolecular complexes of **1**. The salts are insoluble in the solvents used for the NMR investigations, especially $CaCl_2$.[17] But with a mixture of anhydrous calcium perchlorate and tetrabutylammonium chloride in $CHCl_3$/DMSO (93 : 7), we were able to carry out isothermal titration calorimetry (ITC) experiments with receptor **1**. The results must not be overinterpreted due to the insolubility problems and also to the fact that the mixture changes the ionic strength. Nevertheless, binding constants for 1 : 1 complexes in the range of 10^3 to 10^4 in $CHCl_3$/DMSO could be determined for $CaCl_2$ (by use of a $Ca(ClO_4)_2$/$n$$Bu_4NCl$ mixture), and for LiCl (by use of a $Li(ClO_4)$/$n$$Bu_4NCl$ mixture) and $n$$Bu_4NCl$.

In conclusion, a facile and accessible synthesis of macrocycle **1** has been described. The ability of **1** to complex LiCl and $CaCl_2$ was proven by means of ^{1}H-NMR and mass analyses. In solution, its conformational change in the presence of guests was analyzed and described using NOESY experiments. All these experiments concentrate on the fact that the neutral macrocycle **1** complexes calcium dichloride in its ion-triplet form. This ion-triplet receptor should be useful in different applications such as selective extraction from solid mixtures (industrial application), membrane transport (calcium is an essential element for biological life, and chloride concentration controls several processes in the cell), chemosensing, homogeneous catalysis and phase transfer catalysis. In our laboratory the screening of some of these applications is work in progress.

Experimental

16,33-Dinitro-6,9,23,26-tetraoxa-3,12,20,29-tetraazatricyclo-[29.3.1.1^{14,18}]hexatriaconta-1(35),14,(36),15,17,31,33-hexaen-2,13,19,30-tetraone (**1**): a solution of 5-nitroisophthaloyl dichloride (1.00 g, 4.03 mmol) in tetrahydrofuran (20 mL) was added dropwise over 20 min to a stirred solution of 1,8-diamino-3,6-dioxaoctane (5.06 g, 5.00 mL, 34.1 mmol) and triethylamine (2.50 mL, 1.83 g, 18.0 mmol) in tetrahydrofuran (20 mL). The solution was stirred for 24 h. The solvent and excess of triethylamine was evaporated under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and washed with water (4 × 50 mL). The combined extracts were dried with magnesium sulfate and evaporated under reduced pressure to yield a yellow solid, which was purified by column chromatography on silica using dichloromethane/methanol/triethylamine (20 : 1 : 1, R_f = 0.47) as eluent to give macrocycle **1** (110 mg, 8%) as a white solid. δ_H (500 MHz; $CDCl_3$/DMSO-d_6 95 : 5 v/v; TMS): 3.59 (8H, m, O–CH_2–CH_2–NH), 3.68 (8H, s, O–CH_2–CH_2–O), 3.71 (8H, t, J = 5.2, O–CH_2–CH_2–NH), 8.39 (4H, t, J = 5.5, NH), 8.77 (2H, s, Ar), 8.84 (4H, d, J = 1.3, Ar); δ_C (125 MHz, $CDCl_3$/DMSO-d_6 95 : 5 v/v, TMS): 39.54, 39.71, 39.88, 40.05, 40.21, 40.38, 40.55 (DMSO-d_6 and CH_2–NH), 69.21, 70.14 (CH_2–O–CH_2), 125.04 (Ar-C-4, Ar-C-6), 131.05 (Ar-C-2), 136.22 (Ar-C-1, Ar-C-3), 148.27 (Ar-C-5), 164.66 (C═O); IR (ATR): $\tilde{\nu}_{max}$/cm^{-1} 3275 (NH), 3091 (Aryl-H), 2866 (CH_2), 1649 (CO), 1580, 1557 and 1528 (C═C), 1123 (C–O–C); m/z (ESI): 669.2284 (M + Na^+, $C_{28}H_{34}N_6O_{12}Na^+$ requires 669.2127).

Acknowledgements

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Notes and references

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13 To provethe chloride complexing abilities of macrocycle **1**, tetrabutylammonium chloride (nBu$_4$NCl) was used as salt. And even in this case, the shifts of the protons are comparable with **1**·LiCl and **1**·$CaCl_2$ complexes. Nevertheless, the NH protons are shifted more when $CaCl_2$ or LiCl was used instead of nBu$_4$NCl (naked chloride). The CIS of the ethylene glycol protons are more similar to the CIS of **1**·$CaCl_2$ than to that of **1**·LiCl.
14 Unfortunately, up to now it was not possible to obtain a single crystal of **1**·$CaCl_2$. Besides, if the complexation shall be exploited in applications such as for instance transport it must be studied in solution anyway.
15 In comparison to the first binding experiments, a slightly higher concentration of DMSO was used in order to ensure a homogeneous organic phase, needed to record reliable NOESY spectra.
16 2D-NOESY experiments with varying mixing times were used to analyze the conformation and mobility of the free macrocycle and the complexes. Using a two-spin approximation and two known distances as a reference, average interproton distances were calculated from all observed NOE intensities after peak integration as described in ESI.‡ In a mobile structure, the distances are physically meaningless *i.e.* they do not describe a single conformation, their differences upon ion binding however indicate changes in the combination of short distances and population of the conformations present.
17 $CaCl_2$ and LiCl are insoluble in the solvent mixture used and are extracted into these solvents only by **1**. Therefore, a titration with portions of the solid salt into a solution of host **1** cannot be interpreted when excess salt is added. For this reason, the preliminary binding studies were done with salts which are soluble in the solvent mixture: $Ca(ClO_4)_2$, $Li(ClO_4)$ and nBu$_4$NCl.

Supplementary Material (ESI) for New Journal of Chemistry

Supplementary Information For:

The first supramolecular ion triplet complex

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Contents:

Supplementary Material (ESI) for New Journal of Chemistry

General Remarks

All reagents were obtained from commercial sources and used without additional purification unless otherwise indicated. 5-Nitroisophthaloyl dichloride was prepared from 5-nitroisophthalic acid and thionyl chloride according to Vögtle and De Cola.[1] 1,8-Diamino-3,6-dioxaoctane was obtained from Fluka. THF was freshly distilled from lithium aluminum hydride (triphenylmethane as indicator). All reactions were carried out in an atmosphere of nitrogen. NMR spectra were recorded with Bruker DRX 500 or AV 600 instruments. Assignments are supported by COSY, HSQC and HMBC. All chemical shifts are referenced to TMS. Mass spectra were recorded with a Finnigan MAT 8200 or MAT 8230. ESI mass spectra were recorded with an Applied Biosystems Mariner Spectrometry Workstation. IR spectra were recorded with a Perkin-Elmer Spectrum 100, equipped with an ATR unit. Elemental analyses were carried out with a EuroEA 3000 Elemental Analyzer from Euro Vector. MALDI-TOF spectra were recorded with a Bruker-Daltonics Biflex III. 4-Chloro-α-cyanocinnamic acid (Cl-CCA) was used as a matrix.

Supplementary Material (ESI) for New Journal of Chemistry

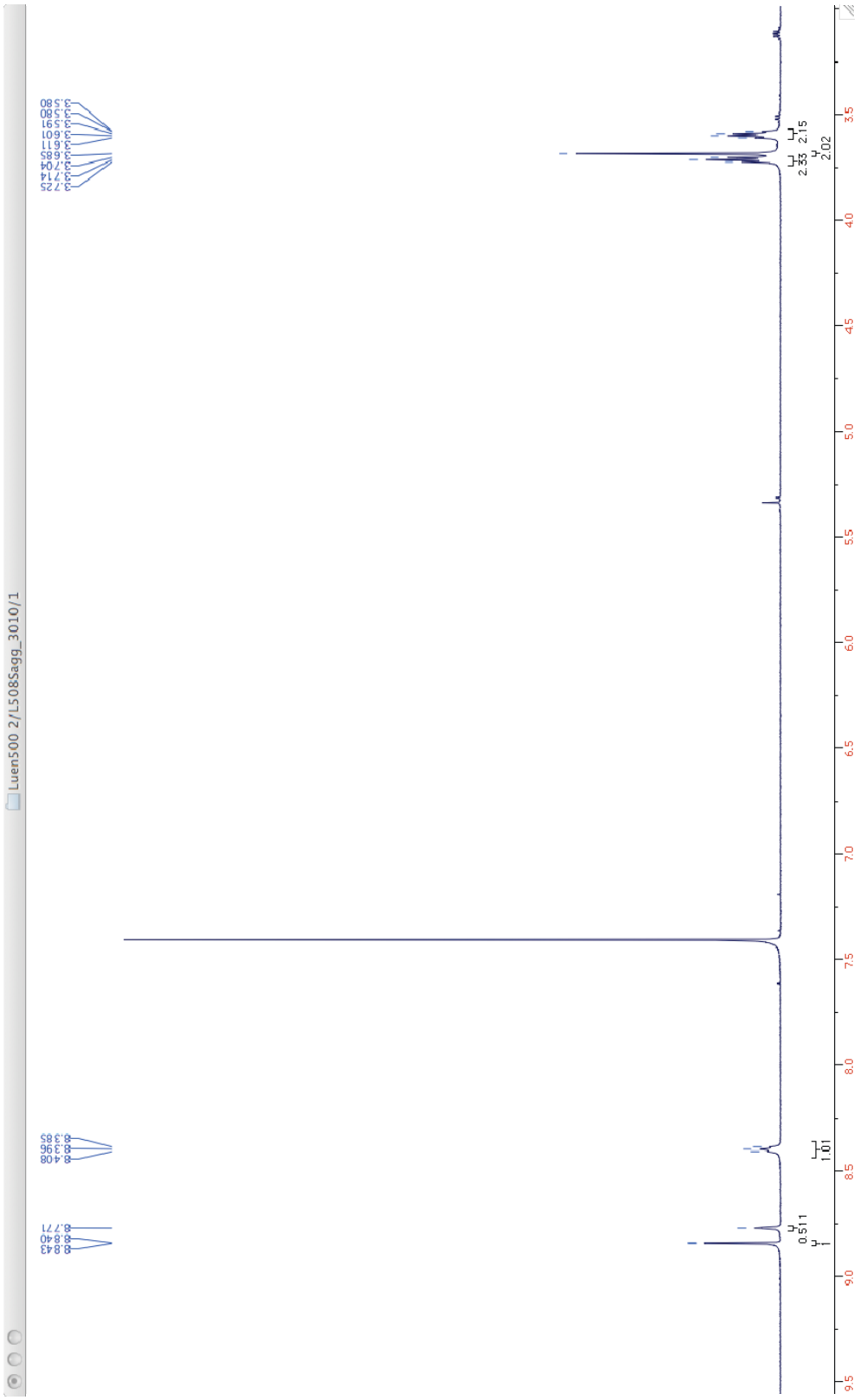

Figure 1: ^{1}H-NMR (500 MHz; 298 K; $CDCl_3$/DMSO-d6 95:5 v/v; TMS) of **1.**

Supplementary Material (ESI) for New Journal of Chemistry

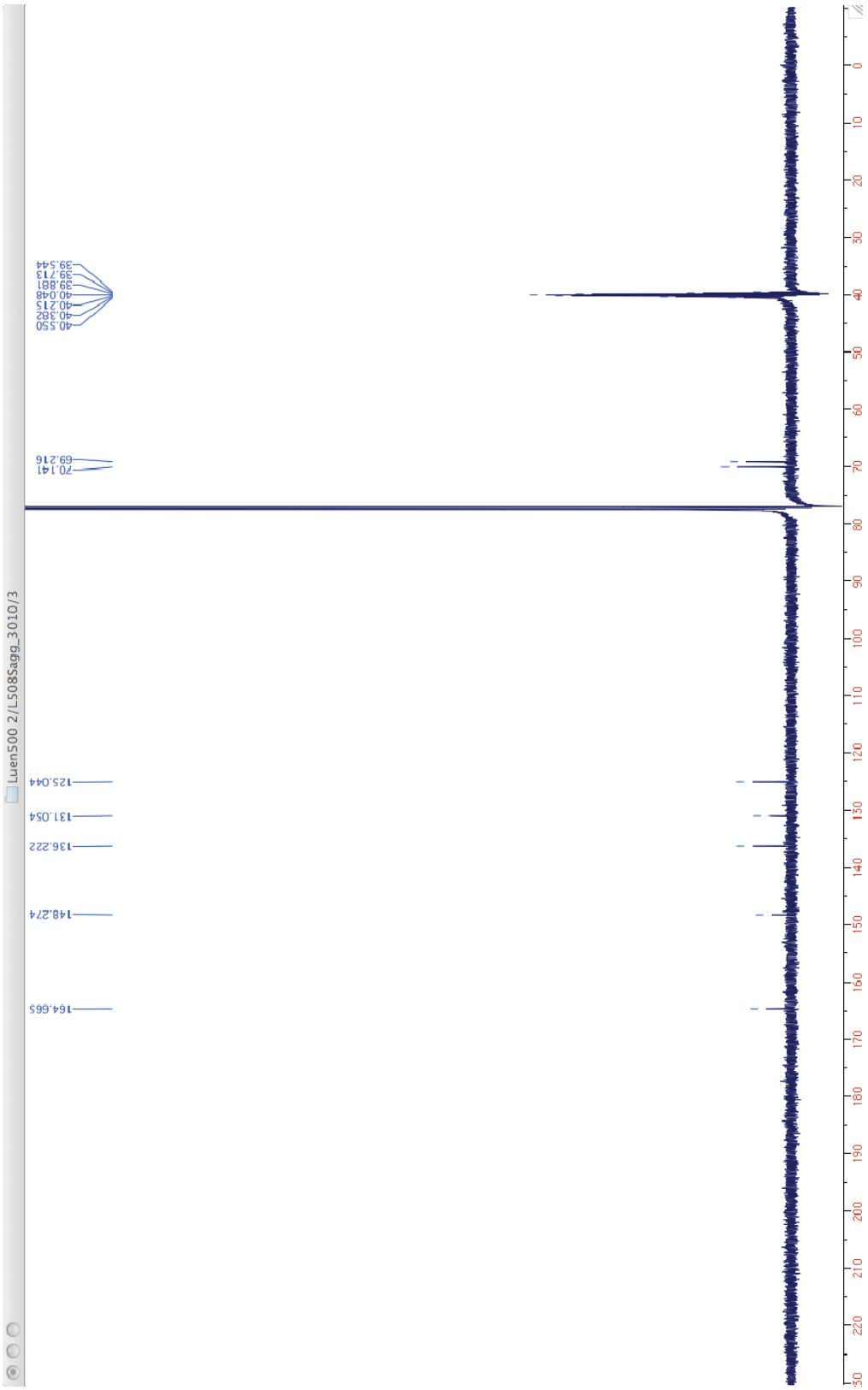

Figure 2: ^{13}C-NMR (125 MHz,298 K, $CDCl_3$/DMSO-d6 95:5 v/v, TMS) of **1.**

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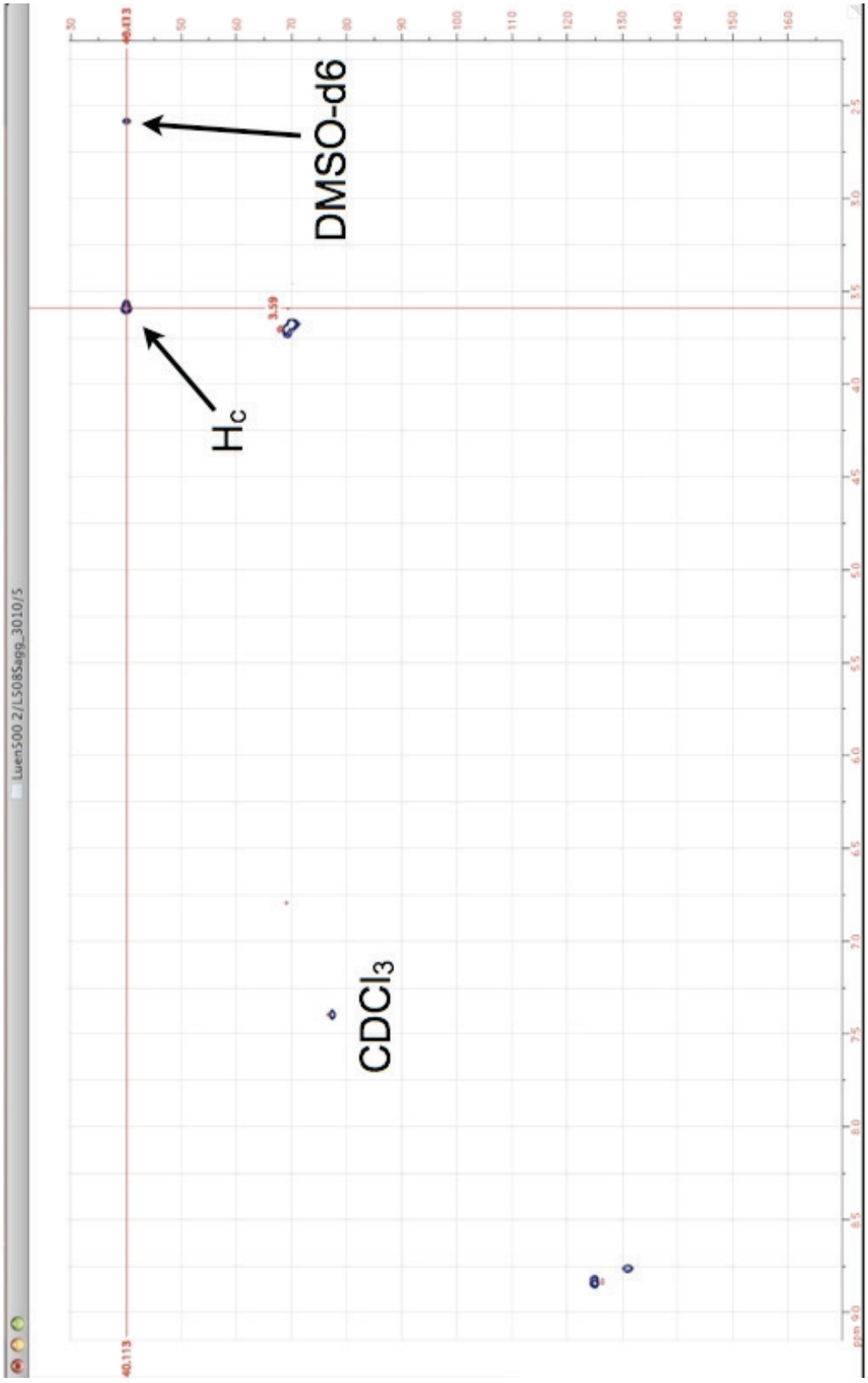

Figure 3: HSQC of **1**. The CH_2NH carbon is overlapping with DMSO-d6 carbons.

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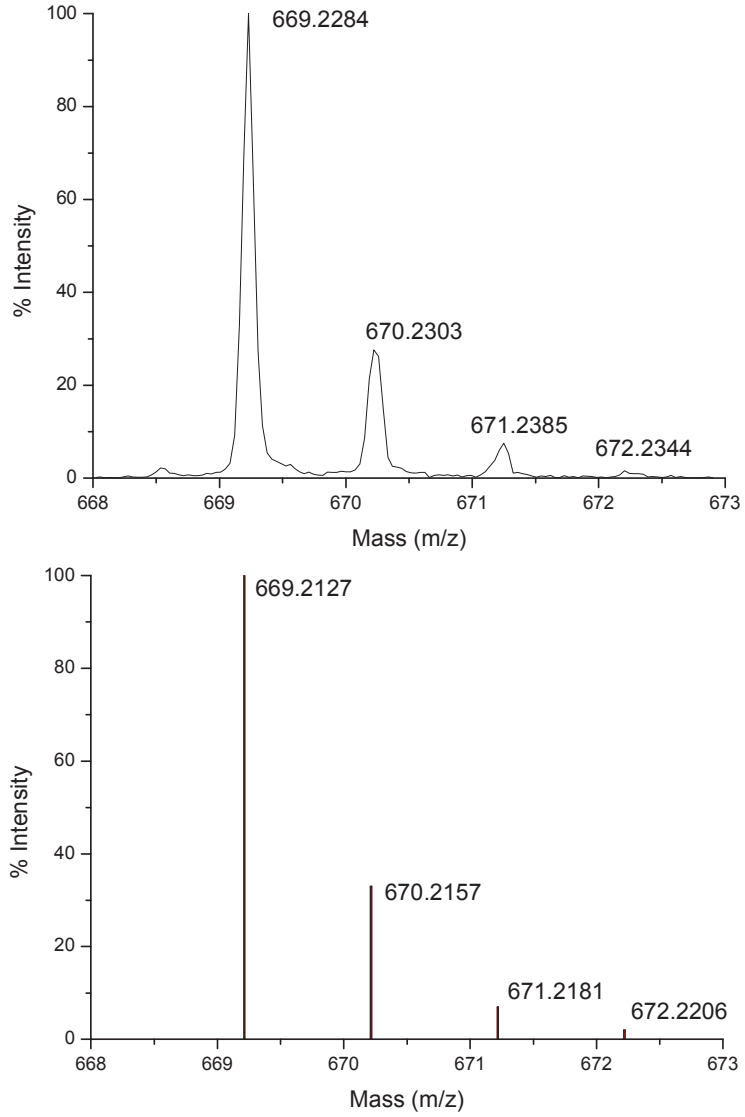

Figure 4: Measured (top) and predicted (bottom): ESI-MS spectra (positive mode) of **1** ($C_{28}H_{34}N_6O_{12}$+Na^+).

Supplementary Material (ESI) for New Journal of Chemistry

^{1}H-NMR Experiment

8.0 mg (1.2 µmol) of **1** was dissolved in 5.0 mL of a mixture of $CDCl_3$/DMSO-d6 (95:5, v/v). 600 µL of this stock solution was then transferred into different NMR tubes containing various excess of salts. The tubes were fluxed with nitrogen, capped and sealed with PARAFILM®. The NMR spectra were recorded after 12 h.

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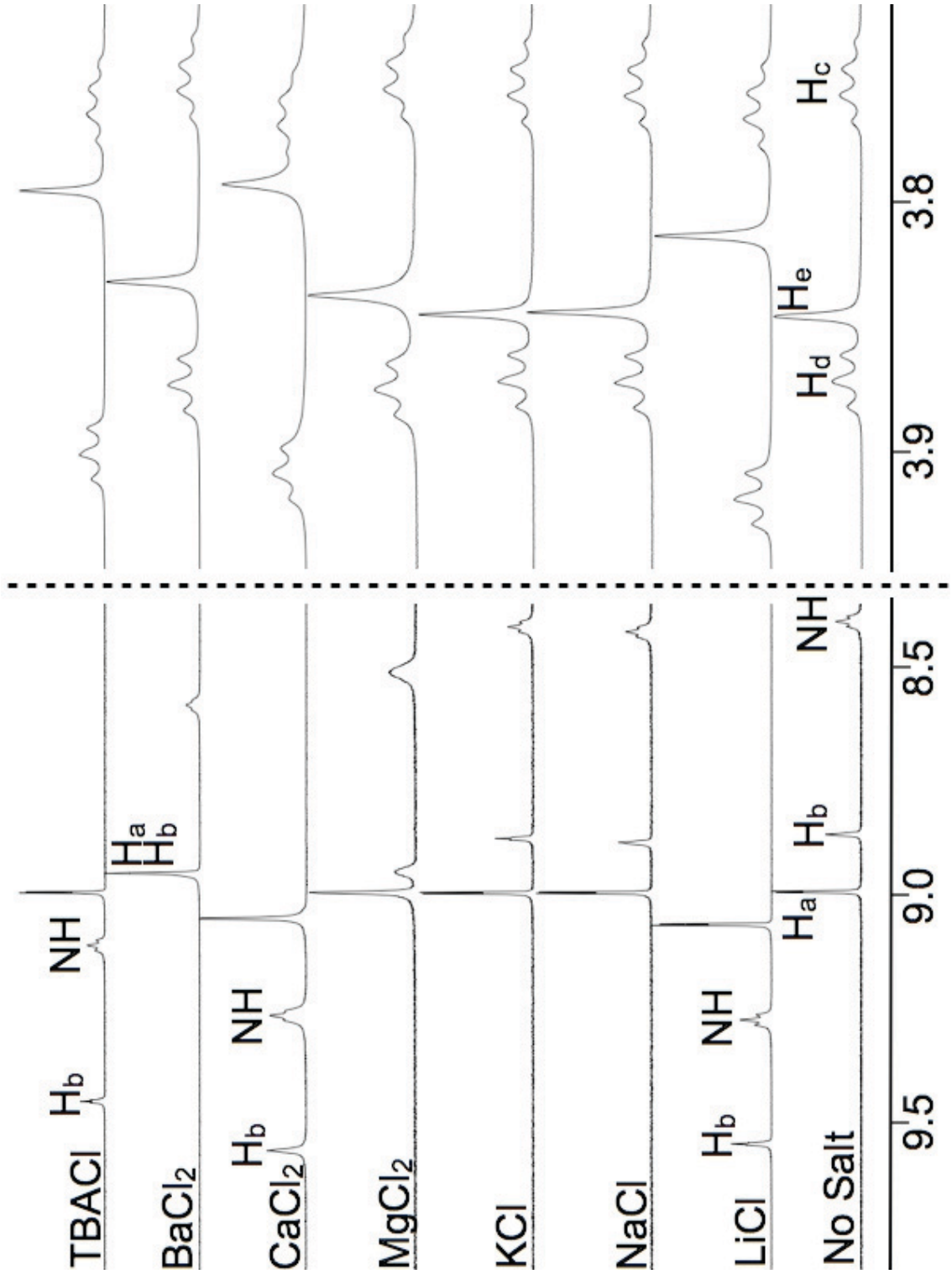

Figure 5: ^{1}H-NMR spectra in presence of different salts.

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MS experiments :

Directly from the NMR tubes, a drop of solution was used to carry out the mass spectrometry experiments.

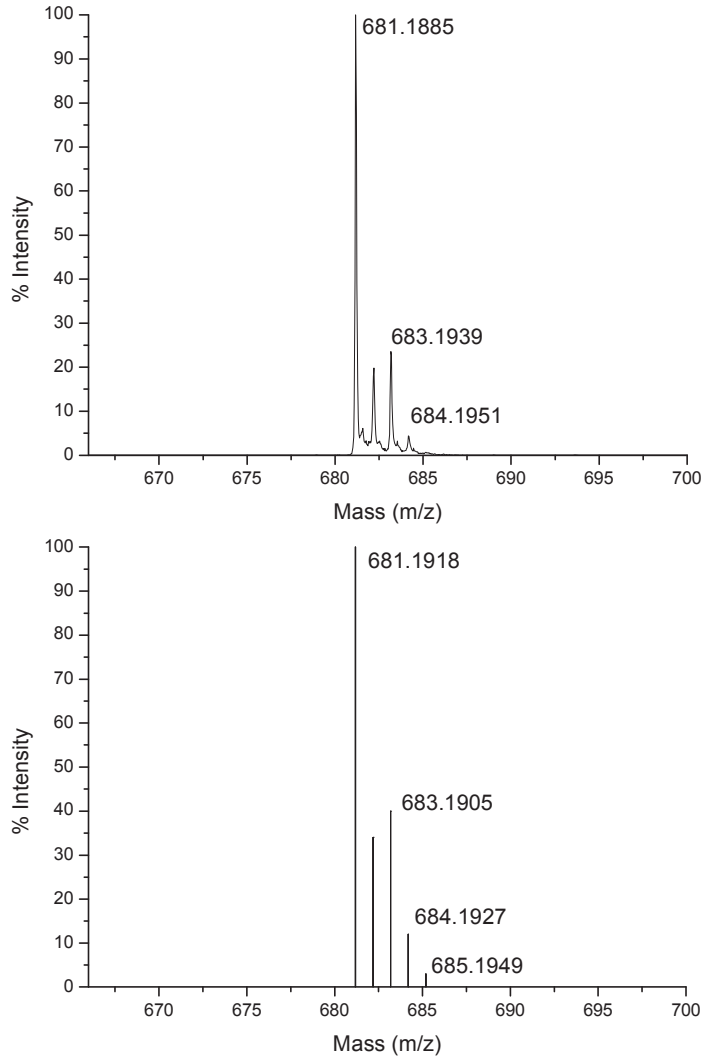

Figure 6: Measured (top) and predicted (bottom): ESI-MS spectra (negative mode) of **1**·$CaCl_2$ ($C_{28}H_{34}N_6O_{12}$+Cl^-).

Supplementary Material (ESI) for New Journal of Chemistry

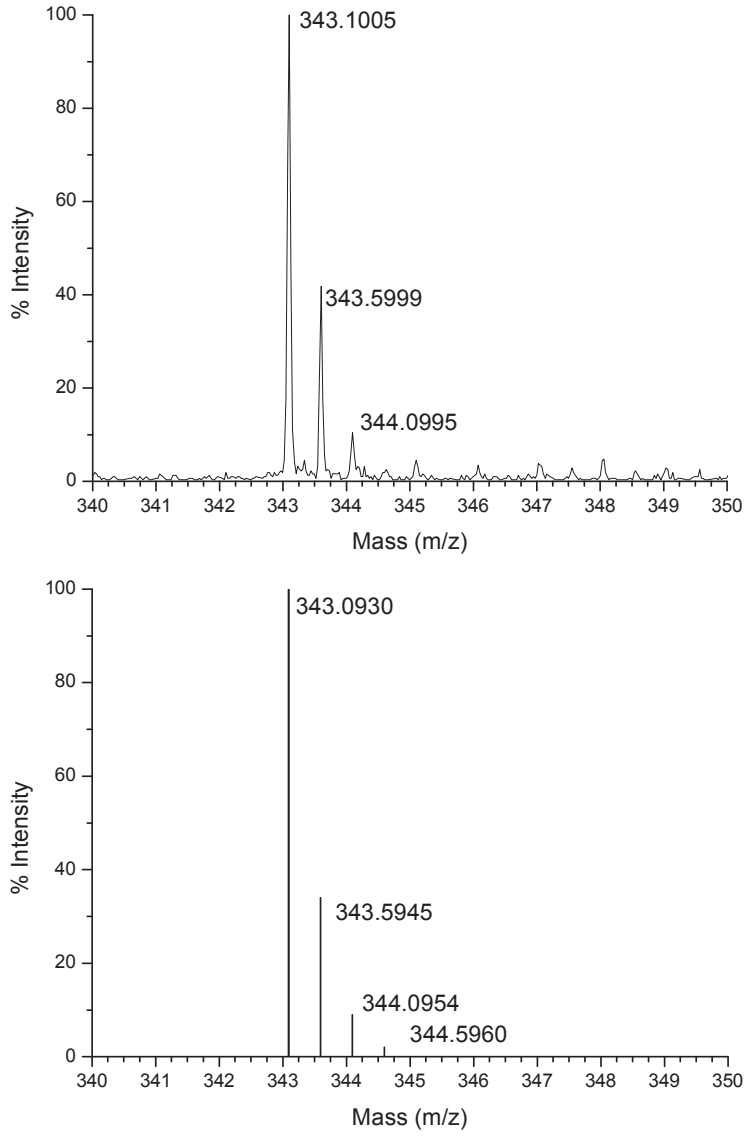

Figure 7: Measured (top) and predicted (bottom): ESI-MS spectra (positive mode) of **1**·$CaCl_2$ ($C_{28}H_{34}N_6O_{12}$+Ca^{2+}/2).

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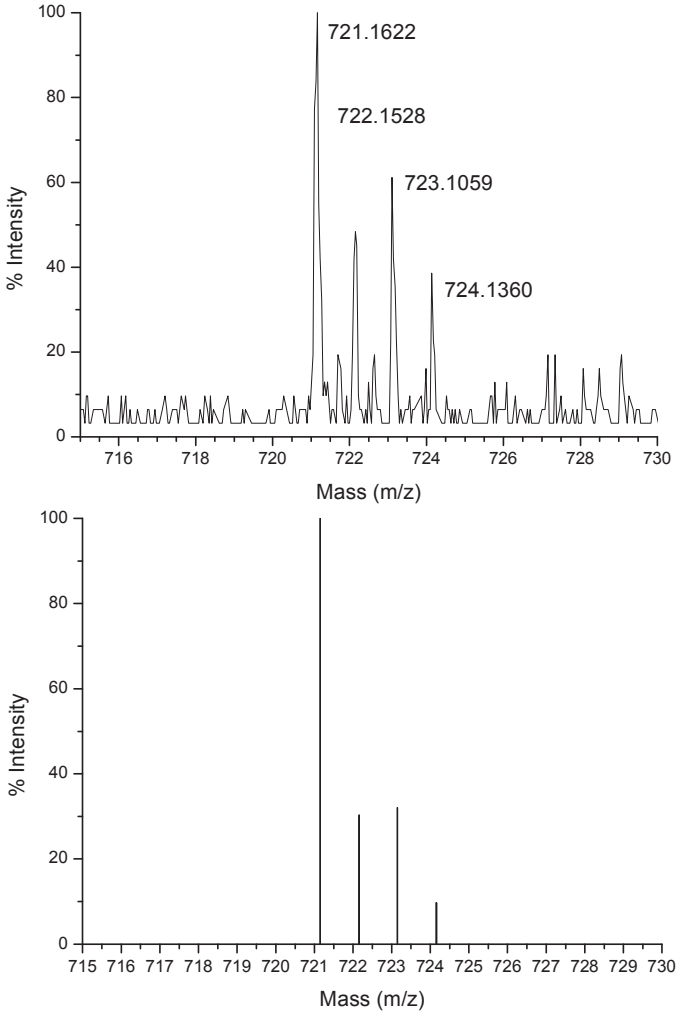

Figure 8: Measured (top) and predicted (bottom): ESI-MS spectra (positive mode) of **1**·$CaCl_2$ ($C_{28}H_{34}N_6O_{12}$+$CaCl^+$).

Supplementary Material (ESI) for New Journal of Chemistry

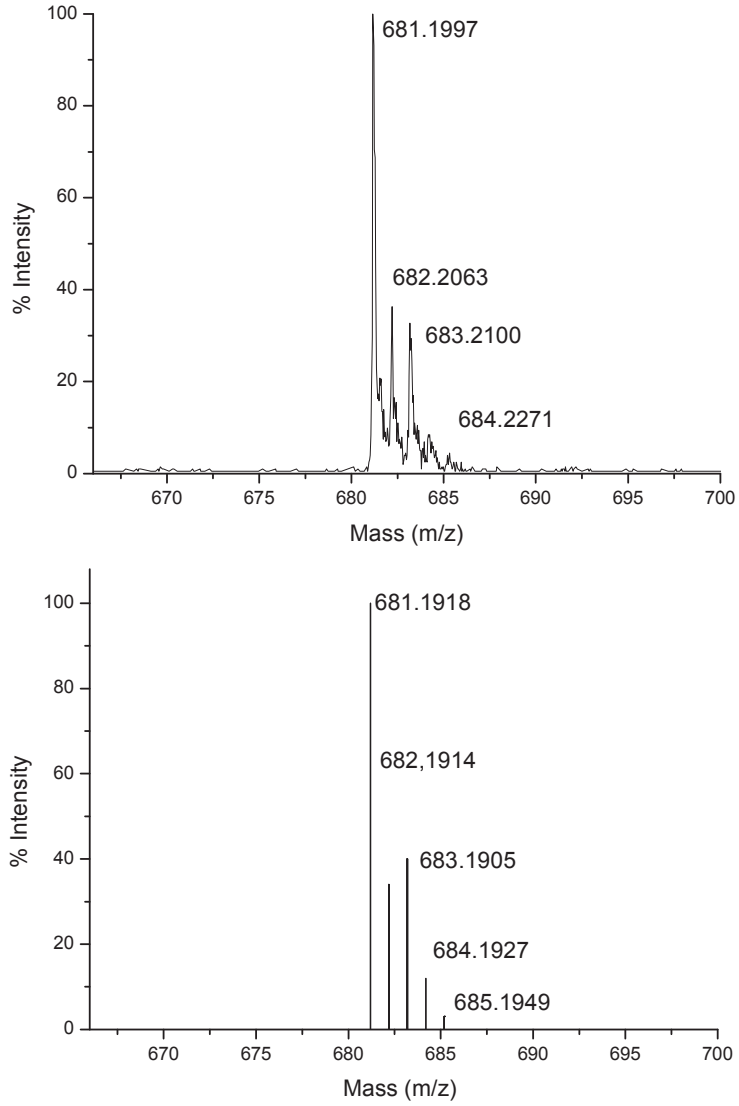

Figure 9: Measured (top) and predicted (bottom): ESI-MS spectra (negative mode) of **1**·LiCl ($C_{28}H_{34}N_6O_{12}$+Cl^-).

Supplementary Material (ESI) for New Journal of Chemistry

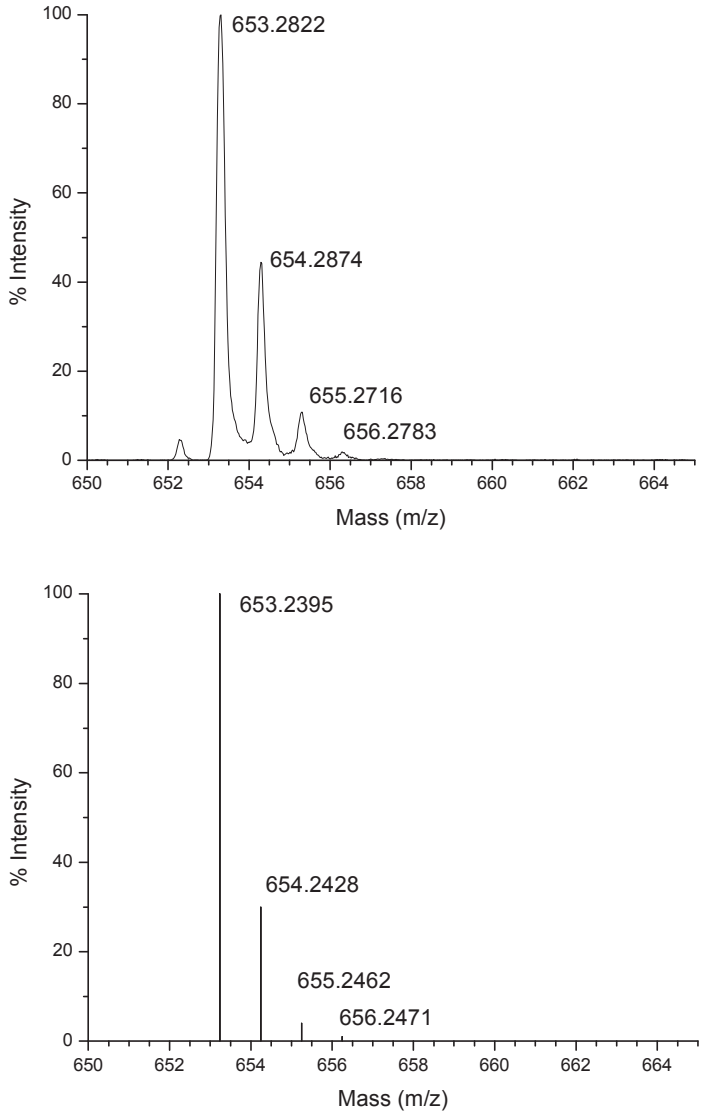

Figure 10: Measured (top) and predicted (bottom): MALDI-TOF spectra (Cl-CCA) of **1**·LiCl ($C_{28}H_{34}N_6O_{12}$+Li^+).

Supplementary Material (ESI) for New Journal of Chemistry

2D-NOESY experiments:

Using the NMR samples prepared as described above, phase sensitive 2D-NOESY experiments were acquired at 298 K with mixing times of 300 and 600 ms on a Bruker DRX500 instrument.

Spectra were acquired with 8 scans and a repetition delay of 2 sec, spectral widths of 4300 Hz, and 2048/128 total data points in F2 and F1 dimensions, respectively.

The data was zerofilled in F1 to 1028 real data points, weighted in both dimension with 90°-shifted squared sinebell function. Cross peaks were integrated after baseline correction. The obtained peak volumes were converted into distances using a two-spin approximation. For intensity calibration, the constant distance of H_a-H_b was used as a reference. When this NOE cross peak was not available due to overlap, the NOE between NH and H_c was used, assuming an average distance of 3.1 Å. All processing was performed with Topspin 2.1 (Bruker Biospin, Germany).

Supplementary Material (ESI) for New Journal of Chemistry

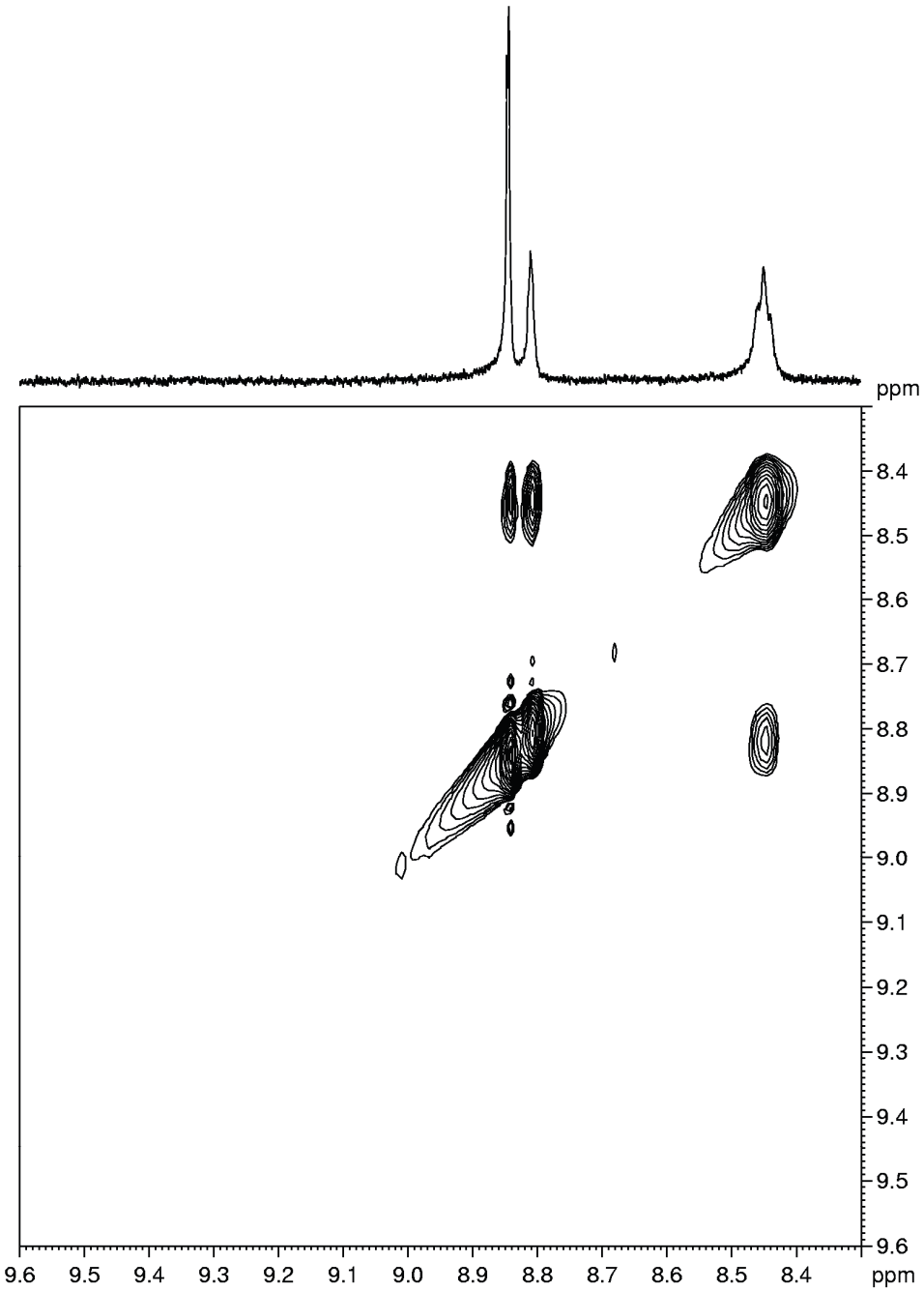

Figure 11: NOESY NMR (500 MHz; 298 K; $CDCl_3$/DMSO-d6 93:7 v/v; TMS) spectrum of **1**.

Supplementary Material (ESI) for New Journal of Chemistry

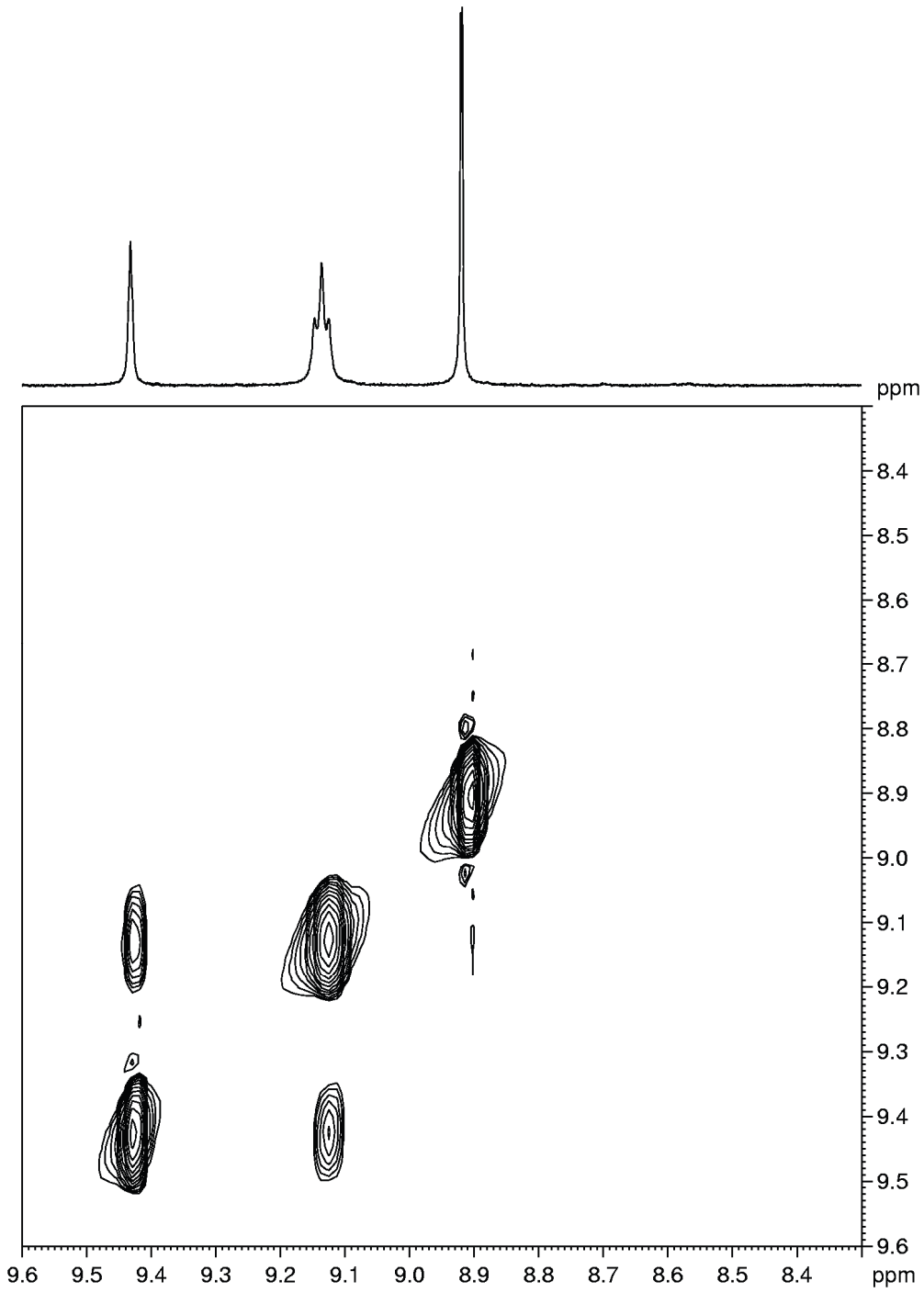

Figure 12: NOESY NMR (500 MHz; 298 K; $CDCl_3$/DMSO-d6 93:7 v/v; TMS) spectrum of **1**·LiCl.

Supplementary Material (ESI) for New Journal of Chemistry

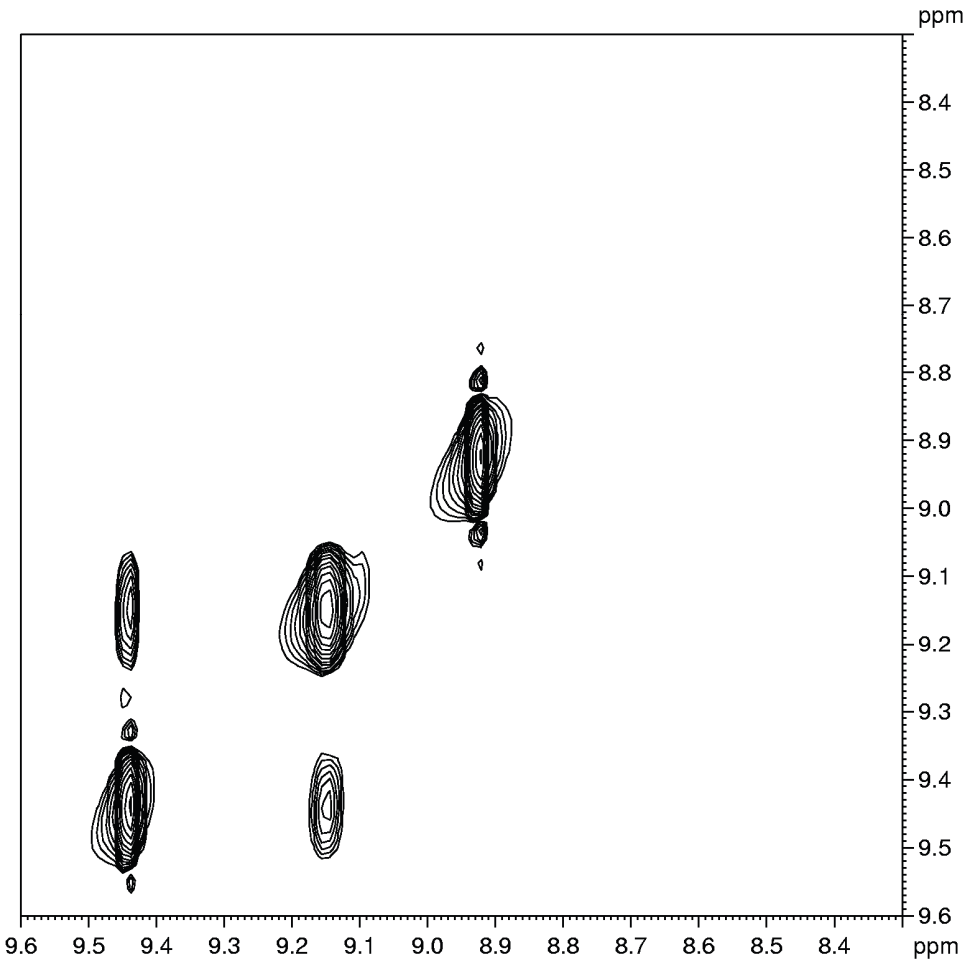

Figure 13: NOESY NMR (500 MHz; 298 K; $CDCl_3$/DMSO-d6 93:7 v/v; TMS) spectrum of **1**·$CaCl_2$.

Supplementary Material (ESI) for New Journal of Chemistry

Quantum mechanical calculations

Quantum mechanical calculations were carried out for **1**·$CaCl_2$. Top and side views for two minimized conformers (U- and S-shaped) are shown in Fig. 14. All calculations were done with Gaussian03.[2] Geometry optimizations were done using HF/6-31G(d). The calculations cannot reflect all aspects of the spectroscopic investigations because (i) those have been carried out in solvent, and (ii) the spectroscopic data are time averaged. Thus the conformers have to be viewed as snap-shots.

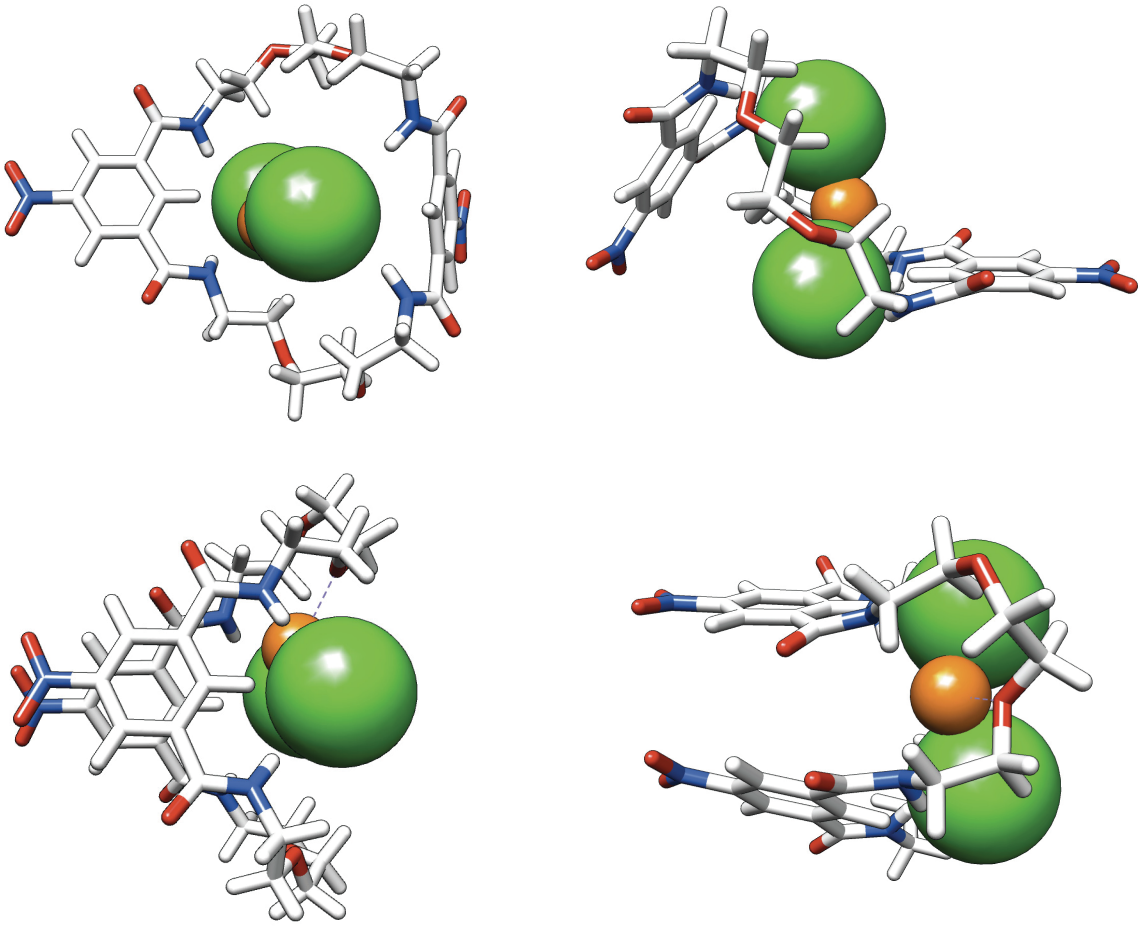

Figure 14: Two calculated conformers of **1**·$CaCl_2$.

[1] A. Dirksen, U. Hahn, F. Schwanke, M. Nieger, J. N. H. Reek, F. Vögtle, L. De Cola *Chem. Eur. J.,* 2004, **10**, 2036 - 2047.

[2] *Gaussian 03, Revision D.02*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N.

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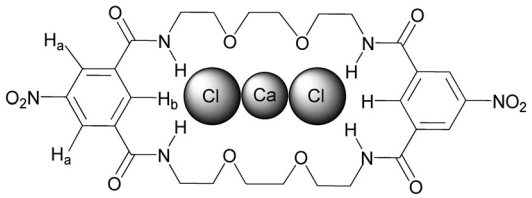
Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

3.7 Supramolecular Ion Triplet Complexes – Dissolution of Solid Salts and Combinatorial Assembly

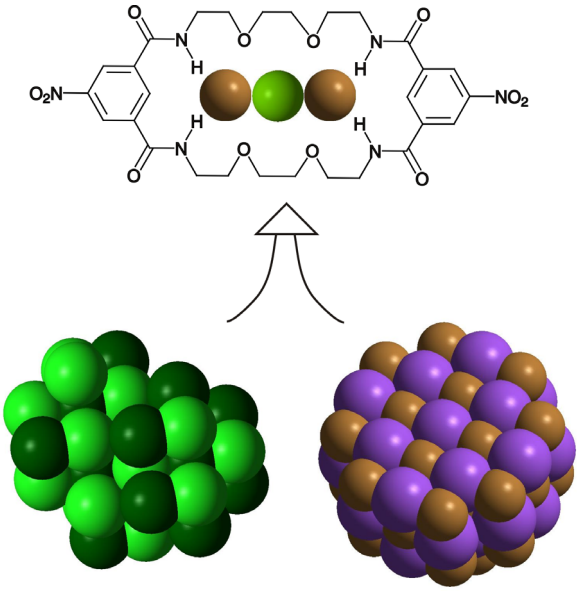
J. Eckelmann, U. Lüning, eingereicht bei *Tetrahedron Letters*.

Im vorherigen Kapitel wurde ein tritoper Makrozyklus vorgestellt, der Calciumchlorid als Ionentriplett binden kann. Die bisherigen Untersuchungen konzentrierten sich dabei auf Alkali- und Erdalkalimetallchloride.



In einem zweiten Schritt wurden nun auch andere Anionen verwendet. Dabei wurden neben den Fluoriden, Bromiden und Iodiden auch Nitrate, Carbonate und Azide untersucht. Es konnte festgestellt werden, dass der Makrozyklus auch in der Lage ist, Calciumbromid und Magnesiumbromid als Ionentriplett zu binden. Für die Bestimmung der Gäste wurde eine Vielzahl von ^{1}H-NMR-Experimenten durchgeführt und die Verschiebung der Protonen beobachtet. Sowohl das *endo*-Proton H_b des Aromaten als auch die NH-Protonen zeigten eine Tieffeldverschiebung, sobald es zur Bindung kam.

Eine interessante Fragestellung war: Ist der Makrozyklus in der Lage, aus zwei Salzen die richtigen Ionen aufzunehmen und als Ionentriplett zu binden? Hierzu mussten Salze verwendet werden, die der Makrozyklus ansonsten nicht bindet. Bei einer Mischung aus Magnesiumchlorid und Natriumbromid war es dem Makrozyklus möglich, Magnesiumbromid zu binden.



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Supramolecular Ion Triplet Complexes - Dissolution of Solid Salts and Combinatorial Assembly

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ABSTRACT

Ion triplet complexes of a macrocyclic bis-isophthalamide receptor **1** with solid alkaline or alkaline earth halides have been prepared. The binding of alkaline earth halides such as calcium chloride and bromide and magnesium bromide was verified by NMR experiments. The energy gain by the complexation of the ion triplet into the receptor does not only overcome crystal packing forces, the cations and anions of the magnesium bromide complex may be picked up separately from magnesium chloride and sodium bromide.

1. Introduction

Supramolecular chemistry started with the complexation of alkaline metal ions into crown ethers.[1,2] Later, receptors for anions were developed,[3,4] and today tailored receptors for a large variety of cations and anions can be chosen.[5-13] In contrast, reports on complexation of ion pairs are scarce,[14-19] and prior to our work on macrocycle **1**,[20] no ion triplet receptor had been reported.

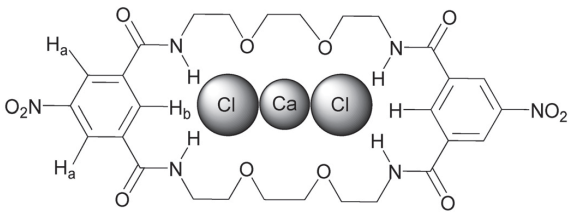

Figure 1: Tritopic macrocycle complex **1·CaCl$_2$** with ^{1}H-NMR assignments.

Receptor **1** is able to dissolve solid calcium chloride as an ion triplet complex into an organic solvent. Because isophthalamides are known to bind chlorides efficiently, we had tested different alkaline and alkaline earth chlorides.[20] But the potential of isophthalamides as receptors is not restricted to chloride ions.[7,12,13,21-23] Therefore, we have investigated the potential of tritopic receptor **1** to dissolve other halides (fluorides, bromides and iodides).

2. Results and Discussion

In contrast to the alkaline and alkaline earth chlorides,[20] lithium iodide for instance is soluble in $CDCl_3$/DMSO (95:5) while calcium chloride is not. The observation of chemically induced shifts (CIS) in the ^{1}H NMR spectra of the receptor **1** upon reaction with a guest salt is therefore less surprising for a soluble salt because no crystal packing forces have to be compensated by the binding forces of the ion pair or triplet in the receptor macrocycle **1**.

The CIS of the NH and the endo CH_b protons (see Figures 1 and 2) were used to investigate the complexation behaviour of this tritopic macrocycle **1**. First, seven different iodides (lithium, sodium, potassium, magnesium, calcium, strontium, and barium iodide) were tested. The signals of macrocycle **1** showed CIS when alkaline earth metal iodides were added but the NMR solutions turned yellow due to redox reactions. Sodium and potassium iodide showed no change in the spectra.

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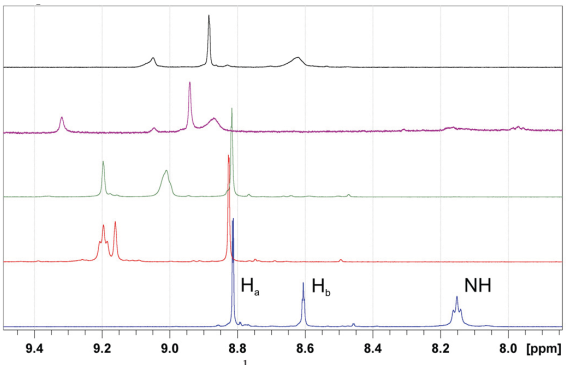

Figure 2: Expanded sections of ^{1}H NMR spectra (500 MHz, 298 K, $CDCl_3$/DMSO-d_6 95: 5) of **1** in the presence of different salts. From bottom to top: No salt, calcium bromide, lithium bromide, magnesium bromide, and barium bromide.

Next, different bromides and fluorides were tested (potassium, calcium, strontium and barium fluoride; lithium, sodium, potassium, magnesium, calcium, strontium, and barium bromide, see table 1). No fluoride salt induced a CIS in receptor **1**. Magnesium, calcium and strontium bromide interacted with macrocycle **1** and in contrast to the iodides, no redox chemistry was observed. In the case of alkaline bromides, only lithium bromide was dissolved by macrocycle **1**. The behaviour of receptor **1** therefore is comparable for lithium bromide and lithium chloride, for which CIS have also been observed.[20] In summary, macrocycle **1** is able to bind selected alkaline and alkaline earth bromides and chlorides.

Table 1: Binding studies of different alkaline and alkaline earth halides into receptor **1** detected by CIS in the NMR signals of **1** in the presence of metal salts.

	F^-	Cl^-	Br^-	I^-	NO_3^-
Li^+		☑	☑	☑[a,d]	
Na^+		☒	☒	☒[c,d]	
K^+	☒	☒	☒	☒[d]	
Mg^{2+}		☒	☑	~[b]	☒
Ca^{2+}	☒	☑	☑	~[b]	☒
Sr^{2+}	☒	☒	~[c]	~[b]	☒
Ba^{2+}	☒	☒	☑	~[b]	

☒ negative, ☑ positive, ~ indeterminable. a) Salt is soluble in NMR solvent mixture, b) sample turned yellow and biphasic, c) precipitation occured, d) sample turned yellow.

Then, in a combinatorial experiment, we have mixed different salts to check, if receptor **1** is able to pick up a matching combination of ions from a mixture of salts which themselves did not lead to CIS when combined with a solution of receptor **1**. Would ions from different salts be selected and combined in the receptor as ion triplets (e. g. calcium with chloride or bromide ions, or magnesium with bromide ions)?

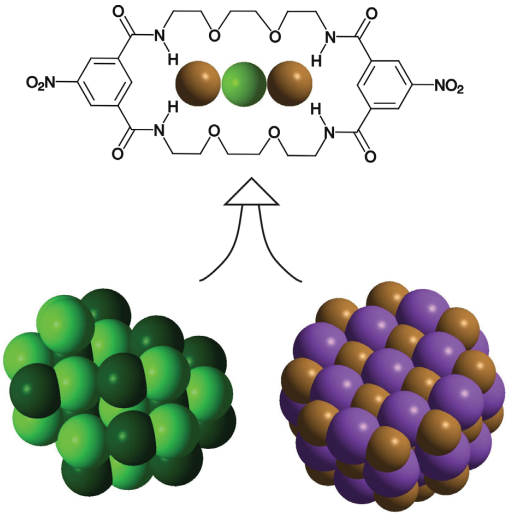

Figure 3: Combinatorial experiment. Macrocycle **1** binds magnesium bromide, when magnesium chloride (left) and sodium bromide (right) were provided.

Three different alkaline earth nitrates (magnesium, calcium and strontium) were chosen as metal sources. Macrocycle **1** was not able to dissolve these nitrates (see Table 1). Then, each nitrate was mixed with sodium chloride or sodium bromide in separate experiments, and a solution of receptor **1** in the NMR solvent mixture was added. In most cases, macrocycle **1** was not able to extract the expected ion pairs. However, when a mixture of magnesium chloride and sodium bromide was used, receptor **1** was able to pick up magnesium and bromide ions from the two salts, and the NMR spectrum showed the CIS of the ion triplet complex of **1**·$MgBr_2$.

This successful combinatorial extraction experiment indicates that (with further tailoring of the receptors) it shall be possible to extract selectively just one combination of ions - as ion pairs in the case of alkaline metal ions or as ion triplets in the case of alkaline earth metal ions - into a respective receptor. Such a selectivity would allow to analyze for a distinct combination of cations *and* anions simultaneously.

3. Experimental Procedure

8.0 mg (1.2 µmol) of macrocycle **1** was dissolved in 5.0 mL of a mixture of $CDCl_3$/DMSO-d_6 (95:5, v/v). Into several NMR tubes containing various salts in solid form in excess, 600 µL of this stock solution per tube was then transferred. The tubes were flushed with nitrogen, capped and sealed with PARAFILM®. The NMR spectra were recorded after 12 h (see Figure 2).

Acknowledgement

We gratefully acknowledge fruitful discussions with Prof. Dr. B. König on this subject.

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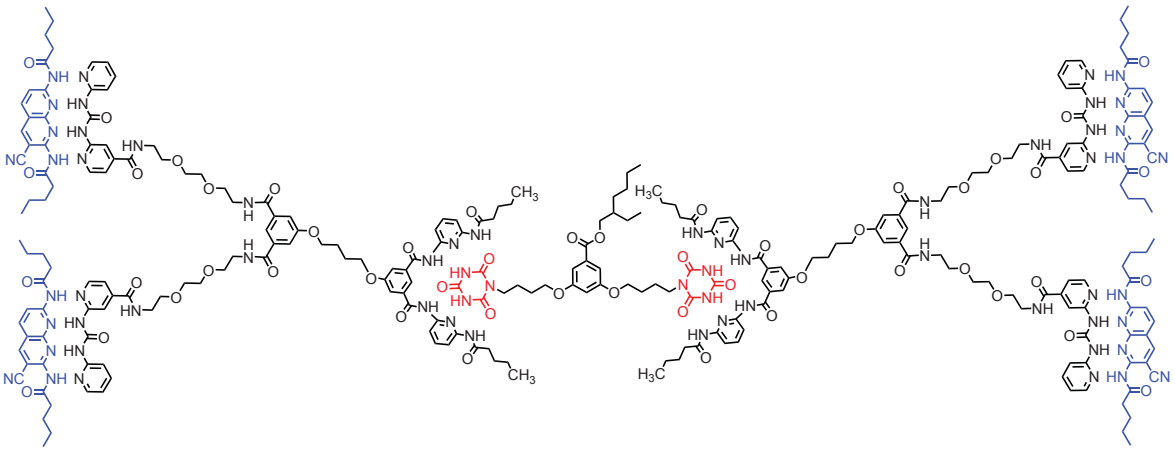
4 Zusammenfassung und Ausblick

Erstmals ist es gelungen, ein supramolekulares Dendrimer der zweiten Generation mit orthogonalen Erkennungsdomänen herzustellen und zu untersuchen. Dieses Dendrimer bestand aus einem ditopen Kernbaustein, einem Verzweigungsbaustein und entsprechenden Endkappen. Der erfolgreich synthetisierte Kernbaustein besitzt zwei Isocyanursäuren (DAD^DAD), die über sechs Wasserstoffbrücken an den Verzweigungsbaustein binden. Der Verzweigungsbaustein besitzt auf der einen Seite einen Hamilton-Rezeptor (ADA^ADA) und auf der anderen Seite zwei Dipyridylharnstoffderivate (ADDA). Die Endkappen sind Naphthyridinderivate, die das Muster DAAD tragen. Durch verschiedene ^{1}H-NMR-Titrationen konnte bestätigt werden, dass die Codierungen orthogonal zueinander sind. Für die Synthese des Verzweigungsbausteins konnte ein neuer Syntheseweg entwickelt werden, so dass dieser erstmals in ausreichenden Mengen für notwendige Experimente zur Verfügung stand.



Zahlreiche Versuche im vergangenen Jahrzehnt zur Synthese des supramolekularen Dendrimers sind an der schlechten Löslichkeit der Einzelkomponenten gescheitert. Durch die Einführung entsprechender löslichkeitsfördernder Gruppen konnten nun die Bausteine ausreichend löslich gemacht werden. Dabei wurden nicht nur Ethylenglycole, sondern vor alledem auch verzweigte Alkylketten (2-Ethylhexylderivate) als racemische Gemische verwendet. Hierbei hat sich herausgestellt, dass Aussagen zur Löslichkeit und Mischbarkeit nicht immer vorhersagbar sind.

Viele verschiedene Hamilton-Rezeptoren konnten hergestellt werden, die durch ihre unterschiedliche Funktionalität in einer Vielzahl von Reaktionen einsetzbar waren. Dabei zeigten ^{1}H-NMR-Titrationen und ITC-Messungen, dass die gewählten Isocyanursäuren stärker binden als die in den vergangenen Jahren verwendeten Barbitursäuren.

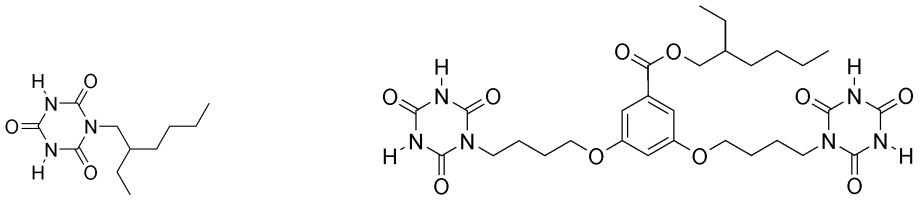
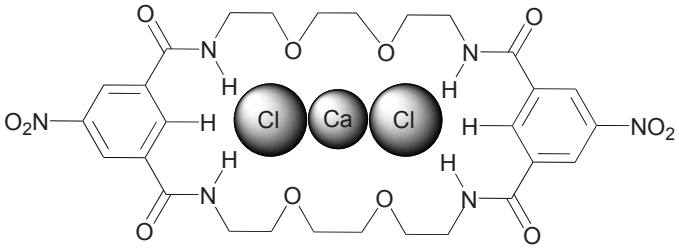
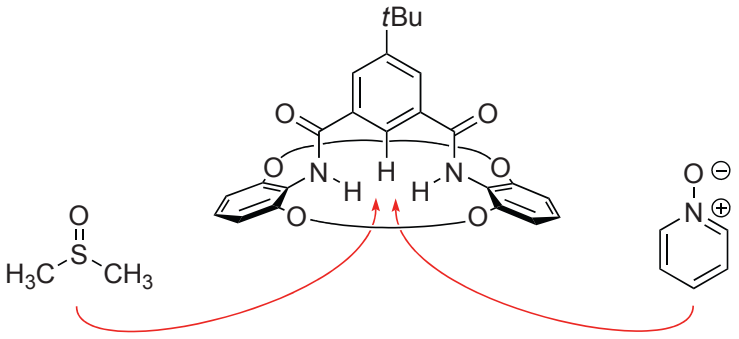


Abb. 4.1: Zwei Isocyanurbausteine, die durch die verzweigten Alkylketten erheblich bessere Löslichkeit zeigen.

Ein wiederkehrendes Motiv in dieser Arbeit sind die Isophthalamide. Dienten sie einerseits als Grundgerüst im Hamilton-Rezeptor, so finden sie auch andererseits Anwendung in der Erkennung von Ionen. In der Arbeit konnte gezeigt werden, dass es erstmals gelungen ist, einen tritopen Makrozyklus zu synthetisieren, der Calciumchlorid als Ionentriplet in organischen Lösungsmitteln binden kann.



Des Weiteren konnte gezeigt werden, dass Isophthalamide, als Grundgerüst in einem konkaven Bimakrozyklus, in der Lage sind, ungeladene Gäste zu erkennen. Dabei wurde eine Screening-Methode entwickelt, um mit wenigen ^{1}H-NMR-Messungen passende Gäste zu erkennen.



Durch die erfolgreiche Synthese des supramolekularen Dendrimers der zweiten Generation stehen nun viele weitere Wege offen. Dabei ist die Entwicklung eines tritopen bzw. tetratopen Kerns eine gute Möglichkeit, um schnell größere Komplexe zu erhalten.

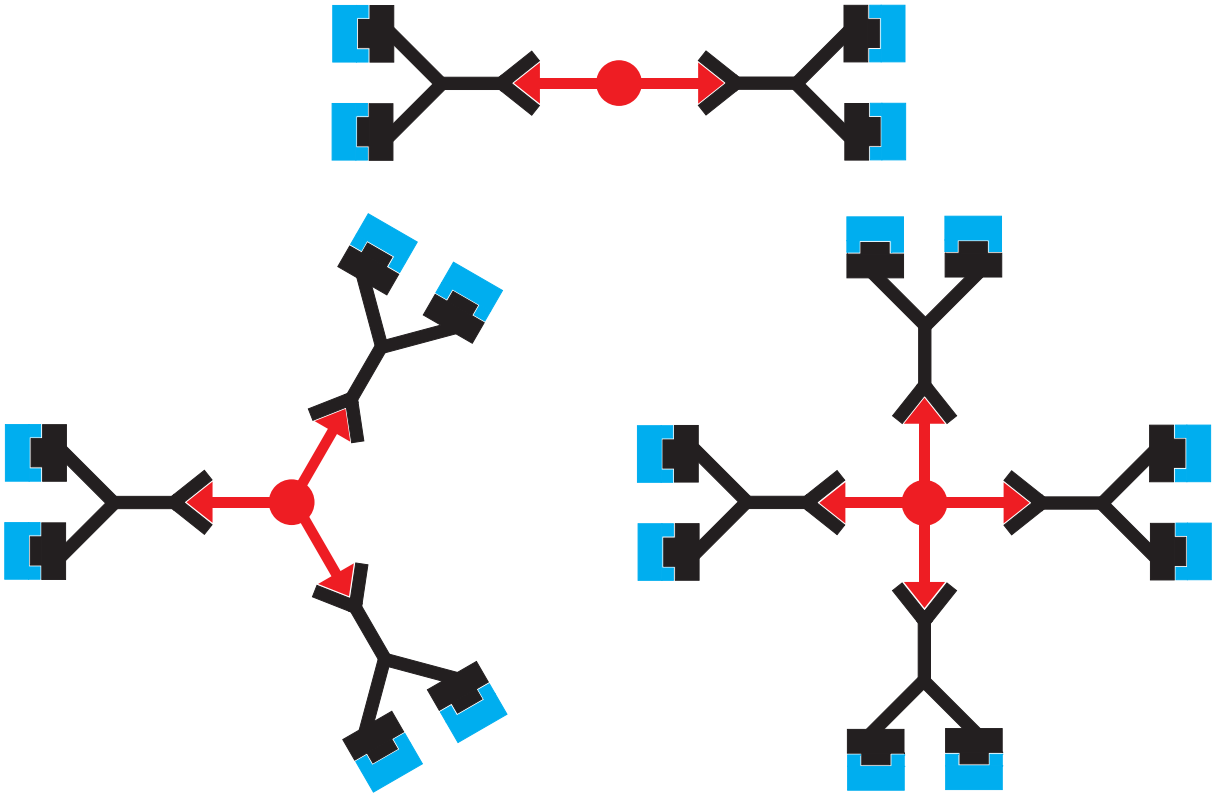


Abb. 4.2: Schematische Darstellung des erhaltenen Dendrimers (2. Generation) und der möglichen Dendrimere ausgehend von einem di-, tri- oder tetratopen Kern (rot), den Verzweigungseinheiten (schwarz) und den Endkappen (blau).

Durch die Verwendung der bereits vorhandenen Verzweigungseinheit (schwarz) und der Endkappen (blau) sollte es auf kurzem Weg möglich sein, mit den neuen tri- und tetratopen Kernbausteinen entsprechende Dendrimere zweiter Generation zu erhalten. Die somit erhaltenen supramolekularen Komplexe besitzen eine Masse von ca. 7300 g mol^{-1} (tritop) bzw. ca. 9700 g mol^{-1} (tetratop).

Als Startmolekül für den Kern bietet sich Phloroglucin an, das über einen Spacer mit drei Isocyanursäuren verbunden wird. Sollte dieser entsprechende Baustein nicht löslich genug sein, so könnte ein Gallussäureester mit löslichkeitsfördernden Alkylketten verwendet werden (s. Abb. 4.3). Durch die verwendete verzweigten Alkylkette erhält man, wie im Kapitel 3.3 und 3.4, eine erheblich bessere Löslichkeit. Auch die Verlängerung der Alkylketten zwischen zentralem Kern und Isocyanursäure würde helfen, die Löslichkeit zu steigern.

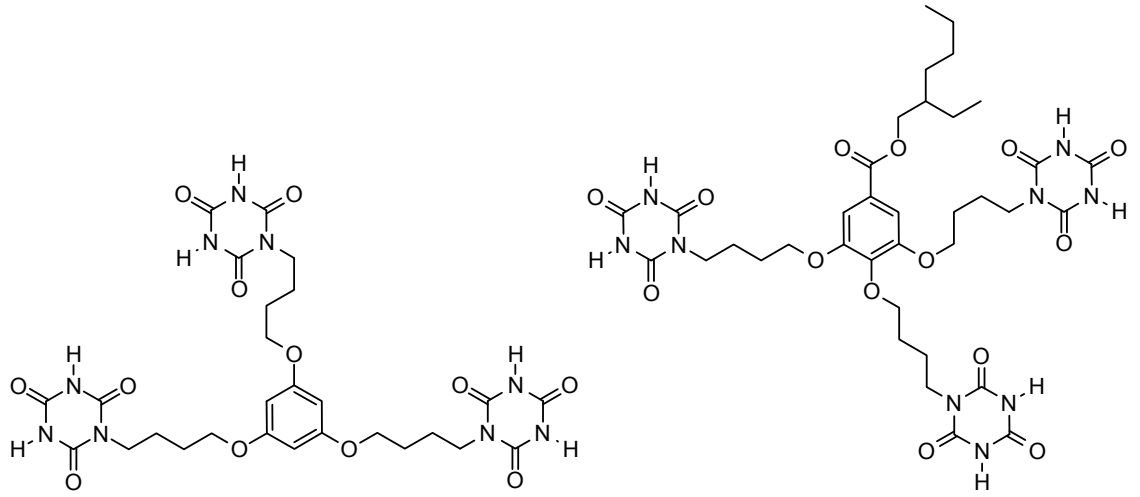


Abb. 4.3: Zwei mögliche tritope Isocyanursäure-Kerne. Synthese ausgehend von Phloroglucin (links) und von Gallussäure (rechts).

Für den Aufbau eines tetratopen Bausteins könnte durch den Verzicht auf planare Aromaten die Löslichkeit in unpolaren Lösungsmitteln erheblich gesteigert werden. Dabei bietet sich als Alternative für den zentralen Kernbaustein der Naturstoff Erythrit an (s. Abb. 4.4).

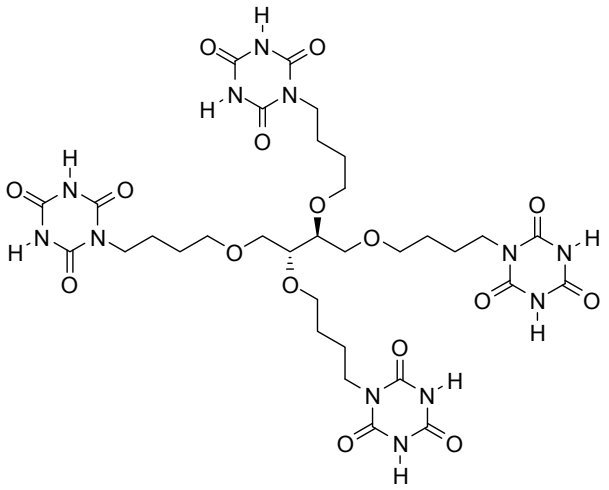


Abb. 4.4: Ein Beispiel für einen tetratopen Kernbaustein mit vier Isocyanursäuren ausgehend von Erythrit.

Für den Aufbau einer neuen Sphäre ist es notwendig, einen weiteren Verzweigungsbaustein zu entwickeln. Hierbei besteht die Möglichkeit, die vorhandenen Endkappen zu modifizieren. Sie besitzen zur weiteren Funktionalisierung Nitrilgruppen und lassen sich durch Hydrolyse in Carbonsäuren umwandeln (s. Abb. 4.5), die anschließend weiter funktionalisiert werden können.[27] Durch entsprechende Synthesen kann an dieser Stelle der Aufbau einer weiteren Verzweigungseinheit ermöglicht werden. Dafür ist ein weiteres Wasserstoffbrückenmuster notwendig, das orthogonal zu den bisher verwendeten Mustern sein muss. Auch müssen

hierfür entsprechend neue Endkappen hergestellt werden. Das Resultat wäre ein Dendrimer dritter Generation.

Zu beachten ist, dass das bisher verwendete DAAD·ADDA Motiv mit $K_{ass} \sim 10^3$ M^{-1} nicht besonders stark bindet. Dadurch kommt es zwar nicht zu Fehlern im Dendrimer, aber ein Teil liegt nicht im Komplex vor.

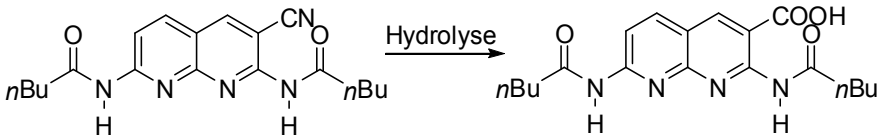


Abb. 4.5: Mögliche Derivatisierung des DAAD-Bausteins zum Aufbau eines neuen Verzweigungsbausteins.

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Eidesstattliche Erklärung

Hiermit erkläre ich, Jens Eckelmann, an Eides statt, dass ich die vorliegende Dissertation selbständig und nur mit den angegebenen Hilfsmitteln angefertigt habe. Die Arbeit entstand unter Einhaltung der Regeln guter wissenschaftlicher Praxis der Deutschen Forschungsgemeinschaft. Inhalt und Form der Arbeit sind von mir eigenständig erarbeitet und verfasst worden. Weder die gesamte Arbeit noch Teile davon habe ich an anderer Stelle im Rahmen eines Prüfungsverfahrens eingereicht. Dies ist mein erster Promotionsversuch.

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