A New Cyclic Pseudopeptide Composed of (L)-Proline and 3-Aminobenzoic Acid Subunits as a Ditopic Receptor for the Simultaneous Complexation of Cations and Anions

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The synthesis and receptor properties of a cyclic pseudopeptide composed of (L)-proline and the nonnatural amino acid 3-aminobenzoic acid in an alternating sequence are described. The structure of *cyclo*[(L)Pro-AB]$_3$ was determined in the solid state by X-ray crystallography and in solution by one- and two-dimensional NMR techniques and FT-IR spectroscopy. The cyclic peptide preferentially adopts conformations comparable with the cone conformation of calixarenes. Similar to calixarenes, *cyclo*[(L)Pro-AB]$_3$ is able to bind cations by cation−π interactions with its aromatic subunits. In some complexes, the peptide NH groups interact additionally with anions and the cyclic peptide thus behaves as a ditopic receptor. The structure of the ternary complex between *cyclo*[(L)Pro-AB]$_3$ and *N*-methylquinuclidinium iodide was determined by X-ray crystallography. Spectroscopic investigations show that this complex has a similar geometry in solution. Stability constants of complexes of the cyclopeptide with various ion pairs have been determined. Crossover experiments show that electrostatic interactions between cation and anion complexed by *cyclo*[(L)Pro-AB]$_3$ result in cooperative effects of either ion on the complexation of the corresponding counterion. The binding properties of *cyclo*[(L)Pro-AB]$_3$ are correlated with its conformation in solution. The properties of related cyclic hexapeptides in which one or two (L)-proline subunits are replaced by (L)-glutamic acid are also described. In comparison with *cyclo*[(L)Pro-AB]$_3$, these peptides possess a reduced cation and anion affinity. Anion complexation is weakened because the amide NH groups at the glutamic acid subunits are involved in strong intramolecular hydrogen bonds and are not available for interactions with other partners. Consequently, the cation complex stabilities also decrease. The amino acid subunits obviously influence the receptor properties of such cyclopeptides by controlling their solution conformation.

Introduction

An important aspect of supramolecular chemistry is the design of artificial receptors.[1] One strategy for the synthesis of such compounds consists of the attachment of additional substituents to preformed cyclic host molecules such as crown ethers, cyclophanes, calixarenes, or cyclodextrins. In this approach, substituents are selected so that they participate in substrate binding and thus improve the receptor selectivity or induce altered behaviors or properties. This strategy has recently been termed the *modular* approach of receptor design.[2] Although many highly selective host molecules have been synthesized in this way, we believe that another approach, namely a *sequential* synthesis, may have several advantages. The sequential assembly allows the deliberate introduction and exchange of individual subunits at defined positions in a cyclic receptor. The sequence of the subunits can be varied systematically in order to study its influence on substrate binding. Furthermore, hits identified by a combinatorial receptor synthesis can be resynthesized easily.

The obvious choice for a cyclic compound accessible by a sequential synthesis is a cyclic peptide. Cyclopeptides have not often been used as artificial receptors so far,[3] probably because they are usually relatively flexible and, despite their cyclic structure, are rarely able to bind substrates in a well-defined cavity. The flexibility of cyclic peptides can be significantly reduced, however, when they are composed of (L)- and (D)-amino acids in an alternating sequence[4] or when they contain rigid subunits such as aromatic[5] or alicyclic[6] spacers. Such conformationally restrained cyclopeptides have been used for the binding of, e.g., amino acids,[6a] aromatic compounds,[5f] or dicarboxylic acids.[5i] Using the same approach, Ishida and co-workers have achieved the catalytic acceleration of 4-nitrophenyl acetate hydrolysis[5d] and the complexation of phosphate anions[5c] with cyclic pseudopeptides composed of 3-aminobenzoic acid and natural amino acids in an alternating sequence (Figure 1). We have recently demonstrated that such peptides (e.g. **1**) are also able to

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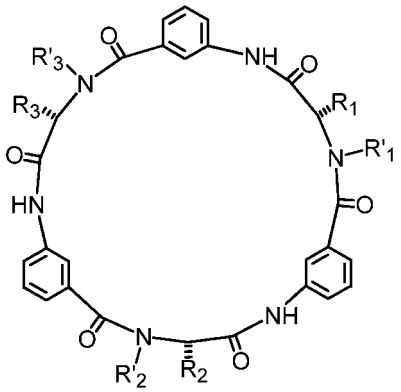

1 $R_1 = R_2 = R_3 = CH_2CH_2COOCH(CH_3)_2$; $R'_1 = R'_2 = R'_3 = H$

2 $R_1 = R_2 = R_3 =$  $R'_1 = R'_2 = R'_3 =$

3 $R_1 = R_2 =$  $R'_1 = R'_2 =$ $R_3 = CH_2CH_2COOCH(CH_3)_2$; $R'_3 = H$

4 $R_1 =$  $R'_1 =$ $R_2 = R_3 = CH_2CH_2COOCH(CH_3)_2$; $R'_2 = R'_3 = H$

Figure 1. Structures of the cyclic hexapeptides **1**−**4**.

bind cations by cation−π interactions.[7] In this respect, they possess receptor properties comparable with those of the structurally related calixarenes.[8] Certain anions, such as tosylate or phenylphosphonate, behave highly cooperatively in the cation complexation of **1**. They bind to the cyclopeptide NH groups and stabilize a receptor conformer that is ideally suited for interactions with positively charged substrates. This behavior can be regarded as an *allosteric* effect.

The stability of cation complexes of **1** is much lower in the presence of anions that cannot act as effectors.[7] This is partly due to the flexibility of the host in solution. Conformations of cyclic peptides such as **1** result from rotations around the single bonds between the aromatic subunits. For the six bonds between two aromatic rings,

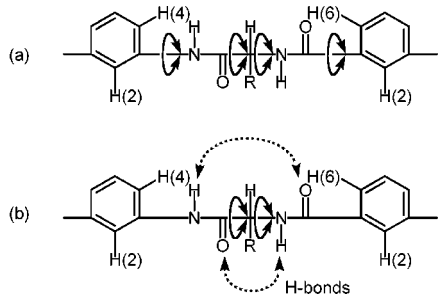

Figure 2. Rotating bonds in a peptide chain between the aromatic residues of **1** (a). Preferred conformation of **1** in 5% $CDCl_3$/DMSO-d_6 (b).

only the rotations around the secondary amides are hindered and the energetically more favored *trans*-amide conformation is more probable. Rotations around all remaining bonds are in principle possible (Figure 2a). Our investigations have shown that, in nonpolar solvents such as $CDCl_3$, **1** preferentially adopts conformations that are stabilized by intramolecular hydrogen bonds. In these conformers, the protons on the aromatic nitrogen atoms point "up" toward H(4) of the adjacent aromatic ring and those on the glutamic acid nitrogen atoms point "down" toward H(2) (Figure 2b). The peptide is nevertheless not completely rigid because rotations around the bonds at C(α) still occur.

One can speculate that it should be possible to improve the receptor properties of **1** by increasing its rigidity. Figure 2a shows that a rotation around the C(α)−N bonds can be prevented by replacing the (L)-glutamic acid subunits with (L)-proline. Here, we report on the synthesis and properties of the new cyclopeptide **2**. We show how the conformational equilibrium and the binding properties of this peptide are affected by the proline subunits. As predicted, **2** possesses improved receptor properties toward cations. But we also find that the cation complex stabilities of **2** depend on the counterions used. In fact, **2** behaves like a ditopic receptor with a variety of ion pairs and binds cation and anion simultaneously.[9] Finally, complexation studies with cyclopeptides in which one (**3**) or two (**4**) proline subunits are replaced by glutamic acid show that, analogously to natural receptors, the binding properties of our artificial peptides depend on the sequence of the subunits from which they are composed.

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Scheme 1. Synthesis of the Cyclic Hexapeptide 2

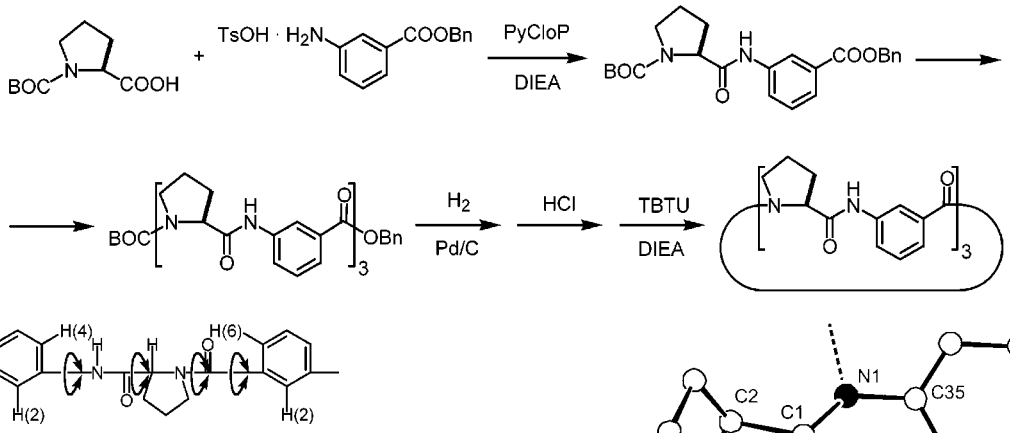

Figure 3. Rotating bonds in a peptide chain between the aromatic residues of **2**.

Results and Discussion

Synthesis and Conformational Behavior of 2. We prepared **2** in the same manner as the previously prepared cyclopeptide **1**.[7] First, the repeating dipeptide subunit was synthesized by coupling BOC-protected (L)-proline with benzyl 3-aminobenzoate. This dipeptide was successively elongated in solution, first to the tetrapeptide and then to the hexapeptide. After complete deprotection, the hexapeptide was cyclized under high-dilution conditions (Scheme 1). The product yield (30−40%) was much better when the cyclization was carried out at 80 °C, which is probably a consequence of the rigidity of the linear precursor.

The binding properties of receptors are determined to a large extent by their conformation in solution. The cavity shape of cyclic host molecules and hence their complexation behavior depends on the number and conformational flexibility of the bonds around the ring. All conformationally nonrigid bonds between two aromatic rings of **2** are indicated in Figure 3. A comparison with the structure of **1** shows that, although the rotation around the N−C(α) bonds is prevented in **2**, the total number of rotatable bonds is identical in both peptides. Because rotations around tertiary amides possess significantly lower energy barriers than those around secondary amides, proline amides are not rigid and *cis*-amides have also to be taken into account.[10]

Initial information about the conformational behavior of the cyclopeptide **2** in solution was provided by its crystal structure (Figure 4). **2** crystallizes as needles from

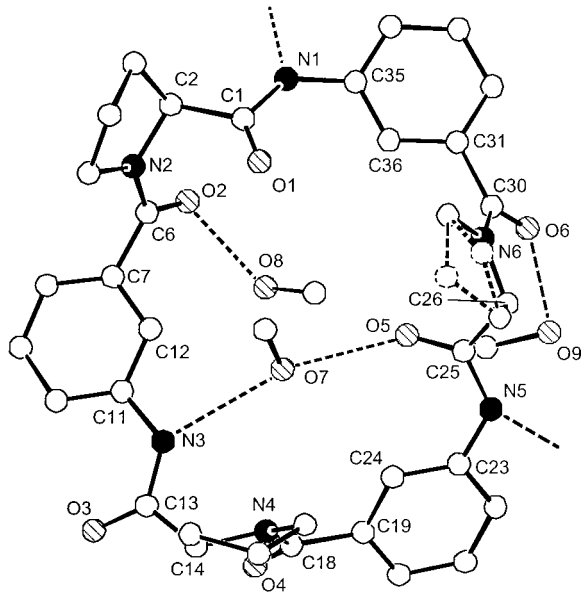

Figure 4. Crystal structure of **2**·3CH_3OH, viewed onto the plane through the three N atoms N1, N3, and N5, showing the O−H···O and N−H···O hydrogen-bonding interactions. Selected interatomic distances (Å): O2···O8 2.734(2), O5···O7 2.755(2), O6···C9 2.713(2), N1···O4′ 2.889(2), N3···O7 2.961-(2), N5···O9′ 2.814(2).

methanol with three solvent molecules (O−H···O) hydrogen bonded to three carbonyl O atoms of each cyclopeptide unit. In addition, each NH group in the cyclopeptide ring forms further intermolecular (N−H···O) hydrogen bonds to adjacent oxygen atoms but only one NH group forms an intercyclopeptide hydrogen bond [N1···O4′ 2.889(2) Å]. Figure 5 shows that all the proline amides adopt trans conformations in the solid state. Moreover, the three aromatic rings in **2** are all tilted in the same direction and thus line the walls of a dish-shaped cavity. In this respect, the structure resembles the cone conformation of the calixarenes.[11] The cavity of the cyclopeptide is certainly shallower, but the capability for guest molecules to interact with faces of the aromatic rings should still be present. In contrast, guest molecules bound by the "cystinophanes" described by Ranganathan and Karle et al. can only interact with the edges of the aromatic subunits.[5i]

Cyclopeptide **2** does not, however, adopt an ideal C_3-symmetrical structure in the crystal. Figure 6 (left) shows the result of superimposing the structure of the cyclopeptide with itself under the operations of idealized C_3 symmetry. The fit (root-mean-square deviation) at 1.301

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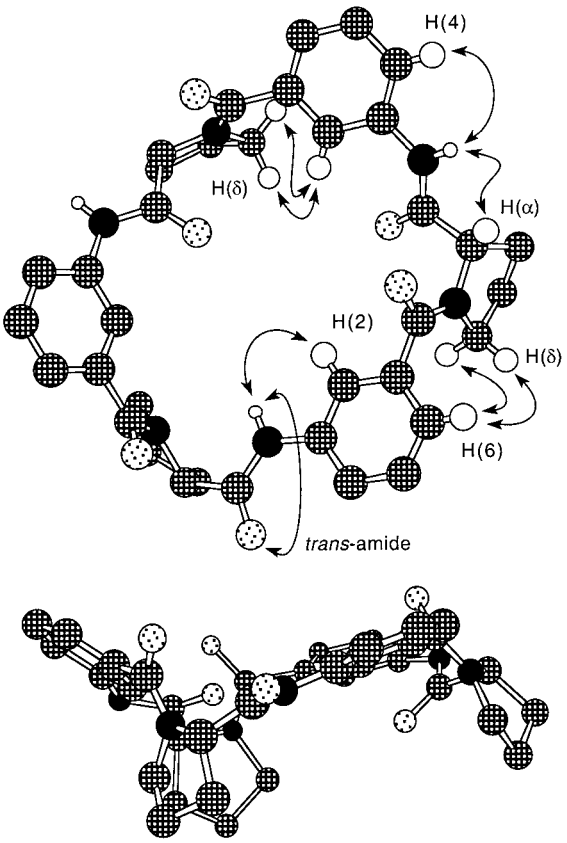

Figure 5. Views of the cyclopeptide ring in **2**·3CH_3OH, showing selected proton−proton relationships.

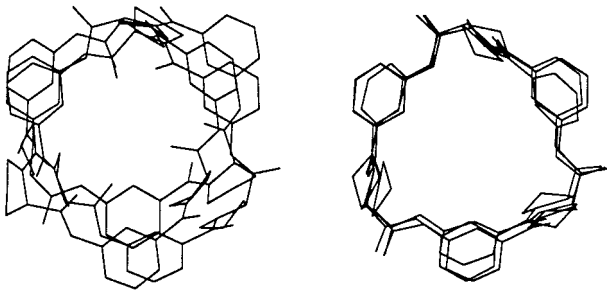

Figure 6. Superposition of solid-state conformations of cyclopeptide in **2**·3CH_3OH (left) and **2**·*N*-methylquinuclidinium iodide (right) with those resulting from rotation by 120° about the normal to the mean plane through the N−H groups, to show the approximation to idealized C_3 symmetry [rms fit: **2**, 1.301 Å; **2**·*N*-methylquinuclidinium iodide, 0.492 Å].

Å is rather bad. Whereas the three proline subunits are similarly orientated with respect to their adjacent aromatic rings, the secondary amide groups are not. The most significant deviation from idealized C_3 symmetry involves the secondary amide at N3, which results from a N−H···O hydrogen-bonded interaction with one of the methanol molecules located at the center of the cyclopeptide ring. The different geometries at the three amide nitrogens N1, N3, and N5 cause two of the aromatic NH protons to be oriented toward H(4) of the nearest aromatic group whereas one is pointed away (Figure 5). It is reasonable to assume that in solution the three secondary amide groups are flexible and in fact able to rotate relatively freely. In contrast, the orientations of the proline groups and aromatic rings would appear to be more fixed.

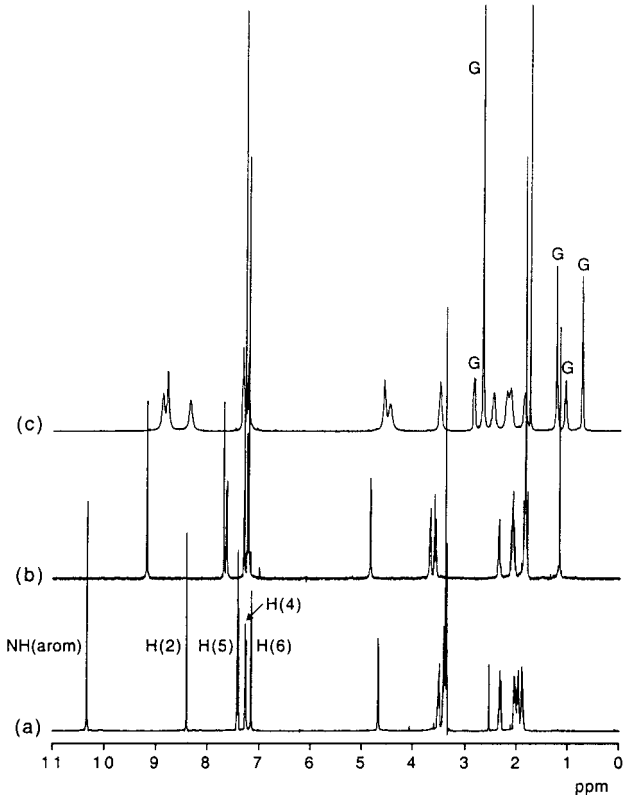

Figure 7. ^{1}H NMR spectra of **2** in DMSO-d_6 (a), $CDCl_3$ (b), and of its complex with $BTMA^+$ iodide in $CDCl_3$ (c) (G denotes the guest signals).

The conformational behavior of **2** in solution was investigated by one- and two-dimensional NMR techniques and FT-IR spectroscopy. The ^{1}H NMR spectra of **2** in $CDCl_3$ and DMSO-d_6 indicate an average C_3-symmetrical structure of the cyclic peptide in these solvents (Figure 7a,b). ^{13}C NMR spectroscopy allows an assignment of the proline amide conformations in solution. The resonances of the β- and γ-carbon atoms in proline rings are particularly sensitive to cis/trans isomerization of the tertiary amides.[12] A comparison of the observed chemical shifts of C(β) and C(γ) with characteristic resonances of these atoms in proline rings with *cis*- or *trans*-amides[12] indicates that *trans*-amides are more probable at the proline subunits of **2** than *cis*-amides. NOESY NMR spectroscopy gives further information about the solution conformation of the peptide. In the spectrum of **2** in $CDCl_3$, cross-peaks between NH−H(2), NH−H(4), and NH−H(α) are observed. Other cross-peaks are visible between H(2)−H(δ) and H(6)−H(δ) (Figure 8). Apart from additional NOE effects between NH−H(β), an almost identical spectrum is observed in DMSO-d_6. Spatial proximities of H(2) and H(δ) as well as H(6) and H(δ) that would give rise to NOE effects are indeed visible in the crystal structure of **2** (Figure 5). It is therefore reasonable to assume that the proline subunits in **2** are similarly oriented in both solution and the solid state. NOE effects between the NH and all of its adjacent protons illustrate the predicted rotation of the secondary amide groups in solution.

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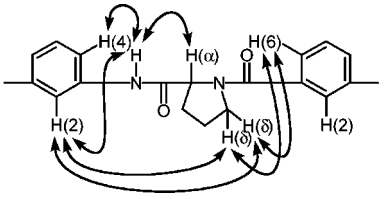

Figure 8. Intramolecular NOE effects in the NOESY NMR spectrum of **2** in $CDCl_3$.

A facile rotation of this group can additionally be inferred from the FT-IR spectrum of **2** in 1% DMSO-d_6/$CDCl_3$. In this spectrum, a band for NH vibrations is observed at 3408 cm^{-1} with a distinct shoulder at ca. 3425 cm^{-1}. The shoulder indicates that the three NH groups of **2** have slightly different environments, possibly because their orientations to the aromatic subunits vary. A weak band between 3325 and 3225 cm^{-1} may be assigned to NH groups involved in intramolecular hydrogen bonds with carbonyl group of adjacent subunits.[13] This interaction cannot be strong, however, because usually hydrogen-bonded NH groups have a significantly larger IR absorption than free ones.[14] Finally, the amide II vibration band is also split and possesses maxima at 1553 and 1553 cm^{-1}, again indicating a rotation of the secondary amide groups. The fact that no significant hydrogen bonding was detected in the FT-IR spectrum indicates that self-association of the cyclopeptide is not very probable in solution. Accordingly, a ^1H NMR dilution experiment in $CDCl_3$ in the concentration range of 2−0.01 mM revealed no significant dependence of the NH resonances of **2** on the cyclopeptide concentration. Self-association of the receptor in solution can therefore be neglected in studies on its binding properties.

In summary, cyclopeptide **2** adopts an averaged C_3-symmetrical conformation in solution that resembles the averaged solid-state structure in Figure 4. In the preferred conformer of **2**, the N−C(δ) bonds at the proline subunits point "down" toward H(2) of the adjacent aromatic ring. The same orientation has been found for the corresponding NH groups in cyclopeptide **1** (Figure 2b). In this respect, the conformation of peptides **1** and **2** are comparable. A conformational stabilization of the secondary amide group by intramolecular hydrogen bonds observed for **1** does not occur in **2**. These amides rotate and the cyclic peptide is not completely rigid. However, since conformers other than those of peptide **1** dominate in solution, the proline subunits have a pronounced influence on the complexing properties of **2**.

Complexation Properties of 2. We have shown that **1** binds cationic substrates, e.g. quaternary ammonium ions, in chloroform.[7] The complexation was demonstrated by the small but significant upfield shift of the ^1H NMR resonances of the guest upon addition of **1**. The upfield shift was explained by an inclusion of the ammonium ion into the cyclopeptide cavity, the result of which brings the guest protons in close proximity to the π-systems of the aromatic rings. Similar effects are usually observed when positively charged guest molecules interact with artificial hosts by cation−π interactions.[15] Dougherty first reported this type of interaction for cyclophanes.[16] Since then it has also been verified for a variety of other synthetic receptors such as calix[*n*]arenes,[8] homooxacalixarenes,[17] and cryptophanes.[18] It has also been emphasized that cation−π interactions are important factors for the complexation of cationic substrates, e.g. acetylcholine, by their natural receptors.[15,19]

An assignment of cation−π interactions to the binding mode in complexes between cations and artificial receptors is simple when the receptor contains few other functional groups apart from aromatic rings. However, the additional amide groups in **1** and **2** may also be able to interact with positively charged guests. We were not able to detect any influence of cation binding on the carbonyl groups of **1** by FT-IR spectroscopy. It is possible that the carbonyls still assist in the complexation of the substrates by increasing the overall negative charge density inside the cyclopeptide cavity. This interpretation is consistent with results of a recent publication, in which a cooperative effect of ester carbonyls on interactions between cations and aromatic esters was described.[20]

For the complex between **1** and $BTMA^+$ iodide, we have determined a stability constant K_a of 300 M^{-1} and a maximum shift of the *N*-methyl groups of the guest in the complex ($\Delta\delta_{max}$) of +0.05 ppm by NMR titration.[7] This method is now a standard tool for K_a measurements in molecular recognition studies and has also been applied in the investigations we present here.[21] Titrations were carried out in $CDCl_3$ with a water content of 0.01% in order to suppress effects of weak intra- or intermolecular hydrogen-bonding interactions. All saturation curves of the investigated complexes of **2** could be fitted on the basis of simple 1:1 equilibria, hence $K_a = c_{complex}/(c_{host} \cdot c_{guest})$. The stability constants in Tables 1, 2, and 4 have been determined repeatedly, and the experimental errors in our measurements were usually below 20%.

Cyclopeptide **2** behaves completely differently from **1** in the complexation of $BTMA^+$ iodide. The addition of this salt to solutions of **2** in $CDCl_3$ results in marked upfield shifts of all $BTMA^+$ protons in the ^1H NMR spectrum with a maximum shift of, e.g., the *N*-methyl protons of up to −1.1 ppm. Complex formation furthermore causes a significant change of the host spectrum (Figure 7c). Besides pronounced shifts of the aromatic as well as the aliphatic protons of **2**, all signals become very broad. This line broadening is most probably due to a reduced flexibility of the host in the complex. The stability constant of the complex is almost 2 orders of magnitude larger than the corresponding one of **1** and amounts to

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Table 1. Stability Constants K_a and Maximum Chemical Shifts $\Delta\delta_{max}$ of Complexes of 2 with Various Ammonium Iodides ($CDCl_3$, T = 298 K)

ammonium iodide	K_a(cation)		K_a(iodide)		K_a(iodide)/ K_a(cation)
	K_a[a]	$-\Delta\delta_{max}$	K_a[a]	$+\Delta\delta_{max}$	
acetylcholine	11 000	1.15	18 700	0.84	1.7
$BTMA^+$	21 100	1.11	31 500	0.83	1.5
N,*N*-dimethyl-pyrrolidinium	35 700	1.15	55 700	0.83	1.6
N-methyl-quinuclidinium	42 200	1.16	82 800	0.85	2.0

[a] Error limits of K_a < 20%.

21 100 M^{-1} when the upfield shift of the *N*-methyl group is followed by a NMR titration. Surprisingly, a smaller K_a of 7320 M^{-1} results when the shift of the *n*-butyl CH_3 group is analyzed. This effect has not been observed for the complex between $BTMA^+$ iodide and **1** where the two stability constants calculated from the shifts of the *N*-methyl and the *n*-butyl CH_3 group of the guest are of the same order of magnitude (K_a(*N*-methyl) = 300 M^{-1}; K_a(*n*-butyl CH_3) = 380 M^{-1}). The fact that the *N*-methyl protons *and* the *n*-butyl CH_3 protons of $BTMA^+$ both shift upon complexation by **1** or **2** suggests that the geometry of the complexes is disordered with the *N*-methyl group of the guest pointing either into or toward the exterior of the hosts. Similar results have been obtained for complexes of related quaternary ammonium ions with calixarenes.[8g,17b,18] But in the case of peptide **2**, the geometry with the cationic headgroup included into the cavity obviously also leads to the more stable complex.

To evaluate the influence of guest structure on the stability of complexes of **2**, NMR titrations were carried out with a number of other quaternary ammonium iodides. With the exception of acetylcholine, all the investigated iodides have simple aliphatic or alicyclic cations so that their interactions with **2** are not complicated by binding mechanisms such as $\pi-\pi$ interactions or hydrogen bonding. The results are summarized in Table 1. The maximum upfield shift $\Delta\delta_{max}$ is of the same order for all of the investigated ammonium ion complexes. The stability constants range from 11 000 M^{-1} for acetylcholine iodide to 42 200 M^{-1} for *N*-methylquinuclidinium iodide when the shifts of the *N*-methyl protons were used for the nonlinear regression. Again, smaller values for K_a resulted when the shifts of protons remote from the cationic headgroup of the guest were analyzed.

The stability constants of the ammonium iodide complexes of **2** are unusually large. For cation$-\pi$ interactions between cations and neutral artificial receptors in $CDCl_3$, stability constants $<10^3$ M^{-1} have been reported so far,[8,16,17] with only very few exceptions.[17a,18] It is therefore unlikely that cation$-\pi$ interactions are solely responsible for complex formation. Most probably, additional effects contribute to the stability of these complexes.

We were able to crystallize the complex of **2** with *N*-methylquinuclidinium iodide and determine its crystal structure (Figure 9). The structure provides valuable information about the interactions between the cyclopeptide and the substrate. It demonstrates that **2** binds both the cation and the anion simultaneously. As predicted, the cation is held in the shallow dish-shaped cavity of **2** where it can interact with the aromatic subunits of the cyclopeptide (Figure 10). Clearly, not only is the *N*-methyl headgroup of the ammonium ion able to enter the cavity but the whole bicyclic ring can be accommodated. Such a configuration would explain the upfield shift of all the guest protons on complexation. In solution, one would certainly expect a fast equilibrium between different orientations of the cation inside the cavity.

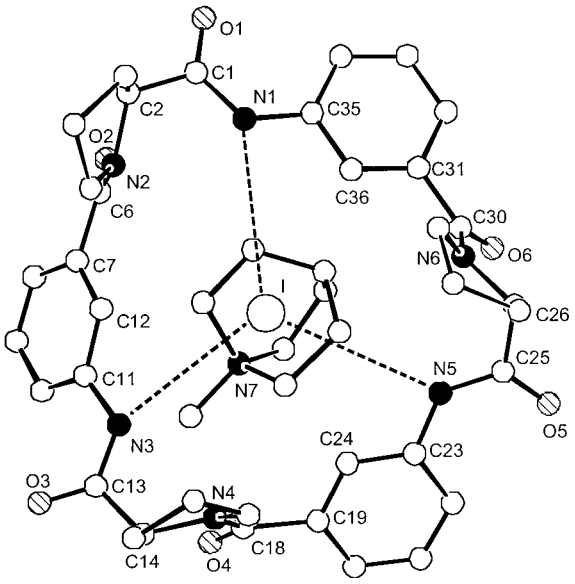

Figure 9. Crystal structure of **2**·*N*-methylquinuclidinium iodide, view as in Figure 4, showing the N−H···I^- hydrogen-bonding interactions between the neutral cyclopeptide and the I^- anion [N1···I 4.360(5), N3···I 3.956(5), N5···I 4.081(5) Å].

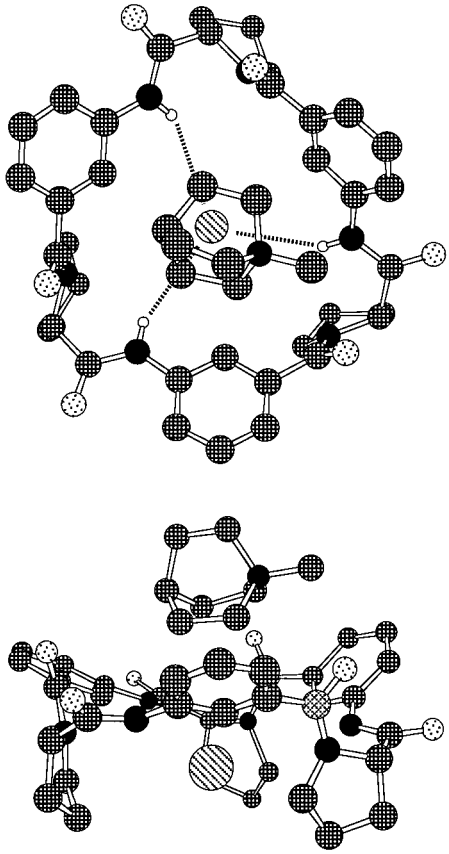

Figure 10. Side and top views of the **2**·*N*-methylquinuclidinium iodide complex, showing the arrangement of the cation and anion with respect to the cyclopeptide ring.

Reetz has found that α-methylene protons of tetrabutylammonium cations interact with carbonyl groups of

enolates by hydrogen bonding.[22] In the crystal structures of such complexes, a distance of ca. 3.30 Å between the negatively charged oxygen atoms and the α-C atoms of the ammonium ions was found. In our case, the shortest distance between a neutral peptide carbonyl oxygen atom and an α-C atom is 3.75 Å. Moreover, all carbonyl groups point outward away from the center of the complex. We therefore believe that directed hydrogens bonds between the guest and the neutral carbonyl groups of the host are not very probable. Nevertheless, we cannot rule out that the carbonyl groups cooperatively contribute to guest binding by electrostatic interactions. It should also be noted that all the proline amides have trans conformations in the crystal. The torsion angles involving these amides deviate slightly from 180°, with a maximum deviation of 13° (C26−N6−C30−C31 −167.1(4)°). Conformations of proline amides seem not to be restricted to either syn or anti, which may be one of the reasons for the unusual complexing properties of **2**.

In the ternary complex of **2**, the iodide anion is bound at the smaller opening of the cyclopeptide. There it is surrounded by the proline rings and appears to interact with all three NH groups, which are all directed toward the I^- anion (Figure 10). Such N−H···I^- interactions between the iodide ion and NH groups of secondary amides are not unknown, e.g., lunarine hydroiodide (N−H···I^- 3.73−3.66 Å)[23] or 4′-*N*-methylstaurosporine methiodide (N−H···I^- 3.78 Å).[24] The N−H···I^- distances in **2**·*N*-methylquinuclidinium iodide at 3.96−4.36 Å are somewhat longer, but this is probably a result of the steric repulsive influence of the neighboring proline rings. Figure 10 shows views of the complex which illustrate this point. The anion sits 4.40−4.96 Å from the centroids of the proline rings and approximately in the plane defined by them (perpendicular distance: 0.19 Å) and 1.41 Å above the plane through the three NH groups.

As a result of anion binding, the cyclopeptide adopts an almost C_3-symmetrical conformation, with all three NH groups pointing toward the center of the cavity. Figure 6 (right) shows the result of superimposing the structure of the cyclopeptide with itself under the operations of idealized C_3 symmetry. As the comparison with the uncomplexed **2** (Figure 6, left) clearly shows, the C_3 point symmetry of the cyclopeptide in **2**·*N*-methylquinuclidinium iodide is almost exact. This occurs despite an unsymmetrical crystal environment, caused in part by the presence of one molecule of $CDCl_3$ per cyclopeptide in the crystal.

Spectroscopic investigations show that **2** behaves as a ditopic receptor also in solution. The interaction of **2** with cations is evident in the upfield shift of the guest protons in the ^{1}H NMR spectra. The interaction with iodide can be demonstrated by FT-IR spectroscopy. In the spectrum of the $BTMA^+$ iodide complex, one broad band is visible in the NH stretching region at 3348 cm^{-1}. Compared with the spectrum of free **2**, this band is shifted toward lower frequencies by 60 cm^{-1}, which can be attributed to interactions between NH groups and the anions.[14] Furthermore, besides minor shifts of all C═O vibrations, only one amide II band is observed indicating that the rotation around the secondary amides of **2**, which is observed for free **2**, does not occur anymore. As in the crystal, a C_3-symmetrical conformation of **2** seems to be stabilized by the simultaneous interaction of all three NH groups with the iodide anion.

Additional information on the interactions of **2** with the anion can be derived from NMR spectroscopy. An assignment of the peptide conformation in the complex by NOESY NMR spectroscopy was not possible because broadening of the host signals upon addition of $BTMA^+$ iodide prevented the measurement of suitable spectra. None the less, important information can be gained from the ^{1}H NMR spectrum itself. Clearly, the electric field of anions bound at the narrower opening of **2** should influence the resonances of only those proline protons that point toward the center of the cavity. Indeed, a significant downfield shift of only one of the two proline H(δ) signals is observed upon complexation of ammonium iodides by **2**. NOESY NMR spectroscopic investigations of the related ammonium tosylate complex, which will be discussed below, show that this signal indeed corresponds to the inner H(δ) protons of **2**. Its shift can be used to determine the K_a of the iodide complex of **2** quantitatively. The iodide complex stabilities of the salts that have also been used for the determination of the cation stability constants are summarized in Table 1. Evidently, the stability of the iodide complex is not independent of the counterion. A stronger complexation is found for the more stable ammonium complexes, and the iodide complex is generally 1.5−2 times more stable than the corresponding cation complex. It can be speculated that the iodide complexation is influenced by subtle effects caused by the complexation of the cation on the conformation of **2**. For example, inclusion of the bulkier ammonium ions in the cyclopeptide cavity is expected to result in the aromatic subunits at the upper rim being pushed somewhat apart. This would slightly decrease the diameter of the cavity at its narrower opening and lead to the observed stronger interaction of the NH groups of the cyclopeptide with iodide.

The high stabilities of the ammonium iodide complexes in Table 1 can now be easily explained by electrostatic interactions between the bound ion pairs that, in addition to cation−π interactions, stabilize the cation complexes of **2**. Similar effects have been observed for cation complexes of **1** in the presence of tosylate anions,[7] but in contrast to **2**, no cooperative effect of iodide on the complexing behavior of **1** could be detected. The strong intramolecular hydrogen bonds in **1** seem to prevent a complexation of this anion. A simultaneous anion and cation complexation can only be achieved with ions that can form stronger hydrogen bonds to NH. In the case of **2**, the amide groups of the cyclopeptide are not significantly involved in intramolecular hydrogen bonds and an interaction with iodide is possible.

It can consequently be expected that **2** is also able to bind other anions. Table 2 illustrates that the $BTMA^+$ complex stability indeed depends on the nature of the anion. The cyclopeptide forms the most stable $BTMA^+$ complexes when tosylate is the counterion. A similar behavior has been detected for **1**. Stability constants $>10^6$ are difficult to determine accurately by NMR titration, but Table 2 certainly reflects the expected trend in the dependence of K_a on the nature of the anion. FT-IR and ^{1}H NMR spectroscopic investigations of the complex between $BTMA^+$ tosylate and **2** indicate strong hydrogen

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Table 2. Stability Constants K_a and Maximum Chemical Shifts $\Delta\delta_{max}$ of Complexes of 2 with Various BTMA$^+$ Salts ($CDCl_3$, T = 298 K)

	K_a(R-$N(CH_3)_3$)		K_a(n-butyl CH_3)		
BTMA$^+$	$K_a(1)^a$	$-\Delta\delta_{max}$	$K_a(2)^a$	$-\Delta\delta_{max}$	$K_a(1)/K_a(2)$
TFPB$^-$	1550	0.17	1560	0.32	1.0
picrate	1260	0.70	1140	0.28	1.1
iodide	21 100	1.11	7320	0.35	2.9
tetrafluoro-borate	205 000	0.99	17200	0.33	11.9
tosylate	5 050 000	1.16	204 000	0.26	24.8

[a] Error limits of K_a < 20%.

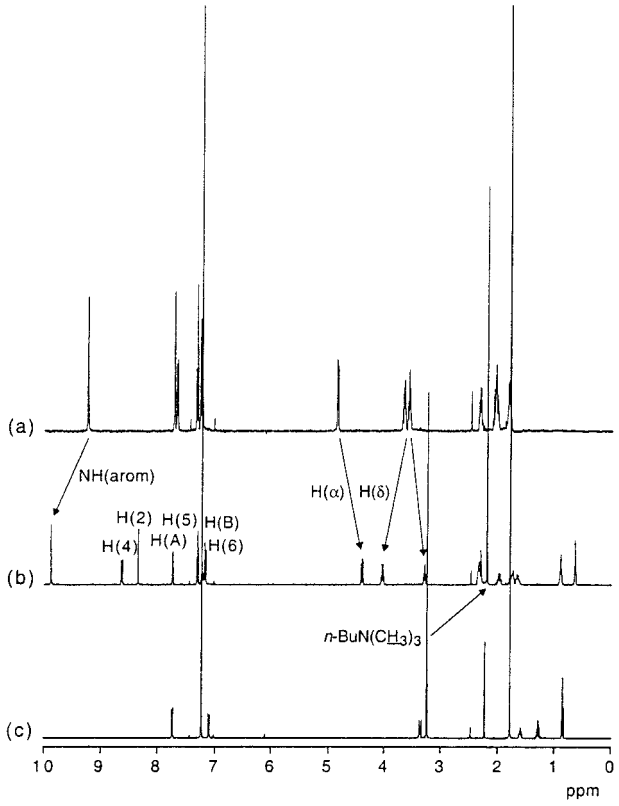

Figure 11. ^{1}H NMR spectra of **2** (a), BTMA$^+$ tosylate (c), and the complex between **2** and BTMA$^+$ tosylate (b) in $CDCl_3$.

bonds between the tosylate oxygen atoms and the NH groups of the cyclopeptide. The NH protons of **2**, for example, are shifted downfield by +0.62 ppm in the ^{1}H NMR spectrum, and the NH bond vibration is located at only 3292 cm^{-1} in the IR spectrum. In fact, the complex is so stable that, in an equimolar mixture of **2** and BTMA$^+$ tosylate, the conformational equilibrium is shifted almost completely toward the side of the complex and sharp signals are observed in the ^{1}H NMR spectrum (Figure 11). This enables the determination of the complex structure in solution by NOESY NMR spectroscopy. The NOE effects that are important for the assignment of the complex geometry are depicted schematically in Figure 12. These effects are consistent with a conformation of **2** similar to the one in the crystal structure of the complex (Figure 10). An intermolecular cross-peak is visible between the tosylate aryl protons and the same H(δ) protons of **2** that shift downfield upon addition of the guest. On one hand, this result shows that tosylate is bound to the narrower opening of the cyclopeptide and is arranged parallel to the proline rings. On the other hand, the signal of the H(δ) protons can now be easily assigned to protons that point toward the center of the

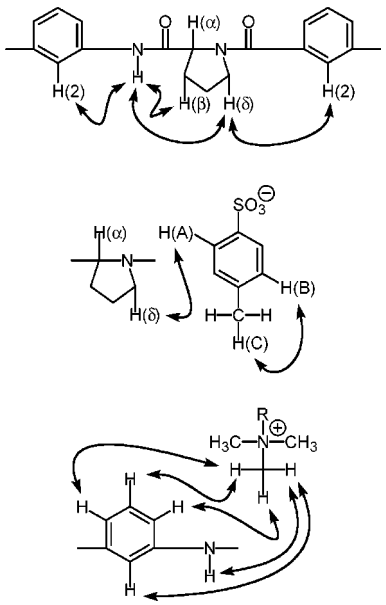

Figure 12. Intra- and intermolecular NOE effects in the NOESY NMR spectrum of the complex of **2** with BTMA$^+$ tosylate in $CDCl_3$.

Table 3. NH and C=O Vibration Bands in the FT-IR Spectra of Complexes of 2 with Various BTMA$^+$ Salts (c = 2 mM in 1% DMSO-d_6/$CDCl_3$)

anion	ν(NH)	ν(C=O)$_{pro}$	ν(C=O)$_{amide\ I}$	ν(C=O)$_{amide\ II}$
	3425/3408	1622	1690	1553/1533
TFPB$^-$	3421	1622	1691	1558/1535
picrate	3420/3409	1622	1689	1554/1534
iodide	3348	1629	1687	1535
tetrafluoro-borate	3374	1630	1685	1541
tosylate	3292	1627	1683	1549

cyclopeptide. The outer H(δ) protons of **2** only experience a small upfield shift upon complexation of BTMA$^+$ tosylate. Cross-peaks between the BTMA$^+$ N-methyl and the aromatic and NH protons of **2** show that, in solution, the cationic head of the guest is inserted deeply into the dish-shaped cavity of the receptor.

The BF_4^- anion seems to interact with the NH groups of **2** by NH···F bonds. Results of the FT-IR-spectroscopic characterization of this and all other anion complexes of **2** are summarized in Table 3. In three complexes of **2**, the ones with tosylate, tetrafluoroborate, and iodide counterions, a higher K_a was observed for the N-methyl than for the n-butyl CH_3 group of the cation (Table 2). This effect is stronger for anions that interact better with the cyclic peptide. Indeed, it is not surprising that electrostatic interactions between the anion located at the bottom of the cyclopeptide cavity and the guest favor a complex geometry with the cationic headgroup of the guest closer to the anion. With two of the investigated anions, picrate and tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB$^-$), this effect was not observed, however. In both cases, the stability constants of the N-methyl and n-butyl CH_3 groups of BTMA$^+$ are of the same order of magnitude, and even those of the N(α)CH_2 groups of the cations (K_a(N(α)CH_2) for picrate 1270 M^{-1} and for TFPB$^-$ 1340 M^{-1}) are comparable. Furthermore, the BTMA$^+$ complex stabilities of **2** are similar in the presence of either anion.

Since the NMR resonance of the inner H(δ) protons of **2** ($\Delta\delta$ < +0.03 ppm) and the IR spectrum of the cyclic

Table 4. Stability Constants K_a and Maximum Chemical Shifts $\Delta\delta_{max}$ of Complexes of 1−4 with BTMA$^+$ Iodide ($CDCl_3$, T = 298 K)

	K_a(R-$N(CH_3)_3$)			K_a(*n*-butyl CH_3)			$K_a(1)/K_a(2)$
cyclopeptide	$K_a(1)^a$	$-\Delta\delta_{max}$	-ΔG	$K_a(2)^a$	$-\Delta\delta_{max}$	$-\Delta G$	
2	21100	1.11	24.7	7320	0.35	22.0	2.9
3	3860	0.82	20.5	3360	0.89	20.1	1.1
4	850	0.49	16.7	800	0.56	16.6	1.1
1	300	0.05	14.1	380	0.02	14.7	0.8

[a] Error limits of K_a < 20%.

peptide are not significantly affected by the presence of picrate or TFPB$^-$ (Table 3), specific interactions between these anions and the peptide are not visible. From other molecular recognition studies it is in fact known that the large lipophilic anion TFPB$^-$ does not interfere in interactions between a cation and a receptor.[25] The splitting of the N−H vibration and amide II bands in the FT-IR spectrum indicates that **2** is conformationally flexible in solution in the presence of both anions. The cyclopeptide is nevertheless able to interact with BTMA$^+$, and complex formation must now be primarily due to cation−π interactions. Since the peptide is not preorganized by interactions with an anion, the maximum chemical shifts $\Delta\delta_{max}$ of the BTMA$^+$ *N*-methyl groups are reduced. We have detected a similar behavior for **1** in the absence of effector anions.[7]

The stability of the BTMA$^+$ picrate or the TFPB$^-$ complex of **2** is 3−4 times larger than that of the BTMA$^+$ iodide complex of **1**. Despite the conformational flexibility of **2**, the proline-containing cyclopeptide obviously forms significantly more stable complexes with BTMA$^+$ than **1**, which may certainly be attributed to the rigidity of the proline subunits.

The different $\Delta\delta_{max}$ values of the BTMA$^+$ protons in the presence of TFPB$^-$ or picrate show that the two anions still influence cation complex formation of **2** differently. Possibly the geometry with which BTMA$^+$ is included into the cyclopeptide cavity is not the same. We could therefore not completely eliminate the effects of anions on the cation complex formation of **2**. Especially in nonpolar solvents a relatively strong ion pair aggregation has to be considered and the cation may still be oriented in close proximity of the cation even after complexation by the host. In fact, the dependence of the cation affinity of artificial receptors such as calixarenes on the nature of the anion has often been attributed solely to ion pair aggregation.[8e,g,17a] In the case of cyclopeptide **2**, however, it is evident that specific interactions of the anions with the receptor may also be responsible for an anion effect on cation binding.[26]

Complexation Properties of 3 and 4. The mixed cyclopeptides **3** and **4** have been obtained by cyclization of linear hexapeptides with the appropriate subunit sequences. It can be expected that their binding affinities toward, e.g., BTMA$^+$ iodide will range between those of **1** and **2**. Table 4 and Figure 13 show that such a behavior

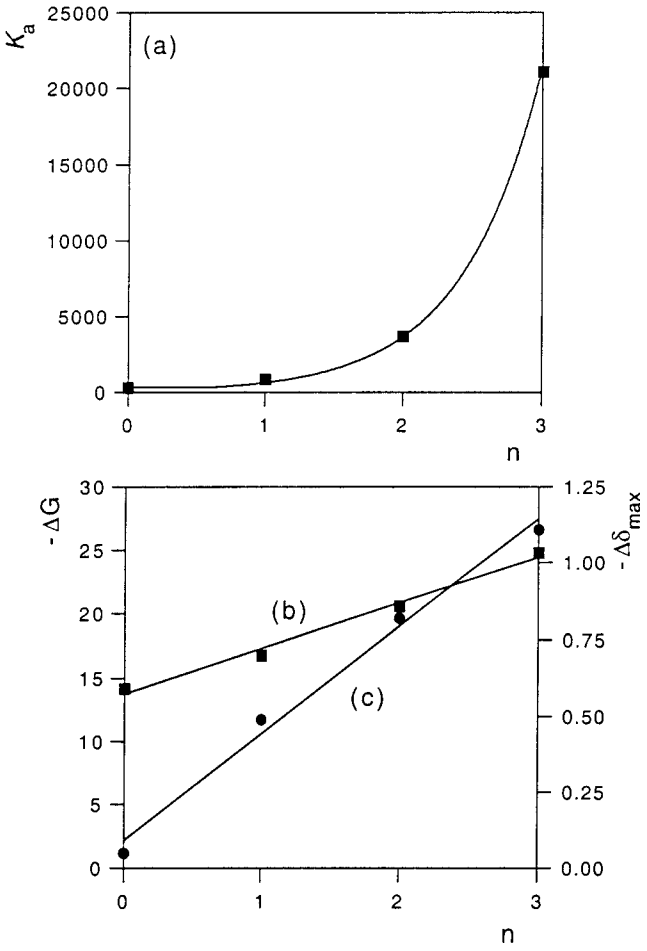

Figure 13. Plots of stability constants K_a (a), free enthalpy of complex formation (ΔG) (b), and $\Delta\delta_{max}$ (c) of complexes of **1**−**4** with BTMA$^+$ iodide vs number of proline residues *n* (K_a in M^{-1}, ΔG in kJ mol^{-1}, $\Delta\delta_{max}$ in ppm, T = 298 K).

was indeed observed. In Figure 13, the dependencies of the stability constants K_a, the free enthalpy of complex formation ΔG, and the maximum shift $\Delta\delta_{max}$ on the number of proline residues in the ring are plotted. The graphs show an exponential increase of K_a when the number of proline residues in the receptor rises from $n = 0$ to $n = 3$. Consequently, a linear relationship is found when ΔG is plotted against n. From the slope of this graph one can calculate that the stability of the BTMA$^+$ iodide complexes increases on average by −3.6 kJ mol^{-1}/additional proline residue in the cyclopeptide. Figure 13c also shows a relatively good linear relationship between $\Delta\delta_{max}$ and *n*. This dependence indicates that the more proline subunits the cyclopeptide receptors contain, the better they are preorganized for the complexation of cations. We have shown that the preorganization of **2** is not only due to the rigidity of the proline subunits but also to interactions of the cyclopeptide NH groups with the anion. Interactions with iodide have not been detected in the glutamic acid containing cyclopeptide **1** because the amides in this peptide are involved in intramolecular hydrogen bonds. In principle, such hydrogen bonds should always be possible when a receptor of the general structure depicted in Figure 1 contains natural amino acids other than proline. Indeed, significant hydrogen bonding of the NH groups was detected in the FT-IR spectra of **3** and **4**. The number of possible intramolecular hydrogen bonds is directly proportional to the number

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of glutamic acid subunits in the ring. Therefore, the decrease of cation complex stability with increasing number of glutamic acid subunits can be attributed to a successive loss of the iodide affinity of the cyclopeptides. The more glutamic acid subunits these peptides contain, the fewer NH groups are free to interact with the anion. The reduced iodide complex stabilities of **3** and **4** can be indirectly derived from the decreasing stability differences when different $BTMA^+$ protons are monitored in the titrations (Table 4).

Our investigations illustrate that the choice of subunits has a significant effect on the conformational behavior of the cyclopeptides and, consequently, their binding properties. Knowledge of the influence of individual subunits should in principle enable one to modulate the properties of such host molecules deliberately by choosing an appropriate subunit sequence.

Conclusions and Outlook

In certain aspects, the cyclopeptides presented in this paper have properties similar to calixarenes. In solution, they adopt conformations comparable to the cone conformation of calixarenes. Moreover, they are able to bind cations by cation−π interactions with their aromatic subunits. However, in contrast to simple calixarenes, the aromatic rings are not their only binding sites. The presence of NH groups allows additional interactions with anions by hydrogen bonding. Simultaneous cation and anion complexation has already been described for cyclopeptide **1**.[7] In this paper we have extended this approach with the introduction of the new cyclopeptide **2**. Receptor **2** is able to bind a variety of ion pairs and can therefore be regarded as a new ditopic receptor. We have found that the nature of the cationic guest affects the affinity of the cyclopeptide toward the corresponding anion and vice versa. The cooperativities of various cations and anions have been quantified independently and could be furthermore correlated with specific effects of the ions on the conformation of **2** in the complexes. We could also demonstrate that the binding properties of the presented cyclopeptides are determined by influences of their subunits on the preferred solution conformation of the host. A detailed knowledge of the influence of individual subunits may facilitate the syntheses of receptors with predictable properties. This approach is highly flexible with regard to the nature of the subunits. In addition, the introduction of functional groups either in the aromatic or the aliphatic subunits of the cyclopeptides which are able to serve as additional binding sites can be realized easily. Studies on the design of new and efficient artificial host molecules on the basis of similar cyclopeptides are in progress.

Experimental Section

Materials. All solvents were dried according to standard procedures prior to use. DMF pA was purchased from Fluka and was used without further purification. PyCloP was prepared according to the literature procedure.[27] TBTU was purchased from Bachem. For chromatographic separations either ICN silica gel 32−63 (ICN Biomedicals) or a Merck LiChroprep RP-8 (40−63 μm) prepacked column, size B (310−25), was used. Elemental analyses were carried out at the Pharmaceutical Institute of the Heinrich-Heine-University, Düsseldorf, Germany. The syntheses of AB-OBn·TsOH, Boc-Glu(O*i*Pr)-OBn, Boc-[AB-Glu(O*i*Pr)-AB]$_2$-OBn, Boc-[AB-Glu(O*i*Pr)-AB]$_3$-OBn, and *cyclo*[AB-Glu(O*i*Pr)-AB]$_2$ have been described elsewhere.[7] The following abbreviations are used: TsOH, toluene-4-sulfonic acid; Bn, benzyl-; BOC, *tert*-butoxycarbonyl-; DIEA, *N*-ethyldiisopropylamine; TFA, trifluoroacetic acid; PyCloP, chlorotripyrrolidinophosphonium hexafluorophosphate; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; Glu, glutamic acid; Pro, proline; AB, 3-aminobenzoic acid.

Host−Guest Titrations. Stock solutions of the cyclopeptide (**2**, 1 μmol/800 μL; **3**, **4**, 2 μmol/800 μL) in $CDCl_3$ (water content 0.01%) and of the corresponding guest (0.4 μmol/200 μL for **2**, **3**; 0.2 μmol/200 μL for **4**) in 1% DMSO-d_6/$CDCl_3$ were prepared. Altogether 11 NMR tubes were set up by adding increasing amounts of the host solution (0−800 μL) to 200 μL of the guest solution. All samples were made up to 1 mL with $CDCl_3$, and their ^{1}H NMR spectra were recorded. Chemical shifts were calculated by using the $CHCl_3$ signal at 7.27 ppm as internal standard. The shifts of, e.g., the *N*-methyl protons of the guest were plotted against c_{host}/c_{guest}. From the resulting saturation curve, K_a and $\Delta\delta_{max}$ were calculated by a nonlinear least-squares fitting method for 1:1 complexes using the SIGMA Plot 3.0 (Jandel Scientific) software package.[21] The same set of NMR spectra could also be used for the determination of the stability of the cyclopeptide iodide complexes. For this, the chemical shifts of the inner H(δ) protons of **2** were plotted against c_{guest}/c_{host}. For the determination of the chemical shift at $c_{guest} = 0$ a spectrum of the pure cyclopeptide in 0.2% DMSO-d_6/$CDCl_3$ was recorded. The stability constant could be calculated from the resulting saturation curve by taking into account that this time protons of the host and not of the guest have been monitored.

General Procedure for Hydrogenation of Benzyl Esters. The ester is dissolved in methanol (50 mL/mmol). After addition of 10% Pd/C (100 mg) the resulting reaction mixture is hydrogenated at 1 atm for about 2 h. Completeness of reaction is checked by TLC. The catalyst is filtered off through a layer of Celite and washed with methanol. The solution is evaporated to dryness in vacuo.

General Procedure for Cleavage of *N-tert*-Butoxycarbonyl Groups. Method A. The carbamate is dissolved in CH_2Cl_2 (5 mL). The resulting solution is cooled with an ice bath, and trifluoroacetic acid (5 mL) is added dropwise. The reaction mixture is stirred for 1.5 h at 0−5 °C. Afterward, the solvent is evaporated in vacuo. The residue is dissolved in ethyl acetate, and the solution is extracted twice with 10% Na_2CO_3 solution and three times with water. The organic layer is dried, 1 N HCl (1 mL/mmol) is added, and the mixture is evaporated to dryness in vacuo.

Method B. The carbamate is suspended in 1,4-dioxane (20 mL). The resulting suspension is cooled with an ice bath, and a 6 N solution of HCl in 1,4-dioxane (40 mL) is added dropwise. The reaction mixture is stirred for 2 h at 0−5 °C. Afterward, the solution is evaporated to dryness in vacuo.

Dipeptide BOC-(L)Pro-AB-OBn. 3-Aminobenzoic acid benzyl ester toluene-4-sulfonate (2.39 g, 6.00 mmol) and BOC-(L)-proline (1.81 g, 8.40 mmol) as well as PyCloP (3.54 g, 8.40 mmol) are dissolved in CH_2Cl_2 (120 mL). At room temperature, DIEA (3.96 mL, 22.8 mmol) is added dropwise, and the reaction mixture is stirred overnight. Afterward, the solvent is evaporated in vacuo, and the product is isolated chromatographically (1:1 ethyl acetate/hexane) from the residue. The product solidifies during drying in vacuo: yield 2.49 g (98%); mp 52−55 °C; $[\alpha]^{25}_D = -59.0$ ($c = 2$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C, TMS) δ 1.33 (s, 9H), 1.86 (m, 3H), 2.19 (m, 1H), 3.38 (m, 2H), 4.30 (dd, $J = 8.3/4.1$ Hz, 1H), 5.35 (s, 2H), 7.43 (m, b, 6H), 7.67 (td, $J = 7.7/1.2$ Hz, 1H), 7.88 (2 × dd, $J = 8.1/1.1$ Hz, 1H), 8.22 (t, $J = 1.9$ Hz, 1H), 9.86 (s, 1H). Anal. Calcd for $C_{24}H_{28}N_2O_5$ (424.5): C, 67.91; H, 6.65; N, 6.60. Found: C, 67.70; H, 6.81; N, 6.67.

Tetrapeptide BOC-[(L)Pro-AB]$_2$-OBn. BOC-(L)Pro-AB-OBn (0.89 g, 2.10 mmol) is deprotected at the terminal amino group according to method A. An equivalent amount of the same dipeptide is hydrogenated. Both components as well as

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PyCloP (1.2 equiv, 2.52 mmol, 1.06 g) are dissolved in CH_2Cl_2 (20 mL/mmol). At room temperature, DIEA (3.4 equiv, 7.14 mmol, 1.24 mL) is added dropwise, and the reaction mixture is stirred overnight. Afterward, the solvent is evaporated in vacuo, and the product is isolated chromatographically (ethyl acetate) from the residue. The product is triturated with hexane to afford a white solid: yield 1.26 g (94%); mp 133 °C (softening from 105 °C); $[\alpha]^{25}_D = -106.0$ ($c = 2$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C, TMS) δ 1.34 (s, 9H), 1.90 (m, 6H), 2.16 (m, 1H), 2.27 (m, 1H), 3.39 (m, 2H), 3.58 (m, 2H), 4.23 (dd, $J = 8.3/3.8$ Hz, 1H), 4.58 (m, 1H), 5.36 (s, 2H), 7.17 (d, $J = 6.8$ Hz, 1H), 7.39 (m, b, 7H), 7.64 (d, $J = 7.2$ Hz, 1H), 7.67 (td, $J = 7.7/1.3$ Hz, 1H), 7.75 (s, b, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 8.20 (s, b, 1H), 9.72 (s, 1H), 9.95 (s, 1H). Anal. Calcd for $C_{36}H_{40}N_4O_7 \cdot H_2O$ (658.7): C, 65.64; H, 6.43; N, 8.50. Found: C, 65.49; H, 6.46; N, 8.24.

Hexapeptides. A dipeptide is deprotected at the terminal amino group according to method A. An equivalent amount of a tetrapeptide is hydrogenated. Both components as well as TBTU (1.1 equiv) are dissolved in DMF (30 mL/mmol). At room temperature, DIEA (3.2 equiv) is added dropwise, and stirring is continued for 2 h. Afterward, the reaction mixture is poured into water (150 mL/mmol). The pH is adjusted to ca. 4 with 1 N HCl, and the suspension is stirred for another 10 min. The precipitate is filtered off, washed with water, and dried. According to TLC, the product is usually obtained in high purity by this procedure and can be used for the following step without further purification. A small amount is purified chromatographically (1:15 methanol/CH_2Cl_2) for characterization.

BOC-[(L)Pro-AB]$_3$-OBn: yield 92%; mp 186 °C (softening from 147 °C); $[\alpha]^{25}_D = -144.8$ ($c = 2$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C, TMS) δ 1.34 (s, 9H), 1.93 (m, 9H), 2.39 (m, 3H), 3.38 (m, 2H), 3.57 (m, 4H), 4.23 (dd, $J = 8.3/3.7$ Hz, 1H), 4.59 (m, 2H), 5.36 (s, 2H), 7.17 (d, $J = 6.6$ Hz, 2H), 7.43 (m, b, 8H), 7.65 (m, 3H), 7.76 (s, b, 2H), 7.86 (d, $J = 7.7$ Hz, 1H), 8.21 (s, b, 1H), 9.73 (s, 1H), 9.83 (s, 1H), 9.95 (s, 1H). Anal. Calcd for $C_{48}H_{52}N_6O_9 \cdot H_2O$ (875.0): C, 65.89; H, 6.22; N, 9.60. Found: C, 65.88; H, 6.15; N, 9.51.

BOC-(L)Glu(O*i*Pr)-AB-[(L)Pro-AB]$_2$-OBn: yield 92%; mp 136 °C (softening from 127 °C); $[\alpha]^{25}_D = -76.1$ ($c = 2$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C, TMS) δ 1.16 (d, $J = 6.2$ Hz, 6H), 1.34 (s, 9H), 1.79−2.47 (m, b, 12H), 3.39 (m, 2H), 3.59 (m, 2H), 4.24 (dd, $J = 8.3/3.6$ Hz, 1H), 4.64 (m, 2H), 4.88 (sept, $J = 6.3$ Hz, 1H), 5.36 (s, 2H), 7.17 (d, $J = 7.2$ Hz, 1H), 7.35 (m, b, 8H), 7.58 (dt, $J = 8.0/1.4$ Hz, 1H), 7.65 (d, $J = 8.3$ Hz, 1H), 7.69 (dt, $J = 8.2/1.6$ Hz, 1H), 7.76 (m, 2H), 7.89 (2 × dd, $J = 8.2/1.1$, 1H), 8.02 (s, 1H), 8.81 (d, $J = 7.4$ Hz, 1H), 8.24 (t, $J = 1.8$ Hz, 1H), 9.73 (s, 1H), 9.85 (s, 1H), 10.01 (s, 1H). Anal. Calcd for $C_{51}H_{58}N_6O_{11} \cdot H_2O$ (949.1): C, 64.54; H, 6.37; N, 8.86. Found: C, 64.50; H, 6.42; N, 8.94.

BOC-[(L)Glu(O*i*Pr)-AB]$_2$-(L)Pro-AB-OBn: yield 94%; mp 108−113 °C; $[\alpha]^{25}_D = -56.1$ ($c = 2$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C, TMS) δ 1.17 (m, 12H), 1.39 (s, 9H), 1.86−2.44 (m, b, 12H), 3.60 (m, 2H), 4.14 (m, 1H), 4.64 (m, 2H), 4.89 (sept, $J = 6.3$ Hz, 2H), 5.35 (s, 2H), 6.61 (d, $J = 7.6$ Hz, 1H), 7.18 (d, $J = 8.2$ Hz, 1H), 7.39 (m, b, 8H), 7.59 (dt, $J = 8.0/1.2$ Hz, 1H), 7.65 (m, 2H), 7.78 (m, 2H), 7.86 (d, $J = 7.9$ Hz, 1H), 8.01 (t, $J = 1.7$ Hz, 1H), 8.20 (m, 2H), 9.76 (s, 1H), 9.90 (s, 1H), 9.96 (s, 1H). Anal. Calcd for $C_{54}H_{64}N_6O_{13}$ (1005.1): C, 64.53; H, 6.42; N, 8.36. Found: C, 64.38; H, 6.64; N, 8.37.

Cyclopeptides. The linear hexapeptides are first hydrogenated. Afterward, they are deprotected at the terminal amino group according to method B. For cyclization, a completely deprotected hexapeptide is dissolved in DMF (100 mL/mmol), and DIEA (3.2 equiv) is added. The resulting mixture is heated to 80 °C, and a solution of TBTU (1.1 equiv) in DMF (20 mL) is added dropwise. Stirring is continued for 2 h at 80 °C. The solvent is then evaporated in vacuo. The residue is stirred with diethyl ether overnight (**2**) or triturated with water (**3**, **4**). The crude product is filtered off, dried, and purified chromatographically. At first, an initial purification step is carried out using a silica gel column (10:1 CH_2Cl_2/MeOH). The resulting material is dissolved in a small amount of DMF and further purified by using a RP-8 column.

***cyclo*[(L)Pro-AB]$_3$ (2).** For the RP-8 column, initially 1:10 1,4-dioxane/H_2O is used as eluent. Gradually it is changed to 1:5 1,4-dioxane/H_2O and then to 1:2.5 1,4-dioxane/H_2O, with which the pure product is eluted. The product is recrystallized from methanol: yield 43%; mp >250 °C (softening from 243 °C); $[\alpha]^{25}_D = -66.8$ ($c = 2$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS) δ 1.82−2.03 (m, 9H), 2.28 (m, 3H), 3.39 (m, 3H), 3.46 (m, 3H), 4.64 (dd, $J = 8.2/3.6$ Hz, 3H), 7.11 (d, $J = 7.5$ Hz, 3H), 7.22 (d, $J = 8.1$ Hz, 3H), 7.38 (t, $J = 7.9$ Hz, 3H), 8.38 (s, 3H), 10.31 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C, TMS) δ 24.5 C(γ), 29.4 C(β), 49.3, 59.8, 118.1/118.2, 119.5/119.6, 120.4, 128.5, 138.1, 138.8/138.9, 168.7, 170.2/170.3. Anal. Calcd for $C_{36}H_{36}N_6O_6 \cdot 2H_2O$ (684.7): C, 63.15; H, 5.89; N, 12.27. Found: C, 63.44; H, 5.86; N, 12.22. CI-MS (NH_3) [m/z (relative intensity)]: 666 (100) [$M + NH_4^+$], 649 (2) [$M + H^+$].

Crystal Structure Analysis of 2.[28] Data: $C_{39}H_{48}N_6O_9 \cdot (CH_4O)_3$ $M_r = 744.83$, colorless prism, crystallized from methanol, crystal size 0.24 × 0.36 × 0.40 mm, $a = 8.490(1)$ Å, $b = 19.624(1)$ Å, $c = 22.681(2)$ Å, $V = 3779.0(5)$ Å^3, $T = 100$ K, orthorhombic, space group $P2_12_12_1$ (No. 19), $Z = 4$, $D_c = 1.31$ g cm^{-3}, $\mu = 0.09$ mm^{-1}; Siemens SMART diffractometer, Mo Kα X-radiation, $\lambda = 0.710\ 73$ Å, 42307 measured reflections, analytical absorption correction ($T_{min} = 0.964\ 96$, T_{max} 0.986 52), 14 253 unique ($\theta_{max} = 33.9°$), 9608 (gt) with $I > 2.0\sigma(F_o^2)$. The structure was solved by direct methods[29] and refined by full-matrix least squares[30] on F^2 for all data with Chebyshev weights, with $R = 0.052$ (gt), $R_w = 0.123$ (all data), 514 parameters, $S = 0.979$, H atoms riding, disordered methylene group [0.66(1):0.34(1)], max shift/error 0.001, and residual $\rho_{max} = 0.362$ e Å^{-3}.

Crystal Structure Analysis of 2·*N*-Methylquinuclidinium Iodide.[28] Data: $C_{36}H_{36}N_6O_6[I]^-[C_8H_{16}N]^+ \cdot CDCl_3$, $M_r = 1022.19$, colorless prism, crystallized from toluene/deuteriochloroform, crystal size 0.11 × 0.14 × 0.24 mm, $a = 13.7350(2)$ Å, $b = 14.7780(2)$ Å, $c = 22.3104(3)$ Å, $V = 4528.5(1)$ Å^3, $T = 100$ K, orthorhombic, space group $P2_12_12_1$ (No. 19), $Z = 4$, $D_c = 1.50$ g cm^{-3}, $\mu = 0.94$ mm^{-1}, Nonius KappaCCD diffractometer, Mo Kα X-radiation, $\lambda = 0.710\ 73$ Å, 41 057 measured reflections, analytical absorption correction ($T_{min} = 0.827\ 23$, $T_{max} = 0.922\ 37$), 9888 unique ($\theta_{max} = 27.5°$), 7241 (gt) with $I > 2.0\sigma(F_o^2)$. The structure was solved by direct methods[29] and refined by full-matrix least squares[30] on F^2 for all data with Chebyshev weights, with $R = 0.056$ (gt), $R_w = 0.158$ (all data), 559 parameters, $S = 1.04$, H atoms riding, absolute configuration determined [Flack parameter −0.03(2)], max shift/error 0.001, and residual $\rho_{max} = 2.317$ e Å^{-3} (1.615 Å from Cl1).

***cyclo*[(L)Glu(O*i*Pr)-AB-[(L)Pro-AB]$_2$] (3).** For the RP-8 column, initially 1:2 MeOH/H_2O is used as eluent. Gradually it is changed to 1:1 MeOH/H_2O and then to 2:1 MeOH/H_2O, with which the pure product is eluted. In case it is not obtained white after this column, another one on silica gel can be carried out with acetone as eluent: yield 34%; 206−214 °C; $[\alpha]^{25}_D = -33.0$ ($c = 2$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS) δ 1.15 + 1.16 (2 × d, $J = 6.3$ Hz, 6H), 1.85−2.49 (m, b, 12H), 3.51 (m, 4H), 4.67 (m, 3H), 4.86 (sept, $J = 6.2$ Hz, 1H), 7.12 (d, $J = 7.6$ Hz, 1H), 7.20 (m, 2H), 7.40 (m, b, 4H), 7.50 (m, 2H), 8.04 (t, 1H), 8.41 (t, 1H), 8.73 (t, 1H), 8.46 (d, $J = 7.9$ Hz, 1H), 10.28 (s, 1H), 10.33 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C, TMS) δ 21.5, 24.4, 24.6, 26.6, 29.3, 29.4, 30.5, 49.3, 49.4, 53.1, 59.7, 60.1, 67.1, 117.9, 118.0, 119.2, 119.6, 120.5, 120.7, 121.5, 122.6, 128.5, 128.7, 135.7, 137.8, 137.9, 138.4, 138.8, 139.1, 166.9, 168.6, 168.7, 169.9,

(28) The crystallographic data (without structure factors) for **2** and **2**·*N*-methylquinuclidinium iodide have been deposited as supplementary publications CCDC-126020 and CCDC-126021 at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained from the following: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Telefax +44-1223/336-033. E-mail: deposit@ccdc.cam.ac.uk.)

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170.3, 170.4, 171.7. Anal. Calcd for $C_{39}H_{42}N_6O_8 \cdot H_2O$ (740.8): C, 63.23; H, 5.99; N, 11.34. Found: C, 63.51; H, 5.98; N, 11.33. CI-MS (NH_3) [*m*/*z* (relative intensity)]: 740 (100) [M + NH_4^+], 723 (2) [M + H^+], 680 (4) [M − *i*PrOH + NH_4^+].

***cyclo*[(L)Glu(O*i*Pr)-AB]$_2$-(L)Pro-AB] (4).** For the RP-8 column, initially 1:2 MeOH/H_2O is used as eluent. Gradually it is changed to 1:1 MeOH/H_2O, 2:1 MeOH/H_2O, and then to 3:1 MeOH/H_2O, with which the pure product is eluted. In case it is not obtained white after this column, another one on silica gel can be carried out with acetone as eluent: yield 43%; 172−177 °C; $[\alpha]^{25}_D = -28.2$ (*c* = 2, methanol); ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS) δ 1.16 (m, 12H), 1.85−2.45 (m, b, 12H), 3.45 (m, 1H), 3.54 (m, 1H), 4.58 (m, 1H), 4.67 (m, 2H), 4.87 + 4.89 (2 × sept, *J* = 6.3 Hz, 2 × 1H), 7.17 (dt, *J* = 7.5 Hz, 1H), 7.32 (dt, *J* = 7.9 Hz, 1H), 7.42 (m, b, 6H), 7.68 (d, *J* = 8.0 Hz, 1H), 8.01 (t, 1H), 8.35 (t, 1H), 8.73 (t, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 7.7 Hz, 1H), 10.25 (s, 1H), 10.31 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C, TMS) δ 21.5, 24.6, 26.2, 26.5, 29.4, 30.4, 30.6, 49.4, 53.1, 53.5, 59.9, 67.0, 67.1, 117.8, 118.8, 119.1, 120.6, 121.0, 121.4, 121.9, 122.5, 122.6, 128.6, 128.7, 135.1, 135.2, 137.7, 138.3, 138.7, 139.1, 166.9, 167.3, 168.4, 169.9, 170.0, 170.4, 171.7. Anal. Calcd for $C_{42}H_{48}N_6O_{10} \cdot H_2O$ (814.9): C, 61.91; H, 6.18; N, 10.31. Found: C, 61.87; H, 6.26; N, 10.26. CI-MS (NH_3) [*m*/*z* (relative intensity)]: 814 (100) [M + NH_4^+], 797 (2) [M + H^+].

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Supporting Information Available: FT-IR spectrum of **2** in 1% DMSO-d_6/$CDCl_3$, NOESY NMR spectra of **2** and its $BTMA^+$ tosylate complex in $CDCl_3$, and crystal data, bond lengths and angles, atomic coordinates, and anisotropic thermal parameters for **2** and its complex with *N*-methylquinuclidinium iodide. This material is available free of charge via the Internet at http://pubs.acs.org.

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