Tetazac: A Novel Artificial Receptor for Binding ω-Amino Carboxylates

F. P. Schmidtchen

Lehrstuhl für Organische Chemie und Biochemie der TU München, 8046 Garching, FRG

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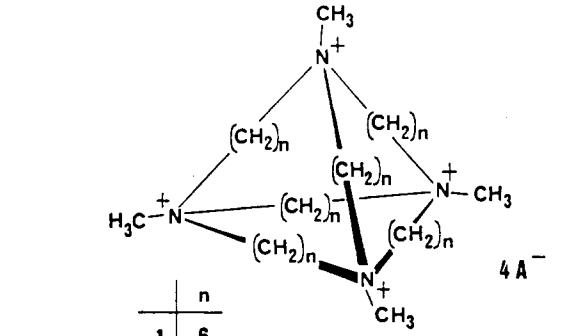
Our concept to produce linearly connected polytopic artificial receptors was developed in order to enhance binding selectivity while conserving a reasonable synthesizability of the host compound. A first step in this direction involves the synthesis of Tetazac (**6**) consisting of two subunits connected by one *p*-xylene bridge. The attachment of a primary ammonium group binding aza crown moiety **3a** to a tetrahedral anion host **1** should give a receptor configuration suitable for complexing ω-amino carboxylates like GABA (**4**) in protic solutions. The synthesis of **6** followed a convergent strategy and produced the target receptor in 28 steps in 2% overall yield. Complexation studies by NMR and ion-selective potentiometry indicate that either subunit in the ditopic host **6** is functional in binding their respective monotopic guests. Collaborative action of the substructures in the binding of zwitterionic species was deduced from comparing the association constants (K_{as}) in 90% aqueous methanol determined by competition with K^+ ion to those obtained with the structurally closely related but monotopic host Amazac (**7**). Though absolute K_{as} values are higher with **7**, the ditopic host **6** shows greater selectivity for hydrophobic or zwitterionic ammonium salts by a factor of 3 or 2.5, respectively. No difference in binding γ-aminobutyric acid (GABA, **4**) or 6-aminohexanoic acid (**24**) to **6** was found (log K_{as} = 2.4), indicating the flexibility of this artificial ditopic receptor.

Selectivity in natural receptors appears to result from a precise arrangement of binding functions that converge to form a geometrically and functionally complementary cavity for the specific substrate. This principle has been mimicked in artificial host systems, too.[1] The more successful approaches follow the strategy to place anchor groups, which by themselves bind to certain structural moieties of the guest, on macrocycles in order to ensure a well-defined spatial relationship between them.[2-5] However, pursuing this route to multitopic artificial receptors, one may foresee aggravating difficulties because the synthetic effort will grow excessively.

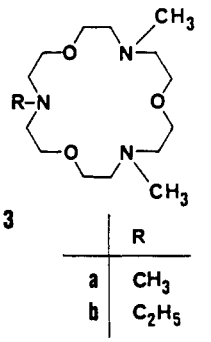
An alternative is to couple anchor groups in a linear unbranched or branched fashion choosing the connector links according to the flexibility required. Since substrate binding in this case requires a special folding of the receptor with the guest acting as a template, one must expect inferior selectivity compared to a host having the same number and types of anchor groups preorganized on a macrocycle. The anticipated loss in selectivity may be compensated or even outmatched by the sheer number of binding functions that can be incorporated into a linear polytopic receptor much more readily than into its macrocyclic counterpart.

As a consequence the concept of linear multisite receptors does not appear to be well suited for selective binding of small guest species, because they cannot provide a sufficient number of independently recognizable functions. Instead, larger and biologically relevant compounds (hormones, nucleotides, vitamins, coenzymes, some metabolites and drugs) provide attractive candidates for complexation by open-chain polytopic hosts. Binding these multifunctional and frequently charged substrates in protic solutions still presents a challenging problem, because one cannot rely on hydrophobic interactions that have been used as the most powerful force between lipophilic guests and vast majority of artificial hosts.[1-5] Rather, anchor groups must be selected and combined that are capable of binding the ionized and heavily solvated substructures of the guests. Compared to the opulent variety of artificial receptor groups for hydrophobic and cationic species, the selection of anion-complexing agents is still very limited.[6]

Macrotricyclic quaternary ammonium salts **1** and **2** have been shown to bind anions in aqueous solution by incorporation of the guest into their molecular cavities.[7] These

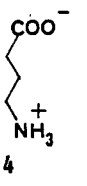


n
1 6
2 8



3

R
a CH_3
b C_2H_5



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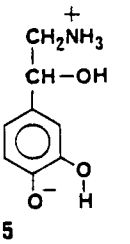

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(1) (a) Tabushi, I. *Tetrahedron* **1984**, *40*, 269. (b) Murakami, Y. *Top. Curr. Chem.* **1983**, *115*, 107. (c) Sirlin, C. *Bull. Soc. Chim. Fr.* **1984**, II 5. (d) Purmal, A. P.; Nikolaev, L. A. *Russ. Chem. Rev.* **1985**, *54*, 466. (e) Schmidtchen, F. P. *Top. Curr. Chem.* **1986**, *132*, 101.

(2) (a) Fujita, K.; Ejima, S.; Imoto, I. *Chem. Lett.* **1985**, *11*. (b) Fujita, K.; Ejima, S.; Imob, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1277. (c) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614. (d) Harada, A.; Furue, M.; Nozakura, S. *Polym. J.* **1980**, *12*, 29.

(3) (a) Lai, Ch.-F.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 5179. (b) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993.

(4) (a) Sutherland, I. O. *Chem. Soc. Rev.* **1986**, *15*, 63. (b) Johnson, M. R.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1979**, 306, 309. (c) Jones, N. F.; Kumar, A.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1981**, 990. (d) Kotzyba-Hibert, F.; Lehn, J.-M.; Vierling, P. *Tetrahedron Lett.* **1980**, *21*, 941. (e) Hamilton, A. D.; Lehn, J.-M.; Sessler, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 311. (f) Kotzyba-Hibert, F.; Lehn, J.-M.; Saigo, K. *J. Am. Chem. Soc.* **1981**, *103*, 4266.

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(6) (a) Kimura, E. *Top. Curr. Chem.* **1985**, *128*, 113. (b) Gelb, R. I.; Lee, B. T.; Zompa, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 909. (c) Pierre, J.-L.; Baret, P. *Bull. Soc. Chim. Fr.* **1983**, II, 367. (d) Dietrich, B.; Guilhem, J.; Lehn, J.-M.; Pascard, C.; Sonveaux, E. *Helv. Chim. Acta* **1984**, *67*, 91. (e) Dietrich, B. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic: London, 1984; Vol. 2, p 337.

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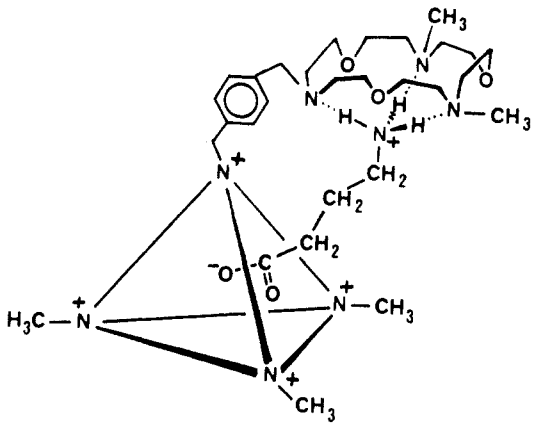


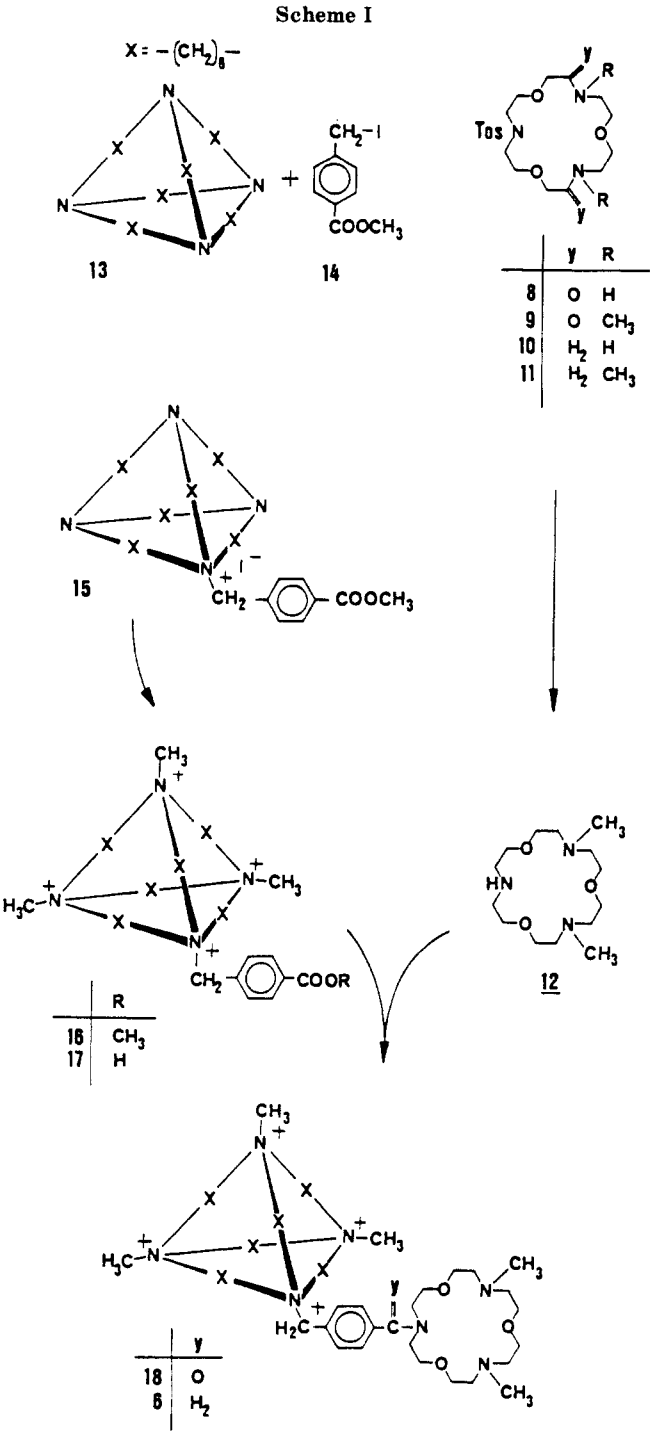
Figure 1. Conceptual binding mode of a zwitterionic ω-amino carboxylate to the ditopic host Tetazac (6).

hosts are rather indiscriminate toward the anionic guests except for a strict size limit and a strong preference of 2 for hydrophobic species. The change of reactivity experienced by the guest on inclusion complex formation may be visible as a catalytic effect of 2 and can be interpreted in terms of a desolvation phenomenon of the anionic function.[8,9] Though rather unselective hosts, 1 and 2 hold the advantages of easy modifiability via quaternization of the parent macrotricyclic tertiary amines and the unambiguous structure of the anion–host inclusion complex.

The first step on the way toward multilocular linear receptors requires the attachment of another binding group to create a ditopic artificial host molecule. Our choice of an aza crown ether 3[4f,10] from the arsenal of primary ammonium binding groups opened the opportunity to construct a host molecule suitable for complexation of zwitterionic species. Some of these play important physiological roles, e.g. the neurotransmitter γ-aminobutyric acid (4, GABA) or the hormone noradrenalin (5). The possible host–guest complex structure that guided our thoughts is depicted in Figure 1.

The attachment of one anion host at a nitrogen center in 3 leaves another two similar sites for propagation toward polytopic hosts. In addition, the complexing capability of 3 may be tuned by protonation, and it has been reported that its pattern of nitrogen atoms leads to a particularly favorable stability ratio of the primary ammonium vs. the alkali-metal complexes (~10:1),[10] so that competition with ubiquituous monovalent cations is minimized. The connecting bridge of anion- and cation-binding subsites had to meet two fundamental requirements: Since the monotopic moieties are invisible by UV detection, a UV chromophore was to be introduced to aid in the analysis. This can be achieved employing an aromatic unit that coincidently satisfies the second condition: the restriction of internal rotations in the bridge compared to an aliphatic chain of the same length in order to reduce flexibility. Thus, the simplest representative of a linear polymodular host is the ditopic receptor 6. We name it 6-Tetazac to abbreviate the rational expression while maintaining information on its construction from the small tetrahedral anion host 1 (six methylene groups between the quaternary nitrogens) and the aza crown ether 3. Here we report on

Scheme I



the synthesis of 6 and some of its complexation properties, in particular with respect to its selectivity features relative to the monotopic analogue 7 (Amazac).[11]

Results and Discussion

(1) Synthesis of Tetazac (6). The modular structure of 6 a priori suggests a convergent synthetic strategy preparing the monotopic receptor units separately and tying them together by a *p*-xylene bridge in the last steps. Whereas the attachment of the tetrahedral anion-binding subsite to the connector unit must proceed via quaternization of the parent tertiary amine, there was a choice of coupling reactions to fix the aza crown portion depending on the oxidation state of the bridging moiety. Amide formation between a benzoic acid derivative and a sec-

(7) (a) Schmidtchen, F. P. *Angew. Chem.* **1977**, *89*, 751; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 720. (b) Schmidtchen, F. P. *Chem. Ber.* **1980**, *113*, 864. (c) *Ibid.* **1981**, *114*, 597. (d) Schmidtchen, F. P.; Müller, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1115.

(8) Schmidtchen, F. P. *J. Chem. Soc., Perkin Trans. 2* **1986**, 135.

(9) (a) Schmidtchen, F. P. *Chem. Ber.* **1984**, *117*, 725. (b) *Ibid.* **1984**, *117*, 1287.

(10) Lehn, J.-M.; Vierling, P. *Tetrahedron Lett.* **1980**, *21*, 1323.

(11) Schmidtchen, F. P. *Tetrahedron Lett.* **1984**, *25*, 4361.

ondary aza crown ether amine followed by reduction of the tertiary amide to the corresponding tertiary amine **6** appeared to be the most reliable sequence. This path (Scheme I) required the preparation of the aza crown ether **12** capable of reacting in the prospected manner only. The synthesis of **12** could be developed starting from the monoprotected compound **8**, which could be obtained in nine steps following a published route.[12] The conversion of **8** to the target building block **12** was elaborated by two pathways with comparable success. N-Alkylation of the macrocyclic amide **8** furnished the *N,N'*-d methyl compound **9** (78%). Subsequent reduction by borane/THF led to the monoprotected aza crown macrocycle **11**. Alternatively, reduction of **8** (BH_3/THF) gave the bis(secondary amine) **10**,[12] which was subjected to Eschweiler–Clarke methylation to give **11**. Cleavage of the blocking tosyl function was cleanly accomplished by HBr/AcOH/C_6H_5CH, yielding the ready-to-couple aza crown module **12** in overall yield 13% for 12 steps.

The appropriate coupling partner for the macrocyclic secondary amine **12** was the benzoic acid derivative **17** (Scheme I) carrying the anion host in the para position. To prepare this compound, a monofunctionalization of the parent macrotricyclic tertiary amine **13**, itself obtainable[7b] in 11 steps (5%) from commercial chemicals, is needed. The quaternization of **13** containing four equivalent nitrogen centers of comparable reactivity in general should lead to a mixture of products differing in the degree of alkylation, but owing to the high symmetry of **13**, isomers cannot be formed. Thus a separation according to charge seemed straightforward. Even this proved not to be necessary, since in the reaction of **13** with α-iodotoluic ester **14** in ether the monoalkylated quaternary salt **15** precipitated from the apolar solution, thereby escaping further reaction. Permethylation of the remaining nitrogen atoms and subsequent alkaline cleavage of the ester produced the fully quaternized but monofunctionalized tetrahedral substructure **17** (56% yield from **13**).

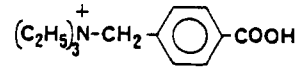
When the amide-forming linkage of the subsites was monitored, **12** and **17** required a fast and reliable analytical method to separate and quantify hydrophilic highly charged organic cations. We developed an HPLC ion-pair separation[13] that helped to choose appropriate condensing agents. The most efficient system for amide formation was found with Mukaiyama's reagent.[14] This proved to be far superior with respect to product yield and handling to a variety of other condensing methods including acid chloride, acid anhydride, carbonyldiimidazole, and carbodiimide. With this clean coupling reaction (85% yield) at hand, we turned to the last reduction step, which proved to be the major obstacle in the whole synthesis. The methods of choice to convert tertiary amides to the corresponding amines are reductions with complex hydrides.[15] However, these require a minimum solubility of the substance to be reduced in the aprotic reaction medium. The amide **18** owing to its saltlike character obviously could not meet this condition, because it was recovered unchanged from reactions employing $LiAlH_4$/ether or borane/THF as reducing agents. The problem was to find a solvent with high solubilizing power but stable toward hydride—preferably borane—reagents. Nitromethane appeared to be first choice, since nitro compounds are resistant to attack by borane but dissolve quaternary ammonium salts readily. Thus, employing a major excess of borane as the dimethyl sulfide complex in nitromethane at 90 °C with short reaction times (6 min) to avoid the deterioration of the product occurring on prolonged heating the freely soluble BF_4 salt of **18** could be transformed to 6-Tetazac (**6**) in 85% yield. With this sequence our ditopic receptor target molecule **6** can be prepared in 28 steps from commercial material in a calculated overall yield of 2% (longest linear sequence 16 steps).

Table I. Association Constants K_{as} (±30%, Mean Values of Six to Eight Determinations) of the Halide Inclusion Complexes of Tetazac (6) in D_2O as Determined by 200-MHz ^1H NMR (eq 1)[a]

	K_{as}, M^{-1}	$\Delta\delta_{max}$, Hz
Cl^-	500	31
Br^-	6670	50
I^-	2700	70

[a] Observed pH 9.8–10.2.

The last steps on this pathway were guided by the pilot synthesis of **7**. The preparation of this analogue lacking the anion-binding site served a dual task. Reaction conditions could be elaborated with a less precious material, and additionally the end product **7** represents a highly desired monotopic receptor to which binding features of 6-Tetazac can be related in order to elucidate the value of the ditopic design.



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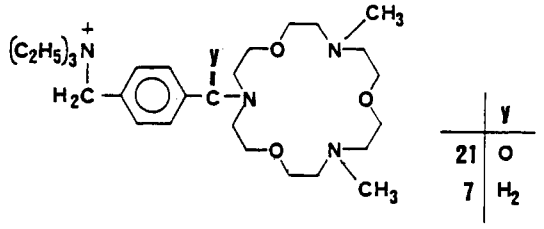

	Y
21	O
7	H_2

(2) Complexation Properties. To evaluate the characteristics of **6** as a selective complexing agent for zwitterionic species in solution it was hoped to benefit from NMR methods since they could provide the most direct access to the determination of the stabilities and structures of the host–guest complexes.[4] For a promising start it was shown that the halide anions interact with **6** in weakly alkaline D_2O in much the same way as its monotopic ancestor **1**;[1e] i.e., the NMR signals of the α-NCH_2 groups and the exo NCH_3 groups of the tetrahedron progressively move into opposite directions on addition of increasing amounts of guest anions. This is the usual picture expected from guest exchange in inclusion complexes happening beyond the time limit of the spectrometer. There was no indication of an extra interaction of a halide anion with the crown ether moiety, nor could we detect a cooperation of the two receptor subsites to bind another guest in addition to the one residing within the tetrahedral cavity. Instead, the experimental changes in chemical shift δ_{obsd} were readily analyzed by eq 1 based on a 1:1 host–guest complex stoichiometry and determining the maximum change in chemical shift δ_{max} at a guest to host ratio of at least 30. This furnished the dissociation constants given in Table I.

$$K_{diss} = [guest]_0(\delta_{max}/\delta_{obsd} - 1) + [host]_0(\delta_{obsd}/\delta_{max} - 1) \quad (1)$$

(12) (a) Graf, E.; Lehn, J.-M. *J. Am. Chem. Soc.* **1975**, *97*, 5022. (b) Graft, E.; Lehn, J.-M. *Helv. Chim. Acta* **1981**, *67*, 1040.
(13) Oswald, H.; Schmidtchen, F. P. *J. Liq. Chromatogr.* **1986**, *9*, 993.
(14) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163.
(15) (a) Brown, H. C.; Heim. P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637. (b) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912. (c) Lane, C. F. *Aldrichim. Acta* **1977**, *10*, 49. (d) Brown, H. C.; Narasimhan, S.; Yong, M. C. *Synthesis* **1981**, 441.

The sequence of stabilities of the halide complexes of **6** follows the same pattern found for **1** (K_{diss}: $Cl^- > I^- > Br^-$), but the absolute values of K_{diss} are smaller by a factor of 5–10.[7c] This could arise from the additional positive charge located on the aza crown moiety at this pH (see below) but may as well be due to the absence of a supporting electrolyte present in the earlier potentiometric determination.[7c] The NMR results confirm, however, that the attachment of a second receptor function of the aza crown type does not abolish but rather strengthens anion binding by the tetrahedral anchor groups.

Reports from the literature[4] made us hope to observe the complex formation between an ammonium salt and the aza crown portion of **6** directly by NMR, too. In aqueous alkaline [$N(CH_3)_4^+OD^-/D_2O$] solutions of **6**, the addition of simple primary ammonium salts (e.g., $CH_3NH_3^+BF_4^-$) resulted in rapid transprotonation, i.e. proton donation from the primary amino group to the aza crown receptor. There was no sign of a change in chemical shift as a result of host-guest complex formation at the crown ether site. The substitution of simple primary ammonium salts for ditopic substrates like *O*-phosphorylethanolamine or GABA, which putatively exhibited an increased complex stability in water owing to an extra binding mode of the anionic site with the complementary host substructure (see Figure 1), did not yield positive evidence for the direct interaction of an ammonium group with the crown macrocycle. This failure could originate from the weakness of the complexes in the aqueous medium as well as from a principal invisibility of the anticipated host–guest association by the NMR method.

If the latter reasoning applies, competition experiments between a reporter ion known to complex in a defined fashion and strength and some guest species could reveal their desired association constants. Either receptor subsite in **6** is known to form specific complexes with some monotopic readily analyzable ions. Since our first choice to set up a competition with bromide ion at the anion-binding tetrahedral subsite of **6** failed because of irreproducible potentials of the bromide-selective electrode in the presence of **6**,[16] we turned to the examination of K^+ binding at the aza crown half of the ditopic receptor. This also meant to change the solvent to 90 vol % aqueous methanol, because the stability of the potassium complex, which is easily measured by K^+-selective glass electrodes, requires a medium of smaller solvating power to allow the determination with sufficient precision in competition experiments. The 18-membered aza crown ethers may form complexes with primary ammonium salts differing in structure with respect to conformation of the macrocycle and the mutual positions of the N substituents of host and guest.[4b,17] Therefore, the prospected competition experiments would yield a somehow averaged association constant. In addition, this contains contributions of host–guest complex structures differing in the mode of interaction at the anion-binding subsite. Though the association constant measured cannot strictly be attributed to one particular complex structure, it is the relevant figure, considering a potential application of the receptor, and should certainly allow an answer to the question of participation of both receptor sites in guest binding as well as on the advantages of the ditopic receptor design.

(16) Aza crown ethers can complex Ag^+ ions and may therefore disturb the reading of bromide-selective Ag/AgBr electrodes. See: Cox, B. G.; Stroka, J.; Firman, P.; Schneider, I.; Schneider, H. *Aust. J. Chem.* **1983**, *36*, 2133.

(17) Hodgkinson, L. C.; Johnson, M. R.; Leigh, S. J.; Spencer, N.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2193.

Table II. Protonation Constants (pK_a) of Aza Crown Ethers, Potential Guest Species, and Buffer Compounds in Water and 90% v/v Aqueous Methanol [μ = 0.1 M $(CH_3)_4N^+Cl^-$, T = 25 °C]

	$pK_a(H_2O)$			pK_a(90% v/v MeOH/H_2O)
	I	II	III	
12	10.53	8.29	6.90	9.85
3b	10.78	8.04	6.60	
Amazac (**7**)	10.3	7.6	6.0	9.3
Tetazac (**6**)	10.2	7.5	6.0	9.2
Tyramine (**22**)		9.2[a]		8.75
6-aminohexanol (**23**)		10.62 (20 °C)[b]		9.05
6-aminohexanoic acid (**24**)		10.75[a]		9.5
4-aminobutyric acid (**4**)		10.43[a]		9.7
4-hydroxytetramethyl-piperidin		10.05[c]		8.8
quinuclidin		10.95[d]		8.9

[a] Sober, H. A., Ed. *Handbook of Biochemistry*; The Chemical Rubber Co.: 1968. [b] Girault, R. C. *R. Hebd. Seances Acad. Sci.* **1958**, *246*, 1705. [c] Rosantsev, E. G.; Gintsberg, E. G. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1966**, 571; *Chem. Abstr.* **1966**, *65*, 8735b. [d] Grob, C. A.; Kaiser, A.; Renk, E. *Chem. Ind.* **1957**, 598.

Another complication arises from the strongly basic character of the crown macrocycle. According to the literature[10] the most stable host–guest configuration involves a primary ammonium ion and the unprotonated aza crown moiety, which under rapid transprotonation conditions translates as a complex formed from the primary amino compound, the aza macrocycle, and one proton. Thus, the optimal binding situation would be met at a pH value just in the middle between the pK_a values characterizing the first protonation step of the aza crown subsite and the substrate amino group. If an additional anionic function present in the substrate is bound by the anion receptor site, the pK_a of the amino groups may shift and thereby alter its binding features. The dependence of the complex stability on pH, however, is supposed to be rather shallow between the relevant pK_a's of host and guest, so that the effect of small pK_a shifts on binding may be undetectable, visualizing the experimental error associated with these competition experiments.

As had already been noted by Lehn[10] studying compound **3a**, the aza crown ethers **12**, **3b**, **6**, and **7** display biphasic pH titration curves in water. Introduction of the first proton proceeds with considerably greater ease than uptake of the other two (pK_{a1}–$pK_{a2} > 2.7$ for the all-tertiary amines **3b**, **6**, and **7**). This has been taken as an indication for the formation of a specific hydronium complex, which is stabilized by three hydrogen bonds within the macrocycle.[10] Though the pK_a values of the receptor molecules **6** and **7** could be determined with less precision than in the case of **12** and **3b** lacking additional quaternary ammonium functions,[18] it is apparent from the data of Table II that the introduction of permanent positive charges quite remote form the actual protonation site lowers the basicity of the aza crown moiety by half a pK_a unit. Compared to the loss of basicity experienced on addition of the first cationic center (**3b** → **7**), the influence of three more positive charges however at more distant positions exhibits only a marginal effect (**7** → **6**). This picture is qualitatively conserved switching the solvent to 90% v/v aqueous methanol. Thus, the pK_a data in this solvent reported in Table II are conditional values taken

(18) I thank Dr. I. Thanos, TU München, for calculation of these protonation constants with his novel computer program, which will be published elsewhere.

Table III. Conditional Association Constants K_{as} (at Various pH Values) of the K^+ Complexes of Aza Crown Ethers in 90% v/v Aqueous Methanol [0.1 M $(CH_3)_4N^+F^-$, 25 °C]

	K_{as}, M^{-1} (obsd pH)		K_{as}, M^{-1} (obsd pH)
12	130[a]	7	400 (9.10)
3a	6000[b]	6	290 (9.40)
7	870[a]	6	200 (9.10)
7	580 (9.40)		

[a] Determined in 0.01 M $(CH_3)_4N^+OH^-$. [b] Taken from ref 10.

form the midpoint of the corresponding titration steps without any correction.

Since the binding of the reporter ion K^+ is inhibited by protonation of the aza crown moiety, the pH value must be carefully controlled and kept constant throughout the determination. Appropriate buffer systems must not contain ions capable of interacting with the anion-binding or primary ammonium binding sites of **6** but should show reasonable buffering capacity in the range of pH 9.5–11.0, be readily soluble, and be preferably nonvolatile. These conditions were met by quinuclidine as well as the sterically crowded 4-hydroxytetramethylpiperidine in combination with their fluoride salts.

The experimentally determined concentrations of K^+ were processed by the mass conservation equations to yield the Bjerrum parameter $\bar{n}$, which was plotted according to eq 3. In any case, straight lines were obtained ($r > 0.99$; $0.2 < \bar{n} < 0.8$), confirming an 1:1 host–guest stoichiometry. The association constants taken from the slopes are given in Table III. The comparison of the charged aza crown

$$\bar{n} = [[K^+]_0 - [K^+]]/[host]_0 \quad (2)$$

$$\bar{n}/(1 - \bar{n}) = K_{as}[K^+] \quad (3)$$

ethers **6** and **7** to the neutral symmetrical parent macrocycle **3a**[10] immediately reveals a drastic drop in complexing ability toward potassium ion. A decrease in complex stability in this sense had to be expected, but electrostatic destabilization owing to the positive charge alone does not seem to be the sole source. The basicities (complex stability with a guest proton) of **3a** and **7** in water are nearly identical (Table II). Though water due to its higher dielectric constant (ϵ 78.1) will diminish repulsory interactions with respect to a medium of lower permittivity (90% methanol: ϵ 64[19]), the diminution of stability of the K^+ complex by 7-fold (**3a** vs. **7** in 90% methanol; Table III) cannot be explained on this basis. Rather, an unfavorable conformation for guest complexation enforced by the relatively bulky N substituent may account for the weaker complex stability of **7**. This view is supported by comparing the monotopic host **7** with the novel ditopic receptor **6**. It was already mentioned that the introduction of three additional positive charges (**7** → **6**) lowers the basicity quite moderately (Table II), but the K^+ complexes differ by a factor of 2 in stability. In addition to the electrostatic effect it is apparently the sheer size of the substituent at a nitrogen atom of the crown macrocycle that influences K^+ complex stability.[20]

Complex formation of the aza crown compounds with H^+ or K^+ appears to be mutually exclusive (Table III).

Table IV. Conditional Association Constants K_{as} at Fixed Observed pH of Ammonium Substrates and Aza Crown Ether Hosts in 90% v/v Aqueous Methanol [0.1 M $(CH_3)_4N^+F^-$, 25 °C]

	K_{as},[a] M^{-1} (obsd pH)	
substrate	Tetazac (**6**)	Amazac (**7**)
p-$HOC_6H_4CH_2CH_2NH_3^+$ (**22**)	143 ± 25 (9.10)	165 ± 51 (9.10)
$HOCH_2CH_2CH_2CH_2CH_2NH_3^+$ (**23**)	46 ± 18 (9.10)	155 ± 30 (9.10)
$^-OOCCH_2CH_2CH_2CH_2CH_2$-$NH_3^+$ (**24**)	233 ± 14 (9.40)	300 ± 45 (9.40)
$^-OOCCH_2CH_2CH_2NH_3^+$ (**4**)	248 ± 50 (9.40)	360 ± 10 (9.40)

[a] The limits refer to the range of four to six single estimations rather than to a standard deviation.

This justifies the measures taken to control and adjust the pH value to within 0.01 pH unit. Somewhat surprising, however, is the low stability of the potassium complex of **12**, differing from **3a** only by one NCH_3 substituent.[21]

Incremental addition of amino compounds to solutions of potassium–aza crown ether complexes instantaneously decreased the concentration of uncomplexed K^+ ions. From the shift in equilibrium the association constants of aza crown receptors with primary ammonium guest molecules given in Table IV were calculated. Any of the primary ammonium compounds tested actually were bound by the receptors. A surprising finding, however, was that the conditional association constants without exception were smaller than those for the corresponding K^+ complexes at the same pH. Thus, the favorable RNH_3^+/K^+ selectivity found with **3a** (5–10),[10] which had been a decisive argument for the selection of this type of aza crown ether as an ammonium binding site in polytopic receptors, is inverted. Though a slight decrease of this selectivity ratio was expected visualizing the distortion arising from the less symmetric N-substitution pattern of the aza crown moiety in **6** or **7**, their preference for K^+ binding must arise from unfavorable steric interactions with the ammonium substrate.[20] These had been seen with the alkali cation, too, but they seem even more restrictive with the larger substrate. Moreover, this argument is supported by the higher stability of the complexes of ammonium substrates with the monotopic receptor **7** lacking the bulky tetrahedral cage substituent. The handicap of Tetazac (**6**) in this sense can be estimated from the least sterically demanding and functionalized substrate **23** to amount to a factor of 3.

The primary purpose for designing polytopic receptors is *not* to increase absolute binding of the substrates but to boost the discriminatory capability of the hosts. The comparison of the ditopic receptor Tetazac (**6**) with the structurally related monotopic analogue **7** with respect to the binding of representative guests should reveal the basic selectivity features.

The dependence of complexation on an integral molecular property like the lipophilicity of the guest was tested, comparing tyramine (**22**) and 6-aminohexanol (**23**). These guests possess identical distances of their functional groups but differ in overall lipophilicity. Whereas there is virtually no difference in binding the hydrophobic amine **22** (π = +1.33, calculated from π_x increments[22]) or the hydrophilic

(19) For a short discussion of host–guest complex stability depending on the dielectricity constant of the solvent, see: Lamb, J. D.; Izatt, R. M.; Christensen, J. J. In *Progress in Macrocyclic Chemistry*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1981; Vol. 2, p 68.

(20) Similar observations have been made with other aza crown ethers, too: (a) Chadwick, D. J.; Cliffe, I. A.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1707. (b) Wester, N.; Vögtle, F. *J. Chem. Res. Synop.* **1978**, 400; *J. Chem. Res. Miniprint* **1978**, 4856.

(21) The effect of N substituents on cation complex stability is usually smaller. Cf. ref 21b. (a) Gramain, P.; Frere, Y. *Nouv. J. Chim.* **1979**, *3*, 53. (b) De Jong, F.; Reinhoudt, D. N. *Adv. Org. Chem.* **1980**, *17*, 279.

(22) Hydrophobicity can be rated by the π scale which reflects the free energy change of a compound or group on transfer from water to octanol. See: (a) Tute, M. S. In *Advances in Drug Research*, Harper, N. J., Simmonds, A. B., Eds.; Academic: London, 1970; Vol. 6. (b) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525.

one **23** (π = +0.65) by the monotopic host **7**, the complex of the ditopic host **6** with **22** is about 3-fold stronger than with **23**. The results from anion complexation studies[7c] and the inspection of CPK molecular models leave no doubt that the tetrahedral cage is too small for encapsulation of a benzene ring. Better binding to the hydrophobic guest must be attributed to the more lipophilic character of **6** mediated through the alkylene chains of the tetrahedral cage, to which the benzene ring of **22** may tend to associate from the outside.

Any advantage of the ditopic design of **6** over its monotopic counterpart **7** must become apparent on the binding of zwitterions. Replacement of the hydrophilic primary alcoholic function by a more hydrophilic but negatively charged carboxylate doubles the maximum association constant with **7** as a result of increased overall electrostatic attractions. Under the same conditions the complex with the ditopic host **6** experiences even a 5-fold stability enhancement. The increased selectivity of **6** over **7** by a factor of 2.5 for amino carboxylate complexation must originate exclusively from the structural feature not present in **7**, the anion receptor subunit. There is a cooperation of both receptor subsites in binding appropriately functionalized guests, and this simultaneous recognition of moieties of the substrate shows up as a discrimination against molecules not containing the combination of structural features. The selectivity enhancement though is rather moderate. Moreover, host **6** is incapable of differentiating between substrates of identical substitution patterns but different molecular dimensions. So ω-aminobutyric acids **4** and **24** are complexed with equal efficiency, as is true for the monotopic receptor **7**, too.

These findings and the rather modest selectivity increase, which is of similar magnitude as the one found with bridged cyclodextrins,[2] are supposed to arise from the flexibility of the single bridge connecting the receptor sites. The distance between them can easily be adjusted by simple rotation against each other. This ultimately would lead to disrupture of simultaneous binding of the guest at the two recognition sites and thus would paralyze the molecular basis for selectivity enhancement.

Conclusion

In pursuing our general concept, a ditopic artificial receptor **6** was synthesized designed to complex zwitterionic ω-amino carboxylates in protic solution. The binding constants with some primary ammonium guest species as determined from competition experiments reveal a decrease in absolute binding power of **6** relative to the monotopic analogue **7**. The selectivity in favor of zwitterionic guests, however, is increased 2.5-fold, proving the superiority of the ditopic host design. The mere fact that even the conjunction of two totally synthetic receptor subunits by one freely rotatable bridge shows up in a significant selectivity enhancement lend the extention of our concept to linearly connected polytopic receptors a promising perspective.

Experimental Section

General Procedures. Melting points were determined on a Fischer-Jones apparatus and are uncorrected. Proton NMR spectra were measured on a Brucker WP 200 instrument at 200 MHz or on a Varian T 60 instrument at 60 MHz. ^{13}C NMR spectra were obtained from Brucker WP 200, Brucker HX 90, or Jeol FX 90 instruments operating at 50.3 and 22.6 MHz. Chemical shifts in organic solvents are referenced to $(CH_3)_4Si$ as internal standard (δ 0). In D_2O *tert*-butyl alcohol (δ 1.237) was used as an internal reference in ^1H NMR spectra and CH_3CN (δ 3.30, 121.5) for the same purpose in ^{13}C NMR spectra. Elemental analysis was performed by the microanalytical laboratory of the Chemistry Department of the TU München. Analytical HPLC was done on Waters (Model 6000 pump linked to a M 440 UV and R 401 refractive index detector) or Merck-Hitachi instruments (Model 655 A-11 pump connected to Knauer UV 97.00 and RI 98.00 detectors) equipped with the low-pressure gradient system. We used Macherey-Nagel Nucleosil RP 18 columns (250 × 4 mm) employing methanol/water or acetonitrile/water mixtures containing 10 mM HCOOH and 30 mM $NaClO_4$. The retention volumes reported refer to these standard isocratic conditions.

Solvents were distilled before use except for acetonitrile and nitromethane, which were bought in p.a. quality. Tetrahydrofuran (THF) was dried and freed from oxygen and peroxides by distillation from potassium benzophenone ketyl. Commercial hydride solutions were analyzed by standard gas-volumetric procedures. All other chemicals were of reagent grade and were used as received.

pH-metric titrations in water and in 90% methanol [ionic strength 0.1 M $(CH_3)_4N^+Cl^-$] were performed with a glass electrode in combination with a double-junction Ag/AgCl reference electrode [0.1 M $(CH_3)_4N^+Cl^-$ electrolyte in the corresponding solvent in the bridge] to avoid contamination of the solution by potassium ions. The pK_a values of aza crown ethers (Table II) in water were obtained by curve fitting using an improved computer method.[18]

Determination of Association Constants in 90% Aqueous Methanol. In a thermostated (25 ± 0.1 °C) vessel (15 mL) were introduced a magnetic stirring bar, the tip of a micro piston buret (Metrohm E 457, 500 μL), and the following three electrodes: (a) a double-junction Ag/AgCl reference electrode separated from solution by an electrolyte bridge containing 1 M $(CH_3)_4N^+F^-$ in 90% methanol; (b) a H^+-sensitive glass electrode (Metrohm EA 127 X), which had been calibrated in combination with the reference electrode mentioned above to aqueous buffers between pH 7 and pH 10; and (c) a K^+-sensitive glass electrode (Schott). The vessel was charged with 5.0 mL of a 1 M $(CH_3)_4N^+F^-$ solution containing quinuclidine (total concentration 0.05M) in combination with its fluoride salt in a ratio to produce the desired pH value as measured by the pH electrode joined to a Metrohm E 512 pH meter. Small deviations from the preset pH value were corrected by adding measured amounts of $N^+(CH_3)_4OH^-$ or HF solutions in 90% methanol. The vessel was closed, and a calibration curve for K^+ was obtained by adding aliquots of a 0.1 M potassium fluoride solution in 1 M $(CH_3)_4NF$ in 90% methanol from the buret. The plot of the K^+ potentials measured by an Orion 701 A millivoltmeter vs. log K^+ was slightly curved, but the values could be reproduced to 0.20 mV on dilution. Addition of a solution of the host compound **6** or **7** increased the K^+ concentrations, and these were read from the calibration curve. Further addition of the potassium fluoride solution gave a set of data, which was processed by eq 3 to yield K_{as} of the potassium complex of the host. To the solution containing the host–guest complex ($\bar{n}$ = 0.6–0.8) were added successive portions of an ammonium guest compound, which after readjustment of the pH value set up a new equilibrium with a higher K^+ concentration usable in the calculation of K_{as} of the ammonium guest by simple mass balance equations.

Synthesis. 1-[(4-Methylphenyl)sulfonyl]-7,13-dimethyl-1,7,13-triaza-4,10,16-trioxacyclooctadecane-6,14-dione (9). To a solution of 3.5 g (7.9 mmol) of **8**[14b] in 20 mL of absolute Me_2SO was added 12.5 mL of a 1.33 M solution of dimsylpotassium in Me_2SO.[23] After 5 min the addition of 1.25 mL (20 mmol) of methyl iodide initiated an exothermic reaction, and the dark brown lightened to yellow. Stirring was continued for 1 h. Then, the mixture was poured into 200 mL of dilute aqueous HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with water, dried, and evaporated, and the resulting viscous oil was taken up in 10 mL of THF. Ether was added until a faint turbidity persisted. White crystals separated from this solution, which were recrystallized from absolute THF: 2.9 g (78%); mp 142–144 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 4.24, 4.16, 4.13 (3 s, 4 H), 3.7–3.9 (br m, 4 H), 3.5–3.7 (m, 6 H), 3.3–3.5 (m, 6 H), 3.01, 2.95, 2.92 (3 s, 6 H), 2.42 (s, 3 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 169.4, 168.9, 143.0, 135.9, 129.3, 126.8, 70.3, 69.5, 69.1, 67.1, 49.0,

(23) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

48.2, 47.3, 45.9, 35.2, 33.9, 32.7, 21.0. Anal. Calcd for $C_{21}H_{33}N_3O_7S$ (471.5): C, 53.48; H, 7.05; N, 8.91. Found: C, 53.41; H, 7.11; N, 8.60.

1,7-Dimethyl-1,7,13-triaza-4,10,16-trioxacyclooctadecane (12). Preparation from 9. A 10-g (21.2-mmol) portion of **9** was suspended in 120 mL of absolute THF and the resultant mixture heated to reflux while 122 mL of 0.83 M borane in THF was slowly added. The amide gradually dissolved, giving a clear colorless solution, which was heated under reflux for another 4 h. After cooling, 20 mL of CH_3OH was cautiously added and the solvent stripped off. The residue was boiled with 10% HCl in CH_3OH for 1 h, followed by evaporation. The oil so obtained was taken up in 100 mL of H_2O, made strongly alkaline with tetramethylammonium hydroxide, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and dried, and the solvent was removed in vacuo, which left an oil (8.9 g) that refused to crystallize but gave a ^1H NMR consistent with the proposed structure **11**: ^1H NMR (60 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 2 H), 7.28 (d, J = 8 Hz, 2 H), 3.53 (t, J = 5 Hz) 3.3–3.5 (m, partly covering the t at 3.53, 16 H), 2.62 (t, J = 5 Hz, 8 H), 2.42 (s, 3 H), 2.27 (s, 6 H).

The oil **11** obtained above was dissolved in 10 mL of glacial acetic acid, 4 g of phenol and 50 mL of 35% HBr in acetic acid were added, and the mixture was kept at 80 °C for 24 h. The black solution was concentrated in vacuo, diluted with 30 mL of H_2O, and extracted with CH_2Cl_2 (3 × 50 mL). The pale yellow aqueous layer was evaporated, leaving a viscous oil, which crystallized on addition of absolute ethanol. Filtration and drying in a desiccator (P_2O_5) gave 9.4 g of **12**·3HBr (83%, two steps) as a white powder. A 7.7-g portion of **12**·3HBr was dissolved in 20 mL of CH_3OH, 30 mL of 20% $(CH_3)_4NOH$ in CH_3OH was added, and the solution was evaporated. The residue was distributed between H_2O (30 mL) and CCl_4 (30 mL). The layers were separated, the aqueous phase was extracted with CCl_4 (4 × 25 mL), and the combined organic layers were dried and concentrated. The addition of hexane (25 mL) gave a turbid solution, which was centrifuged, decanted, and evaporated. The oil obtained was distilled in a Kugelrohr apparatus 140 °C (2 Pa) to afford 3.7 g (90%) of colorless oily **12**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.4–3.6 (m, 12 H), 2.69 (t, J = 5.0 Hz, 4 H), 2.60 (m, 8 H), 2.22 (s, 6 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 70.3, 69.0, 68.7, 57.0, 56.9, 49.2, 43.2; MS, m/e (%) 289 (2.7, M^+) 205 (6), 175 (7), 130 (12), 114 (15), 102 (50), 101 (50), 100 (50), 88 (85), 83 (100), 72 (93), 58 (80). Anal. Calcd for $C_{14}H_{31}N_3O_3$ (289.4): C, 58.10; H, 10.80; N, 14.52. Found: C, 57.94; H, 11.02; N, 14.46.

Preparation from 10. A 3.3-g (8-mmol) portion of **10** (obtained by borane reduction of **8**[14b]) was dissolved in 25 g of 98% formic acid. After addition of 5 g of 30% aqueous HCHO and 2 g of H_2O the mixture was refluxed for 20 h. The gas evolution had ceased after 1 h, and at the end of the heating period a heavy colorless oil had separated. The mixture was concentrated in vacuo and the residue distributed between saturated LiOH solution (20 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL); the combined organic phases were dried. Evaporation of the solvent left a colorless oil, which gave a single spot on TLC (Al_2O_3, $CHCl_3$, R_f 0.3) and a ^1H NMR spectrum identical with that of the product obtained by borane reduction of **9**. It was converted to **12** by the same procedure as described above.

1-[[4-(Methoxycarbonyl)benzyl]azonia]-8,15,22-triazatricyclo[13.13.6.6^{8,22}]tetracontane Iodide (15). A 560-mg (1-mmol) portion tetraamine **13** was dissolved in 4 mL of peroxide-free ether. A solution of 308 mg (1.11 mmol) of methyl α-iodotoluate (**14**; crystallized form hexane) in 3 mL of ether was added at once, and the mixture was kept at 4 °C. After a few hours tan crystals began to separate, which were collected 14 days later. Recrystallization from 5 mL of acetonitrile afforded 615 mg (75%) of off-white prisms. Concentration of the mother liquor and cooling to −10 °C gave a second crop (80 mg): HPLC (40% MeOH) R_v = 13.4 mL; mp 190–192 °C; ^1H NMR (200 MHz, CD_3OD) δ 8.07 (d, J = 8.4 Hz, 2 H), 7.58 (d, J = 8.4 Hz, 2 H), 4.53 (s, 2 H), 3.85 (s, 3 H), 3.13 (m, partially covered by solvent), 2.23 (m, 18 H), 1.8 (br, 6 H), 1.38, 1.30 (br overlapping s, 42 H); ^{13}C NMR (50.3 MHz, $CDCl_3$, 60 °C) δ 166.1, 133.2, 132.4, 132.3, 130.2, 62.7, 59.6, 54.0, 53.7, 52.4, 28.5, 27.43, 27.29, 26.8, 25.8, 23.7. Anal. Calcd for $C_{45}H_{81}IN_4O_2$ (837.0): C, 64.5; H, 9.75; N, 6.69. Found: C, 64.1; H, 9.53, N, 6.82.

1-[4-(Methoxycarbonyl)benzyl]-8,15,22-trimethyl-1,8,15,22-tetraazoniatricyclo[13.13.6.6^{8,22}]tetracontane Tetrakis(tetrafluoroborate) (16). A 620-mg (660-μmol) sample of **15** was suspended in 6 mL of acetonitrile. While the mixture was stirred vigorously, 190 μL (3 mmol) of methyl iodide was added. The crystals dissolved within 30 min. Then, 1 g of finely powdered Na_2CO_3 was added and the mixture was heated to 70 °C for 3 h. After standing for 2 days at 20 °C, the mixture was filtered and the residue thoroughly washed with two 2-mL portions of hot CH_3CN. The filtrate was evaporated, and the gum obtained was redissolved in CH_3OH/H_2O (1:2, v/v). Slow addition of a filtered aqueous $NaBF_4$ solution precipitated a brown oil, which crystallized on standing overnight. The precipitate was taken up in CH_3OH (30 mL) and refluxed to give a clear solution. On cooling, an emulsion formed at first, which was centrifuged. From the clear light yellow supernatant separated white crystals, which were collected and dried: 70 °C (7 Pa); 345 mg. A second crop (195 mg) was obtained from the mother liquor on concentration: combined yield 74%; mp >300 °C; HPLC (35% MeOH) R_v = 22 mL, (50% CH_3CN) R_v = 5.4 mL; ^1H NMR (200 MHz, CD_3CN) δ 8.09 (d, J = 8.5 Hz, 2 H), 7.65 (d, J = 8.5 Hz, 2 H), 4.46 (s, 2 H), 3.91 (s, 3 H), 3.4–3.6 (m, ~24 h), 2.88 (s, 9 H), 1.75–2.0 (m, partially covered by solvent resonance), 147 (br s, ~24 H). Anal. Calcd for $C_{48}H_{90}N_4O_2B_4F_{16}\cdot{}^1/_2H_2O$ (1111.5): C, 51.86; H, 8.25, N, 5.04. Found: C, 51.70; H, 7.97; N, 5.21.

1-(4-Carboxybenzyl)-8,15,22-trimethyl-1,8,15,22-tetraazoniatricyclo[13.13.6.6^{8,22}]tetracontane Tetrakis(tetrafluoroborate) (17). A 595-mg (535-μmol) portion of ester **16** BF_4 salt was dissolved in 5 mL of a 1:2 (v/v) mixture of CH_3CN and CH_3OH and the resultant mixture filtered through a Serdolit AS 6 anion-exchange column (volume 10 mL; Cl^- form), which was preequilibrated in the same solvent. The eluate was evaporated and then redissolved in 15 mL of CH_3OH and treated with 1 mL of 40% NaOH(aq). The moderately exothermic reaction was controlled by cooling with water. After 30 min the mixture was acidified (6 N HCl) and evaporated in vacuo. The residue was taken up in 5 mL of H_2O and heated to 70 °C and the product precipitated by dropwise addition of 5 mL of saturated $NaBF_4$ solution. Extractive recrystallization of the microcrystalline material from 5 mL of CH_3OH afforded 513 mg (92%) of white product, which was very hygroscopic: mp >300 °C; ^1H NMR (200 MHZ, D_2O, Cl-salt) δ 8.03 (d, J = 8 Hz, 2 H), 7.61 (d, J = 8 Hz, 2 H), 4.51 (s, 2 H), 3.3–3.5 (br, ~24 H), 2.95 (s, 9 H), 1.7–2.0 (br, ~24 H), 1.5 (br s, ~24 H); ^{13}C NMR (50.3 MHz, CD_3CN) δ 167.8, 134.6, 134.5, 133.5, 131.7, 64.6, 63.5, 61.1, 50.1, 26.7, 26.6, 22.7, 22.6. Anal. Calcd for $C_{47}H_{88}N_4O_2B_4F_{16}$ (1088.5): C, 51.85; H, 8.15; N, 5.16. Found: C, 51.90; H, 8.57; N, 5.57.

Amide 18 from Carboxylic Acid 17 and Aza Crown Ether 12. A 435-mg (400-μmol) portion of acid **17** (as the BF_4 salt) was converted by anion exchange through Serdolit AS 6 to the chloride. The powder obtained on lyophilization was suspended in 4 mL of dimethylformamide (DMF) followed by the addition of 135 μL of triethylamine. Mukaiyama's reagent (1-methyl-2-chloropyridinium iodide, freshly crystallized from CH_3CN; 205 mg, 800 μmol) was added in portions with stirring over a period of 10 min. Then, 136 mg (470 μmol) of aza crown ether **12** dissolved in 500 μL of DMF was added all at once. A sample drawn 5 min later showed complete conversion to the desired product **18** on HPLC analysis. The mixture was diluted with 30 mL of H_2O and evaporated in vacuo. The residue was redissolved in 5 mL of H_2O, acidified (HCOOH), and chromatographed on a Sephadex G 10 column (5 × 40 cm), eluting with 50 mM NaCl + 30 mM HCOOH in water. The first peak (RI detection) washed off the column contained the product **18**. This fraction was evaporated to dryness and extracted with ethanol/isopropyl alcohol (1:1, v/v; 3 × 10 mL). After the solvent was stripped off, the residue was dissolved in 4 mL of H_2O and alkalized (NaOH) and the product precipitated by addition of an aqueous $NaClO_4$ solution. After centrifugation the supernatant was decanted and the residue recrystallized from methanol (−40 °C): HPLC (35% MeOH) R_v = 4.1 mL; mp 208–210 °C; ^1H NMR (200 MHz, CD_3CN) δ 7.54 (d, J = 8.2 Hz, 2 H), 7.47 (d, J = 8.2 Hz, 2 H), 4.37 (s, 2 H), 3.87, 3.75 (2 br, 4 H), 3.4–3.7 (m, ~12 H), 3.2–3.4 (br m, ~24 H), 2.87 (s, 9 H), 2.5–2.7 (br, ~8 H), 2.24 (s, 6 H), 1.7–2.0 (br, partly covered by solvent resonance), 1.44 (br s, ~24 H); ^{13}C NMR (50.3 MHz;

D_2O, fluoride salt, pD >12) δ 176.0, 140.3, 135.6, 131.6, 127.7, 71.2, 71.0, 70.7, 65.9, 64.3, 61.8, 58.6, 58.3, 52.8, 51.4, 49.4, 45.0, 28.0, 27.8, 27.7, 23.7.

6-Tetazac (6). A solution of 406 mg (265 μmol) of amide **18** as the hexakis(tetrafluoroborate) salt (obtained by precipitation of the chloride of **18** from acid solution with $NaBF_4$ solution, filtration, and high-vacuum drying) in 5 mL of CH_3NO_2 was heated to 90 °C. Now 1.3 mL (13 mmol) of borane–dimethyl sulfide complex was added (*caution*! vigorous gas evolution, formation of a white precipitate), and the mixture was stirred for exactly 5 min at 90 °C. A sample drawn from the chilled mixture (ice bath) and acidified showed complete consumption of **18** as judged by HPLC analysis. Excess borane was destroyed by gradual addition of methanolic HCl and the solvent stripped off after cessation of the gas evolution. The residue was again refluxed with 20 mL of 5% methanolic HCl for 15 min, and the residue left on evaporation was taken up in 5 mL of water. This solution was subjected to gel chromatography on Sephadex G 10 (5 × 40 cm), eluting with 50 mM NaCl/30 mM HCOOH in water. The separation was monitored by RI detection aided by HPLC analysis. The fractions containing the product **6** were evaporated, and **6** was extracted into absolute ethanol. The ethanol extract when evaporated and lyophilized from water gave 310 mg of white powder (93% yield as the heptachloride). Further purification was achieved by crystallization of the BF_4^- salt: 200 mg of crude salt was dissolved in 500 μL of acetonitrile. Addition of 4 mL of methanol produced a slightly turbid solution from which colorless microcrystalline material separated: recovery 70%; mp 202–204 °C; ^1H NMR (200 MHz, Cl^- salt in D_2O) δ 7.64 (br, 4 H), 4.51 (s, 4 H), 3.93 (br, ~12 H), 3.3–3.7 (br, ~36 H), 2.95 (s, 15 H), 1.7–2.05 (br, centered at 1.84 ppm, ~24 H), 1.51 (br, ~24 H); ^{13}C NMR (50.3 MHz, fluoride salt in D_2O) δ 142.2, 135.1, 133.3, 129.1, 69.9, 68.6, 68.5, 66.0, 64.2, 61.5, 59.2, 59.0, 56.2, 51.2, 42.3, 27.9, 27.7, 27.6, 23.6; ^{13}C NMR (50.3 MHz, fluoride salt in NaOD/D_2O, pD >12) δ 143.4, 135.2, 133.0, 129.1, 71.0, 70.8, 70.7, 66.3, 64.4, 61.7, 61.2, 58.3, 55.7, 51.4, 45.0, 28.0, 27.8, 27.7, 23.7. Anal. Calcd for $C_6H_{122}N_7O_3B_7F_{28}$ (1609.4): C, 45.52; H, 7.64; N, 6.10. Found: C, 45.95; H, 8.14; N, 6.39.

1-[4-[(Triethylazonia)methyl]benzoyl]-7,13-dimethyl-1,7,13-triaza-4,10,16-trioxacyclooctadecane Bromide (21). A 543-mg (2-mmol) sample of 4-[(triethylazonia)methyl]benzoic acid bromide salt **20** [from methyl 4-(bromomethyl)benzoate (**19**) and triethylamine followed by alkaline hydrolysis] was dissolved in 5 mL of DMF and treated successively with 700 μL of triethylamine and a suspension of 614 mg (2.4 mmol) of 1-methyl-2-chloropyridinium iodide[14] in 2 mL of DMF. Stirring for 15 min at 25 °C was followed by the addition of 607 mg (2.1 mmol) of aza crown ether **12** in 2 mL of DMF. After 30 min the mixture was diluted with 30 mL of H_2O and evaporated in vacuo. The aqueous solution of the residue was separated on a Sephadex G 10 column (5 × 40 cm), eluting with 50 mM NaCl/30 mM HCOOH in water. The first fraction detected by RI contained the desired amide **21** together with an strongly UV-absorbing contaminant (HPLC analysis). To remove this impurity the fraction (130 mL) was concentrated to 14 mL, treated with 1.5 mL of 20% NaOH and heated to 100 °C for 10 min. After cooling, the conversion product of the contaminant was extracted into CH_2Cl_2 (7 × 7 mL). The aqueous phase was acidified by HBF_4 followed by extraction with CH_3NO_2 (3 × 3 mL). The combined organic layers were washed with saturated $NaBF_4$ solution (10 mL), dried ($MgSO_4$), and evaporated. The sticky gum obtained was dissolved in 30 mL of water and lyophilized to yield 780 mg (50%) of white powder: HPLC (20% CH_3OH) R_v = 10.2 mL; ^1H NMR (200 MHz, D_2O, tribromide salt) δ 7.65 (d, J = 8 Hz, 2 H), 7.53 (d, J = 8 Hz, 2 H), 4.49 (s, 2 H), 3.3–4.0 (several little resolved m, ~24 H), 3.27 (q, J = 7 Hz, 6 H), 2.97 (s, 3 H), 2.94 (s, 3 H), 1.41 (t, J = 7 Hz, 9 H); ^{13}C NMR (22.6 MHz, D_2O, trisfluoride salt) δ 175.8, 139.7, 135.3, 131.3, 129.4, 71.0, 70.2, 69.9, 69.6, 69.4, 61.8, 58.3, 54.9, 52.6, 48.9, 44.4, 9.5.

1-[4-[(Triethylazonia)methyl]benzyl]-7,13-dimethyl-1,7,13-triaza-4,10,16-trioxacyclooctadecane Tris(tetrafluoroborate) Chloride (7). A solution of 393 mg (510 μmol) of lyophilized **21** in 5 mL of CH_3NO_2 was heated to 90 °C. Rapid but cautious addition of 2.0 mL of borane–dimethyl sulfide complex resulted in vigorous gas evolution and the formation of a white precipitate, which gradually redissolved. After 5 min at 90 °C the mixture was cooled in ice, and then excess borane reagent was destroyed by slow addition of 4 mL of 10% methanolic HCl. All volatile materials was removed in vacuo, the residue was taken up in 10 mL of CH_3OH/HCl and boiled for 10 min, and the solvent was evaporated again. The solution obtained on addition of 5 mL of H_2O was chromatographed on a Sephadex G 10 column (5–40 cm; elution with 50 mM NaCl/30 mM HCOOH in water). The first peak detectable by RI contained the desired product **7**. Workup of this fraction by evaporation to dryness, extraction into absolute ethanol, evaporation, then dissolution of the residue in 1 mL of CH_3OH, and precipitation with a methanolic $NaBF_4$ solution afforded 210 mg of white microcrystals. Concentration of the mother liquor gave a second crop, 100 mg of identical purity. The material analyzed as the monochloride tris(tetrafluoroborate) salt: HPLC (15% CH_3OH) R_v = 6.0 mL; ^1H NMR (200 MHz, CD_3CN) δ 9.77 (br, ~1 H), 9.45 (br, ~2 H), 7.76 (d, J = 8.2 Hz, 2 H), 7.53 (d, J = 8.2 Hz, 2 H), 4.42, 4.44 (2 s, 2 H), 4.34 (s, 2 H), 3.7–3.9 (m, 12 H), 3.1–3.5 (q, J = 7.3 Hz, superimposed on several m, ~18 H total), 2.83, 2.82 (2 s, 6 H), 1.35 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (50.3 MHz, D_2O, tetrafluoride salt) δ 142.5, 134.8, 133.1, 128.8, 70.4, 69.8, 69.7, 62.4, 60.2, 58.5, 58.4, 55.6, 54.9, 43.8, 9.5. Anal. Calcd for $C_{28}H_{56}N_4O_3ClB_3F_{12}$ (792.7): C, 42.42; H, 7.12; N, 7.06. Found: C, 42.05; H, 7.11; N, 7.09.

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Registry No. **4**, 56-12-2; **6**·7Cl^-, 105206-55-1; **6**·7BF_4^-, 105206-59-5; **6**·7F^-, 105206-60-8; **6**·$Cl^-(BF_4^-)_3$, 105206-65-3; **6**·$Br^-(BF_4^-)_3$, 105206-66-4; **6**·$I^-(BF_4^-)_3$, 105206-67-5; **6**·K^+, 105206-79-9; **6·22**, 105206-68-6; **6·23**, 105229-61-6; **6·24**, 105229-62-7; **6·4**, 105206-69-7; **7**·$Cl^-(BF_4^-)_3$, 105229-60-5; **7**·4F^-, 105206-61-9; **7**·K^+, 105206-78-8; **7·22**, 105206-71-1; **7·23**, 105206-72-2; **7·24**, 105206-73-3; **7·4**, 105206-74-4; **8**, 78631-00-2; **9**, 105206-48-2; **10**, 78600-10-9; **11**, 94224-90-5; **12**, 94224-91-6; **12**·3HBr, 105206-62-0; **12**·K^+, 105206-77-7; **13**, 63702-67-0; **14**, 94224-92-7; **15**, 94224-93-8; **16**·4BF_4^-, 105206-50-6; **16**·4I^-, 94224-94-9; **17**·4BF_4^-, 105206-52-8; **17**·4Cl^-, 105206-53-9; **18**·4ClO_4^-, 105206-54-0; **18**·6BF_4^-, 105229-58-1; **18**·6F^-, 105206-63-1; **18**·6Cl^-, 105206-64-2; **19**, 2417-72-3; **20**·Br^- (methyl ester), 80992-76-3; **20**·Br^-, 67688-76-0; **21**·BF_4^-, 105206-58-4; **21**·3Br^-, 105206-75-5; **21**·3F^-, 105206-76-6; **22**, 51-67-2; **23**, 4048-33-3; **24**, 60-32-2; 2,2,6,6-tetramethyl-4-piperidinol, 2403-88-5; quinuclidin, 100-76-5.