thylidyne carbon (for Nu = $H_2C{=}CH_2$ a subsequent 1,2-hydrogen shift occurs to yield the "hydrocarbation" product). We believe this is a direct result of orbital controlled reactivity. The LUMO of this system was found to consist primarily of a $p\pi$ orbital on the μ-carbon of the methylidyne ligand (see Figure 4), This orbital is oriented perpendicular to the Fe–(μ-CH)–Fe plane and is sterically accessible. Nucleophiles can readily add to this relatively low-lying vacant orbital, Further evidence for either orbital-controlled or charge-controlled reactivity has been found in calculations on the isoelectronic $[CpFe(NO)]_2(\mu\text{-}CH)^+$[39] and $[CpRh(CO)]_2(\mu\text{-}CH_2)$[40] systems which will be presented in a subsequent paper.

Conclusions

We have demonstrated that the Fenske–Hall molecular orbital method provides an accurate picture of the electronic structure of this series of organically bridged dimeric piano-stool complexes and can be particularly useful when applied to the understanding of their reactivity patterns. The method has also provided us a unique and promising approach into the mechanistic aspects of photochemical insertion of alkynes into various organic bridges. Although it is impossible to precisely model the entire reaction coordinate for a given reaction via molecular orbital calculations, we feel that particular electronic interactions of the reactants and/or products can be used to allow an understanding of certain preferred reactivity modes. It is also clear that more detailed studies, e.g., total energy calculations on potential surfaces involved in the photolysis mechanism as well as the wavelength dependence of the photochemistry of piano-stool dimers, are essential to test some of our conclusions.

We are expanding our studies to a wide variety of related piano-stool dimer systems (both homonuclear and heteronuclear) in order to assess the generality of this method for relating reactivity to electronic structure.

Acknowledgment. We would like to thank Professor Charles P. Casey for helpful discussions and critical comments. R.H.C. is grateful to The Ohio State University Graduate School for a Presidential Fellowship.

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Probing the Design of a Novel Ditopic Anion Receptor

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Abstract: In an attempt to increase host–guest selectivity an open chain ditopic receptor **5** composed of two tetrahedral anion binding subunits which are connected by a *p*-xylene bridge was synthesized. The preparation produced the target host **5** in four steps in 23% yield starting from the macrotricyclic modules **4** and **6**. The selectivity advantage of the ditopic receptor design was investigated by using the dimensional probes **10–14**. Association constants of the probes with the ditopic **5** or monotopic **2** were calculated from a Benesi–Hildebrand treatment of the optical effects occurring on host–guest complexation. The comparison of selectivity ratios derived therefrom reveals a sharp increase with **13** and **14** demonstrating the participation of both receptor subunits of **5** in binding these guests. The superiority of the ditopic vs. a monotopic receptor design amounts to a factor of 3. The *p*-xylene connecting unit is sufficiently rigid to define a minimum distance of approach of the two subunits of the ditopic host **5**.

How can selectivity be introduced into chemical reactions? One possibility to approach this fundamental problem[1,2] is to force the reaction partners into spatial and temporal proximity in their ground states prior to any chemical conversion event.[3] This principle is ubiquitous in the living world naming enzymic catalysis, membrane transport, hormonal signal transduction, replication, metabolic regulation, and friend–foe recognition in the immune response as a few shining examples. There is no equivalent in abiotic chemistry at present though the fascinating perspectives of the approach are generally recognized.[4–6] Prerequisite to the rational application of this principle in artificial systems is the availability of host molecules capable of recognizing and specifically binding the reaction partners from a variety of structurally related species. The recognition process may, for instance, exclusively respond to the shape and the molecular dimensions of the guests. Corresponding hosts can be tailored by using synthetic polymers,[7,8] but inorganic analogues (e.g., zeolites) owing their ability to discriminate potential guests by shape to a peculiar crystal structure have already found widespread use in industrial chemistry.[9,10] It is intuitively comprehensible that the guest specificity of these hosts will be optimized the more extensive and precise the surface of the guest can be scanned. Rigid and geo-

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metrically well-defined cavities of a host, which encircle the substrate completely, should therefore guarantee maximum specificity, The picture most appropriate to describe this situation is the lock–key metaphor first used by E. Fischer to illustrate enantioselective enzyme–substrate interaction.[11]

This approach to gain selectivity by geometrical recognition, however, suffers from obvious disadvantages; unspecific binding of smaller molecules in principle cannot be avoided by these hosts. Moreover from the optimal placement of the guest binding site within a rigid and nearly closed cavity of the host one may expect obstruction of rapid guest exchange by considerable barriers for diffusion, which in turn would hamper possible applications of these systems, With respect to this point the fixation of guest size excluding higher homologues or structurally related molecular species may rather be unwelcome.

Natural enzymes apparently are much less rigid[12,13] than has been anticipated, and structural fluctuations seem to be mandatory to their function.[14-16] This led to the conclusion that besides the undoubtedly important geometrical factors it is the *functional* complementarity between substructures in the guest molecule and certain anchor groups of the enzyme that dominates specific enzyme–substrate interactions. This complementarity may be seen directly in the X-ray crystal structures of enzyme–substrate complexes.

The transfer of this complementarity principle to abiotic hosts indeed furnished highly specific receptors,[17-19] if at least two artificial anchor groups were incorporated into a macrocyclic or inherently rigid[20] framework and were thus fixed with respect to their mutual orientations. If two anchor groups were connected only by a freely rotatable bridge, a rather modest selectivity increase was found.[21,22] So far the studies were confined to very simple bisfunctional guests, nevertheless the synthetic expenditure in preparation of the corresponding specific macropolycyclic hosts was considerable. We expect this expenditure to grow excessively, if biologically relevant polyfunctional substrates are to be specifically complexed by artificial receptors. This clearly would impair broader applications of these abiotic hosts.

We consider the open-chain connection of anchor groups to provide a useful alternative. Anchor groups may be arranged in a branched or unbranched fashion to give a set of covalently linked receptor sites, in which their type, the topology, number, and distance together with the mode of their linkage determines guest specificity. The mutual orientation of the anchor groups is not prefigured but rather is to result from the substrate acting as a template. Of course, this arrangement will show inferior selectivity characteristics more than a comparable receptor having the *same* binding functions located in a rigid skeleton. But this concept offers the opportunity to compensate this flaw by the ready attachment of a greater number of receptor sites. The much improved synthesizability of open-chain polytopic receptors, in addition, renders this approach much more flexible to adapt the receptor design to the requirements of the guest structure. Following this pattern artificial hosts may be designed, which recognize a combination of structural elements but not the overall constitution of the substrate. Thus receptors exhibiting a certain range of substrate specificities would result, which again would be beneficial with respect to potential applications.

An impressive proof for the general correctness of our concept to expect extraordinary specificity from a linear attachment of receptor functions, which by themselves possess only small fidelities of guest selectivity, can be drawn from DNA-hybridization experiments.[23,24]

Though energy differences in base pairing of single nucleotides can account for a selectivity of only 10–100[24a] (correct vs. incorrect pairing, e.g., A–T vs. A–C), the alignment of 19 nucleotides to form a special linear oligonucleotide suffices to yield the specificity required to bind to the complementary sequence of the DNA single strand to allow detection and unambiguous identification of the sickle cell anemia gene.[24b] This gene occurs in a single copy in human genome ($\sim 3\text{–}4 \cdot 10^9$ nucleotide pairs) and differs in but one point mutation (A → T) from its normal allele.

Verification of our concept requires some knowledge on the mode of guest binding to the receptor subsites. Our studies on the complexation of anions by artificial hosts in water[25,26] characterized the macrotricyclic ammonium salts **1** and **2** as water soluble nonaggregating receptor molecules, which bind anionic guests by inclusion into their molecular cavities.[27] Complexation was observed, too, if only an anionic moiety but not the entire guest could be encapsulated. If this was not possible owing to unfavorable size relations, no host–guest association was detectable.

A first step on the route toward open-chain polytopic receptors was to be done by connecting the tetrahedral hosts **1** and **2** to afford a ditopic receptor **5**. On the basis of the complexing features of the parent anchor groups **1** and **2** one could expect this combination to be appropriate for binding biologically important nucleotides or sugar bisphosphates. But in the first place we tried to answer another two questions: (i) Does the coupling of two anion hosts already furnish a measurable selectivity advantage in the complexation of ditopic anions? (ii) Does the rigidity of a *p*-xylene bridging unit suffice to distinguish between homologous substrates? An answer to these questions was expected from a synopsis of the association constants of **5** in relation to **2** with a set of anionic guests. These ditopic substrates **10–14** are dimensional probes, because they differ with respect to the fixed distance of two negatively charged functions but not in chemical nature. Here we report details of this study, which had already been described in a preliminary communication.[28]

Synthesis. The straightforward way to couple the two tetrahedral subunits **1** and **2** is via quaternization of the parent macrotricyclic tertiary amines **3** and **4** by a suitable alkylating agent which would finally constitute the spacer unit between the substructures of the ditopic target molecule **5**. A *p*-xylene group was selected as the connecting bridge, because it combines the advantages of high reactivity in the prospected quaternization with a reasonable UV detectability which was a highly desirable feature

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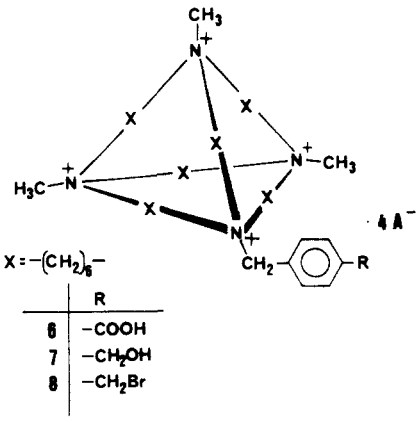
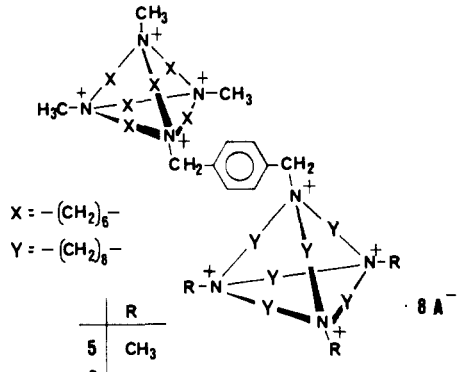
Formula 1



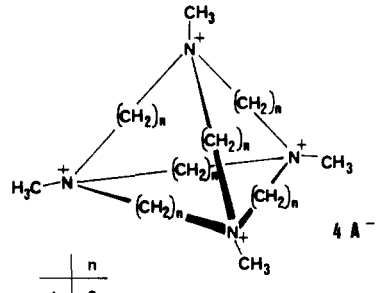
	R
6	-COOH
7	$-CH_2OH$
8	$-CH_2Br$



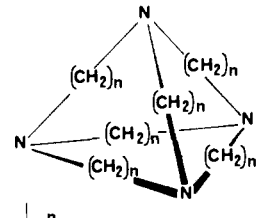
	R
5	CH_3
9	H

to ease monitoring in the further synthesis. Above all this bridging unit is fairly rigid, so that rotations of the subunits with respect to each other hampering concerted substrate recognition at these sites are minimized. A first attempt to react α,α'-dibromoxylene with a mixture of the parent tricyclic tertiary amines and fish out the desired ditopic receptor failed because of complete polymerization. Therefore, a rational synthetic pathway was developed starting from a monofunctionalized version **6** of the smaller tetrahedral host **1**. This had already served as an intermediate in the synthesis of another ditopic receptor molecule[22] and can be prepared by a 14-step sequence.[22,25b] All that is needed to use **6** in the synthesis of **5** is the conversion of the carboxyl function into an alkylating moiety appropriate for attachment of the bigger tetrahedron via a subsequent quaternization step. The reduction of **6** to the alcohol **7** presented problems, because most of the hydride reagents generally used in this type of reaction were inapplicable in this case due to the low solubility of the highly charged salt **6** in the aprotic solvents required. A reagent combination (borane–dimethylsulfide/nitromethane), which had turned out profitable in the reduction of similar saltlike compounds,[22] acting on the tetrafluoroborate of **6** finally furnished the benzylic alcohol **7** in high yield. The transformation of **7** into the benzylic bromide **8** was readily accomplished by using concentrated aqueous HBr.

Formula 2



	n
1	**6**
2	**8**



	n
3	**6**
4	**8**

The parent tricyclic tertiary amine **4**[25b] contains four nitrogen centers fairly distant to each other and thus of comparable reactivity in quaternization. So one had to expect the formation of a mixture of products in a reaction of **4** with **8** differing in the degree of alkylation. There were two alternatives to boost the production of the desired monoalkylated compound **9**: since the big macrotricycle **4** is very sparingly soluble in hydroxylic solvents, one could hope that **9** would precipitate from a properly composed solvent system thereby escaping further reaction. On the other hand, by employing apolar solvents a major excess of **4** could be used favoring the monoalkylated product. This may also be favored kinetically in this medium because dialkylation involves an attack of a highly positively charged alkylating agent onto a substrate of the like charge, and thus this process should suffer from electrostatic repulsion in a solvent of low dielectricity constant. Unfortunately the low solubility of **8** in apolar media prohibited the consequent exploitation of this idea. Rather a compromise was found which afforded a 52% yield of **9** employing a twofold excess of **4**. Although the yield could be increased to 80% if **4** was introduced in a tenfold excess, this route was not followed in the preparative work owing to a short supply of **4**. In any case varying amounts of higher alkylated analogues were formed, which could cleanly be separated from **9** by aqueous gel filtration chromatography. From the elution pattern, which follows the actual molecular size, from the ^1H NMR peak integrals of the compounds eluted, and from their behavior in an HPLC system developed to separate highly charged cations[29] the identity of the higher alkylated products was evaluated.

To complete the synthesis of **5** the remaining nitrogen atoms of the big tetrahedral subunit had to be permethylated. We found by HPLC analysis that on methylation of **9** with methyl iodide or methyl tosylate two products in varying ratios were obtained. Both appeared to be permethylated and coeluted on gel filtration (Sephadex G 25). They could easily be separated by preparative HPLC, but they could not be interconverted by mere heating or warming in the presence of acid or base. The compound eluting more rapidly from the HPLC column presented analytical data consistent with structure **5**. The other exhibited very similar ^1H NMR spectra except for the $N-CH_3$ region. In contrast to **5**, the slower eluting component showed two $N-CH_3$ singlets in a 1:5 area ratio. With respect to the occurrence of distinct in–out isomers in polycyclic ammonium compounds[30,31] this compound was tentatively attributed a mono-in $N-CH_3$ isomeric structure. This assignment is supported viewing the fact that a similar isomer has never been observed if highly reactive methylation agents (e.g., methylfluorosulfonate) have been used for quaternization of **4**.[26a] Apparently these react simultaneously from the outside of the tricycle. Increasing the temperature likewise favors production of the all-out-isomer, presumably on similar grounds. However, the formation of the other isomer could not be completely avoided, so that preparative HPLC separation with severe concomitant losses owing to irreversible adsorption of these highly charged salts was required. In spite of these losses 150 mg of pure ditopic host

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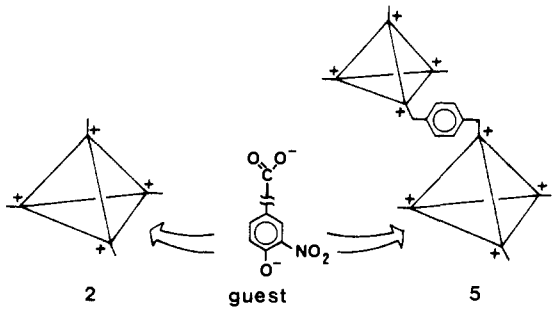
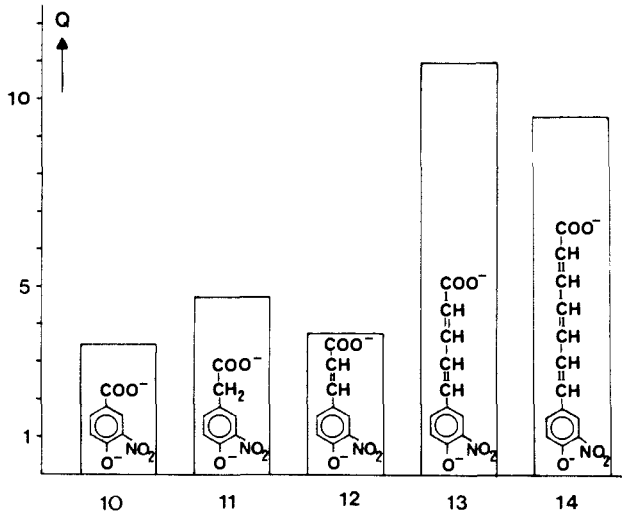
Scheme I



$$Q = \frac{K_{ass}(\text{guest} \subset 5)}{K_{ass}(\text{guest} \subset 2)}$$

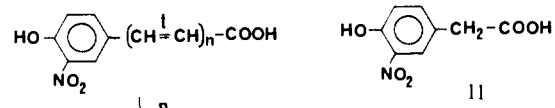


molecule **5** were obtained by this four-step route from **6** (overall yield 23%).

Complexation Studies. Answering the question whether the ditopic host molecule possesses higher selectivity than its monotopic counterparts **1** or **2** certainly depends on the guest studied. It is for instance immediately obvious that **5** will display increased selectivity compared to **1** or **2** for anionic species over neutral or cationic ones simply owing to enhanced electrostatic attraction in the former case. Selectivity enhancements based on integral molecular properties like the overall electric charge or the hydrophobicity thus are not very meaningful to appraise the quality of the molecular design of a host compound. Rather one needs molecular probes which respond to constitutional and configurational host features. In an ideal case a trend analysis of association contants of a particular host with a series of guests differing in but one molecular property relevant to binding could uncover the advantage in selectivity. Selectivity enhancements emanating from the ditopic design of receptor **5** must involve the simultaneous participation of both anchoring subunits in guest binding. This can be studied by using dimensional probes which are virtually identical with respect to their chemical nature but differ in their molecular dimensions. The basic idea is that of a guest molecule having two distinct anionic sites within an adjustable distance to each other, which are, in principle, capable of interacting with both receptor sites in the host. Choosing the distance so small that the guest can be incorporated into one receptor cavity, simultaneous binding at both sites would be prevented. On extending the distance now a point will be reached, where the second receptor site can participate in binding. This extra interaction should be observable as an increase in the association constant if the ditopic host is adequately designed. As can be inferred from related ditopic hosts[17,20,22] the change in K_{ass} will be more dramatic the more rigid the geometric relationship between host and guest is. Thus a number of requirements have to be met by these probes: (i) they must contain functional groups readily recognized and bound by the corresponding complementary host subunits; (ii) they should have an unequivocal binding mode. This implies that a host with dissimilar receptor subsites should be probed by guests offering dissimilar functions for complexation; (iii) these functions must be fixed in the guest skeleton, so that a well-defined distance relation exists; and (iv) the direct determination of the association constants of the host–guest interaction by an easily observable change in a molecular property should be possible.

The latter condition is fulfilled by the *o*-nitrophenolate moiety which experiences a bathochromic shift of its visible absorption band on association to the bigger tetrahedral host subunit.[26a] No shift is observed with the small tetrahedron **1** although CPK-model inspection reveals that any face of **1** is larger than the face of the *o*-nitrophenolate moiety. Consequently its side by side contacts with **1** and **2** are essentially the same. Thus the solvatochromic shift cannot originate from an association from the outside, but rather the host **2** must be able to offer an association mode not available to the smaller analogue **1**. This is one more tessera in the mosaic of findings[26] supporting true penetration of nitroaromatic moieties in host–guest complexation with **2**. Measuring K_{ass} values by analysis of the UV absorption changes of the nitrophenolate exclusively responds to binding happening at the bigger receptor substructure of **5**.

The molecular probes required a second anionic site capable of interacting with the small host subunit. A carboxylate function was chosen, because it had been demonstrated to bind to **1**,[26a] although the mode of association remains somewhat obscure. The carboxylate moiety is certainly smaller than an iodide ion, which was shown by X-ray crystallography to be completely included into the cavity of **1**.[27] It, therefore, should be able to invade the interior of the small tetrahedral host, but direct observation of this process has not been possible. Another reason for the selection of carboxylate was its capability to render the guest molecules water soluble and obviate guest aggregation, which could have been a problem with the more extended probes. Trans olefinic bonds were selected to hold the anionic guest moieties at a fixed distance. The dimensional probes **10–14** containing a chromophoric head group and a carboxyl function at the terminus of a telescope arm adjustable in length in 2.8-Å increments appeared to satisfy all requirements mentioned above. These compounds are either commercially available (**10**, **11**) or are readily obtained by standard condensation (**12**) or Wittig–olefination procedures (**13**, **14**). Except for **11** extensive double bond conjugation as indicated by bathochomic UV band shifts comparing **10** (λ_{max} = 408 nm) with **12**, **13**, or **14** (λ_{max} = 448, 458, 468 (shoulder) nm) warrant considerable rigidity and high fidelity in conservation of the desired charge separation. But even the twist of one or more transoid single bonds into a cisoid conformation would change the overall extension of the probe by no more than 0.7 Å as read from CPK models.



	n
10	0
12	1
13	2
14	3

The association constants of the host–guest interaction of the molecular probes **10–14** with the monotopic and ditopic hosts **2** and **5** were measured by optical methods by using a Benesi–Hildebrand analysis,[32,33] and the results are presented in Table I and Scheme I. The K_{ass} values, of course, do not correspond to one particular host–guest complex structure since at least with

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Table I. Association Constants K_{ass} of the Dimensional Probes **10–14** with the Monotopic **2** and Ditopic **5** Anion Receptors in Water

substrate	$K_{ass}[M^{-1}]$		$Q = K_{ass}(5)/K_{ass}(2)$
	2	**5**	
10	208	714	3.4
11	62	322	5.1
12	556	2041	3.7
13	476	5265	11.1
14	1042	10000	9.6

[a] pH 8.8, 27 °C.

the ditopic receptor **5** several modes of guest binding are conceivable, which would give a contribution to the optical change measured. The aromatic head group of the probe may penetrate the big receptor site of **5** via two different types of tetrahedral faces: those being adjacent to the connecting bridge or the one just opposite to it. Only the former penetration mode can possibly lead to an additional interaction of the carboxylate bearing tail of the probe with the second receptor unit for geometric reasons, Therefore, experimental K_{ass} values will be averaged over all possible association modes, but since the argument rests on the trend analysis rather than on absolute binding data, the final conclusion is not affected by the ambiguity of the complex structure.

The most obvious result from inspection of the data of Table I is that the binding constants of the monotopic receptor **2** are generally smaller than the corresponding values of the ditopic host **5**. This is not surprising because electrostatic interactions of the anionic guests with **5** are enforced compared to **2**, owing to the doubling of the positive charge of the host. Another trend extractable from Table I as well may originate from an integral property of the guest: the association constants with either host increase with elongating the side chain of the probe although electrostatic interactions at least in the case of **2** are weakened, and a concomitant decrease of binding should be expected on this basis. Hydrophobic and dispersion interactions of host and guest, which increase with the length of the side chain, appear to contribute to guest binding and outmatch the loss in electrostatic attraction. The significant role of dispersion forces is particularly obvious from K_{ass} values of **11**, which do not follow the general pattern. In contrast to all the other probes, a saturated carbon atom in **11** hampers conjugation of the anionic sites and thus weakens dispersion interactions by reducing the polarizability (softness) of the guest.

The comparison of the absolute K_{ass} values of **5** does not disclose a pronounced selectivity in favor of a particular chain length of the guest. The advantage of its ditopic design, however, becomes immediately apparent in relation to the monotopic host **2**. The selectivity ratios Q (Scheme I), characterizing the advantage of the ditopic over the monotopic receptor in binding the dimensional probes, do not change much with the distance of the negative charges in **10**, **11**, and **12**. But inserting another trans double bond into the cinnamic acid derivative **12** suddenly boosts the Q value threefold to more than 11. This high level is almost maintained if another spacer group (2,8 Å) is added. These experimental findings are completely compatible with the conceptual ideas outlined earlier and demonstrate the superiority of a ditopic host design in the selective binding of guest molecules. If the anionic guest moieties are fairly close to each other, binding will occur only at the bigger host subsite, Only if the charge separation exceeds a certain limit so that the telescope arm of the guest can span the gap between the receptor subunits, the second anchor group may participate in binding. This additional interaction translates as the selectivity enhancement observed. The set of dimensional guests sufficed to demonstrate that the *p*-xylene bridging unit defines a minimum distance of approach of the tetrahedral binding sites in **5**. Since these groups are freely rotatable against each other, one cannot expect to observe a similarly clear-cut upper limit of molecular dimensions beyond which simultaneous binding of the guest functions would not occur. A fair estimate from CPK-models would place the limiting extension of a completely rigid guest at 30–35 Å. Molecular probes of this size, however, will not meet the rigidity requirements.

Conclusion

Composing a ditopic receptor by coupling two tetrahedral anion binding sites by a *p*-xylene bridge constitutes the initial step toward linear polytopic host molecules. A trend analysis of the binding of suitably constructed dimensional probes demonstrates a selectivity advantage of the ditopic design by a factor of 3. The *p*-xylene connecting unit is sufficiently rigid to define a minimum distance of approach to the anchor groups.

Experimental Section

General Methods. Melting points were determined on a Fischer-Jones apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Brucker WP 200 instrument at 200 MHz and are calibrated to an internal tetramethylsilane (Me_4Si) signal when organic solvents were used or to sodium 4,4-dimethyl-4-silapentanesulfonate (DSS) in water, respectively. ^{13}C NMR spectra were obtained on a Jeol FX 90 instrument operating at 22.6 MHz and used the same internal references. Mass spectra were obtained by electron impact ionization (EI 70 eV) on a Varian CH 5 machine, and IR spectra were measured on a Perkin-Elmer 157 instrument. Elemental analysis were done at the microanalytical laboratory of the chemistry department of the TU München. HPLC used Waters (Model 6000 pump linked to a U6K injector and M 440 UV and R 401 RI detectors) or Merck-Hitachi instruments (Model 655 A-11 pump connected to Knauer UV 97.00 und RI 98.00 detectors) the latter being supplemented with a low-pressure gradient device. We used Macherey-Nagel Nucleosil RP 18 columns (250 × 4 mm) employing methanol/water or acetonitrile/water mixtures containing 10 mM of formic acid and 30 mM of sodium perchlorate. The retention volumes reported refer to these standard isocratic conditions. TLC used commercial silica coated aluminum foils (Merck).

Solvents were distilled before use except for acetonitrile and nitromethane which were bought in p.a. quality. Tetrahydrofuran (THF) was purified by distillation from benzophenone ketyl. Commercial hydride solutions were analyzed by standard gas volumetric procedures. All other chemicals were of reagent grade and were used as received. Compounds **10** and **11** were bought (Aldrich), and **12** was prepared by a published procedure.[34]

Measurement of the Dissociation Constants. The *o*-nitrophenol substrates **10–14** experience bathochromic shifts (10–20 nm) of their long wavelength visible absorption band on addition of the host compounds **2** and **5** in water. Under the proper concentration relation[33] these shifts can be analyzed by a Benesi–Hildebrand treatment[32] by using eq 1 with

$$\frac{h_0 g_0}{\Delta E} = \frac{1}{\epsilon^*}(h_0 + g_0) + \frac{K_D}{\epsilon^*} \qquad (1)$$

h_0 and g_0 being the total concentrations of host and guest, ΔE the experimentally observed absorption change at the wavelength selected, and K_D and ϵ^* the dissociation of the host–guest complex, and the change in the absorption coefficient to be determined, respectively.

In a typical experiment 100 μL of TAPS-buffer (pH 8.8, 0.25 M, Aldrich) containing 0.25 M NaF was mixed with 25 μL of a $1.0 \cdot 10^{-3}$ M aqueous solution of **14** disodium salt and 125 μL of water in a 1 cm/0.5 mL quartz cuvette. After temperature equilibration (27 ± 0.1 °C) in the sample compartment of a Zeiss PM6 photometer the absorbance was read. Successive additions of aliquots of a 50 mM solution of host **5** fluoride in water (6 → 40 μL) yielded a set of absorbance changes at 520 nm which in combination with the corresponding concentrations of host and guest (corrected for dilution) were processed according to eq 1. From the plot of 6–10 single determinations straight lines ($r > 0.98$) were obtained in any case, which yielded the desired 1:1 host–guest dissociation constants.

Synthesis. 3-Nitro-4-(methoxymethoxy)benzaldehyde (15). To 3.34 g (20 mmol) of 3-nitro-4-hydroxybenzaldehyde (Aldrich) and 5.6 mL of triethylamine in 20 mL of absolute THF was added a mixture of 2.8 mL of chlorodimethyl ether and 12 mL of absolute THF with stirring within 30 min while maintaining the temperature below 4 °C. Stirring was continued over night, then the solvent was evaporated, and an aqueous workup afforded 3.5 g of crude **15** which was recrystallized from methanol (2.7 g, 63%: mp 95.5–97 °C; MS, (EI *m/e* (rel intensity) 211 (M^+, 3.6), 150 (2.5), 45 (100); ^{1}H NMR (CD_3CN) δ 9.93 (s, 1 H), 8.29 (d, J = 2 Hz, 1 H), 8.09 (dd, J = 2 Hz, 9 Hz, 1 H), 7.50 (d, J = 9 Hz), 5.42 (s, 2 H), 3.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.8, 154.6, 140.7,

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134.3, 129.9, 126.8, 117.0, 95.3, 57.1; IR (KBr, cm^{-1}) 1690, 1610, 1575, 1530. Anal. Calcd for $C_9H_9NO_5$ (211.2): C, 51.19; H, 4.30; N, 6.67. Found: C, 51.37; H, 4.31; N, 6.69.

5-(3-Nitro-4-hydroxyphenyl)penta-2,4-dienoic Acid (13). To a solution of 236 mg (1 mmol) of methyl 4-diethylphosphonobut-2-enoate[35] in 15 mL of 0.1 M potassium *tert*-butanolate in THF was added 211 mg (1 mmol) of **15**, and the mixture was refluxed for 16 h. the residue obtained after evaporation of the solvent was distributed between CH_2Cl_2 (10 mL) and an aqueous KH_2PO_4 solution (10 mL), and the organic phase was brought to dryness. The resulting oil was treated with 500 μL of trifluoroacetic acid for 5 min at 25 °C, filtered through a glass frit, and concentrated in a vacuum. Redissolution of the residue in 2.5 mL of methanol was followed by the addition of 2.5 mL of 4 N NaOH, and the mixture was boiled for 3 h. After concentrating the dark red solution in a vacuum to ca. 1 mL, it was acidified with 2 N sulfuric acid. The yellow precipitate was collected, carefully washed with water, and recrystallized from isopropyl alcohol to give 100 mg of yellow prisms (42%): mp 217 °C: TLC (SiO_2, $CHCl_3/CH_3OH$ 9:1 v/v) R_f 0.2; ^1H NMR (D_2O/NaOD) δ 7.98 (d, J = 2.5 Hz, 1 H), 7.58 (dd, J = 2.5 H, 9.0 Hz, 1 H), 7.21–7.08 (m, 1 H), 6.81–6.74 (m, 3 H), 5.96 (d, J = 15 Hz, 1 H); ^{13}C NMR (D_2O/NaOD) δ 178.8, 169.7, 144.6, 139.9, 139.2, 136.0, 128.8, 128.3, 128.0, 126.4, 124.3; IR (KBr, cm^{-1}) 1680, 1605, 1525; MS, (EI m/e (rel intensity) 235 (M^+, 100), 217 (40), 189 (16), 172 (13), 156 (18), 144 (49), 116 (23), 115 (61). Anal. Calcd for $C_{11}H_9NO_5$ (235.2): C, 56.17; H, 3.86; N, 5.96. Found: C, 56.13; H, 3.91; N, 5.82.

7-(3-Nitro-4-hydroxyphenyl)hepta-2,4,6-trienoic Acid (14). A solution of 1.84 g (3.8 mmol) of 5-(ethoxycarbonyl)pentan-2*E*,4*E*-dienylphosphonium bromide[36] in 25 mL of toluene and 100 mL of H_2O was shaken with 2 mL of 10% NaOH. The organic phase was separated, and the aqueous layer was extracted twice with 15 mL of toluene. The combined toluene layers were dried ($MgSO_4$), filtered, and after addition of 337 mg (1.6 mmol) of **15** were heated to reflux for 6 h. Then the solvent was removed in vacuum, and the residual oil was dissolved in 2 mL of CF_3COOH and stirred at 20 °C for 15 min. The acid again was stripped off leaving a red oil, which was heated with 5 mL of isopropyl alcohol and 7 mL of 3 N NaOH for 2 h. When the ester had disappeared as judged by TLC (SiO_2, $CH_3OH/CHCl_3$ = 1:9 v/v), the mixture was cooled and acidified with 3 N sulfuric acid. The orange precipitate so formed was collected and recrystallized from acetonitrile (extractor) to yield 184 mg (44%) yellow needles: mp > 300 °C; ^1H NMR (Me_2SO-d_6) δ 8.01 (d, J = 2.1 Hz, 1 H), 7.27 (dd, J = 8.8 Hz, 2.1 Hz, 1 H), 7.27 (dd, J = 15.0, 11.1 Hz, 1 H), 7.15–6.7 (m, 4 H), 6.54 (dd, J = 14.2, 11.2 Hz, 1 H), 5.91 (d, J = 15.0, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 167.5, 151.9, 144.0, 140.4, 137.0, 133.8, 132.8, 130.5, 128.3, 128.1, 123.2, 121.7, 119.5; IR (KBr, cm^{-1}) 1680, 1625, 1590; MS, (m/z) (rel intensity) 262 (15), 261 (M^+, 100), 216 (41), 215 (22), 170 (68), 169 (21), 168 (22), 141 (28), 115 (41).

1-(4-(Hydroxymethyl)benzyl)-8,15,22-trimethyl-1,8,15,22-tetrazoniatricyclo[13,13,6,6^{8,22}]tetracontane Tetrakis(tetrafluoroborate) (7). A solution of 605 mg (556 μmol) of **6**[22] (BF_4 salt) in 5 mL of nitromethane was heated to 75 °C under N_2 when 500 μL (5 mmol) of borane–dimethylsulfide (BMS) was added dropwise. The initially vigorous gas evolution gradually ceased, and the mixture was kept for another 45 min at this temperature. After cooling, 5 mL of methanol was added cautiously, and following cessation of the hydrogen evolution the solvent was removed in a vacuum. The residue was dissolved in 25 mL of hot water, and the product **7** was precipitated by addition of a filtered aqueous $NaBF_4$ solution. Recrystallization from acetonitrile/ethanol yielded 558 mg of white microprisms (92%), which analyzed as a monohydrate: mp > 300 °C; HPLC (35% MeOH): **6** R_v = 7.95 mL, **7** 6.75 mL; ^1H NMR (CD_3OD) δ 7.50 (s, 4 H), 4.66 (s, 2 H), 4.47 (s, 2 H), 3.25–3.45 (br m, 24–26 H), 2.97 (s, 9 H), 1.7–2.0 (br, 24–27 H), 1.5 (br s, 24–26 H); ^{13}C (CD_3CN) δ 145.66, 133.48, 127.95, 126.80, 63.83, 62.48, 59.70, 49.27, 25.94, 21.84. Anal. Calcd for $C_{47}H_{90}N_4OB_4F_{16}{\cdot}1H_2O$ (1092.4): C, 51.66; H, 8.48; N, 5.13. Found: C, 51.72; H, 8.64; N, 5.19.

1-(4-(Bromomethyl)benzyl)-8,15,22-trimethyl-1,8,15,22-tetrazoniatricyclo[13,13,6,6^{8,22}]tetracontane Tetrakis(tetrafluoroborate) (8). A solution of 500 mg (458 μmol) of **7** in 3 mL of 1:3 v/v acetonitrile/methanol was filtered through a 10-mL bed of Dowex 1 × 8 bromide, eluting with 40 mL of methanol. The oily residue obtained on evaporation was di olved in 2 mL of concentrated hydrobromic acid (d 1.49) and kept at 2. °C for 2 days. HPLC analysis showed a 90% conversion which apparently did not increase further. The mixture was concentrated in vacuo to give a sticky gum which again was taken up in 20 mL of concentrated aqueous HBr and left at room temperature for another 2 days. Then **7** had disappeared completely as judged by HPLC. The oil obtained on concentrating the mixture in vacuo was redissolved in 10 mL of methanol and 5 mL of water. To the clean, nearly colorless solution was added 4 mL of a cold saturated $NaBF_4$ solution. The solution was kept in an open crystallizing dish for 2 days; when the white crystals were collected to give 503 mg (95%) of **8** which after drying (80 °C/7 Pa) was analyzed as a monohydrate: mp > 300 °C; HPLC, 35% CH_3OH: R_v = 40.2 mL; ^1H NMR (CD_3CN) δ 7.55 (d, J = 8.4 Hz, 2 H), 7.45 (d, J = 8.4 Hz, 2 H), 4.63 (s, 2 H), 4.32 (s, 2 H), 3.15–3.30 (m, 24 H), 2.86 (s, 9 H), 1.65–1.9 (m, 24–26 H), 1.42 (br s, 24–26 H); ^{13}C NMR (CD_3CN) δ 141.74, 134.01, 130.61, 128.39, 62.48, 59.82, 49.27, 33.20, 25.94, 21.84. Anal. Calcd for $C_{47}H_{89}N_4BrB_4F_{16}{\cdot}1H_2O$ (1155.4): C, 48.85; H, 7.94; N, 4.85. Found: C, 49.08; H, 8.02; N, 5.00.

1-(4-(1-Azonia-10,19,28-triazatricyclo[17,17,8,8^{10,28}]dopentacontylmethyl)benzyl)-8,15,22-trimethyl-1,8,15,22-tetrazoniatricyclo[13,13,6,6^{8,22}]tetracontane Octakis(tetrafluoroborate) (9). A solution of 109 mg (150 μmol) of **4**[25b] in THF (2.5 mL) was mixed with a solution of 54 mg (50 μmol) of its BF_4^- salt in acetonitrile to produce the monocation of **4**. The benzylbromide **8** (115.5 mg, 100 μmol) dissolved in 1 mL of CH_3CN was added, and the progress of the reaction was monitored by HPLC (50% CH_3CN) for the disappearance of **8**. After 4 days at room temperature the clear supernatant was decanted from the sticky precipitate (A) (50 mg) which had separated on standing. HPLC analysis revealed that the solution contained two major products (later found to be the mono- and bisalkylated derivatives of **4**) in addition to unreacted **4**, whereas the residue A consisted of 4 major components with the desired product **9** amounting to ca. 20%. The solution was concentrated to 500 μL by a jet of nitrogen, diluted with 12 mL of absolute ether, and centrifuged. The residue was redissolved in 1 mL of acetonitrile and again precipitated with 12 mL of ether. The ethereal phases obtained on centrifugation were combined and brought to dryness. Extraction of this residue with 3 × 5 mL warm absolute ether left a sticky gum which was combined with the precipitates obtained in the centrifugation steps and taken up into 4 mL of CH_3CN/CH_3OH 1:3 v/v. The solution, which was essentially free of unreacted **4**, was converted to the chloride salt by filtration over Dowex 1 × 8 Cl^- form eluting with methanol. The oil obtained on evaporation was dissolved in water and subjected to aqueous size exlusion chromatography on Sephadex G-25 (3.5 × 86 cm, eluent: 30 mM HCOOH and 50 mM NaCl in H_2O). The separation was followed by RI detection, and the fractions were cut accordingly and analyzed by HPLC. The desired product **9** appeared well-separated in the middle of a three peak pattern. The first one contained the compounds of higher molecular weight preferentially the bisalkylated compound, whereas the smaller last peak supposedly originated from excess inorganic salt. The fraction containing **9** was lyophilized and extracted with ethanol/acetonitrile 1:1 (2 × 5 mL). Evaporation of the solvent, dissolution in water, and addition of aqueous $NaBF_4$ gave a white precipitate which appeared to crystallize on standing in the mother liquor.

Precipitate A was subjected to the same chromatographic purification steps to yield another crop of product **9**. Though the product so obtained was pure by HPLC (impurities by RI 5%) and the NMR spectra were compatible with the assigned structure, elemental analysis remained variable, total yield, 115 mg (54%): HPLC, 50% CH_3CN: R_v = 14.0 mL; ^1H NMR (D_2O, Cl_8^- salt) δ 7.62 (s, 4 H), 4.52 (s, 4 H), 3.40 (br, ~24 H), 3.15 (br, ~24 H), 2.96 (s, 9 H), 1.6–2.0 (br, ~50 H), 1.5, 1.4 (overlapping br s, 70–73 H); ^{13}C NMR (CD_3CN) δ 134.5, 134.2, 131.0, 130.7, 62.7, 60.1, 59.7, 55.6, 55.0, 53.8, 49.4, 28.6, 28.2, 28.0, 27.7, 26.6, 26.1, 24.5, 24.0, 22.8, 22.0.

1-(4-(10,19,28-Trimethyl-1,10,19,28-tetrazoniatricyclo[17,17,8,8^{10,28}]dopentacontylmethyl)benzyl)-8,15,22-trimethyl-1,8,15,22-tetrazoniatricyclo[13,13,6,6^{8,22}]tetracontane Octakis(tetrafluoroborate) (5). A solution of 31 mg (18 μmol) of **9** chloride (obtained from the BF_4^- salt by anion exchange on Serdolit AS 6 Cl^- (Serva)) in 1.5 mL of isopropyl alcohol was heated to 100 °C and stirred when 600 mg of powdered soda and a solution of 100 mg of methyl tosylate in 1 mL of isopropyl alcohol was added over a period of 15 min. Heating and stirring were continued for 6 h, then the mixture was cooled and filtered through a plug of cotton, and the solvent was stripped off. The residue was redissolved in 1 mL of H_2O, acidified with HCl, and extracted with ether (3 × 3 mL). HPLC analysis (50% CH_3OH) of the aqueous phase demonstrated the presence of only two products with R_v = 9.0 mL and 17.4 mL, respectively, in a peak area ratio of 3.5:1. These components were separated by preparative HPLC (column 10 × 250 nm Nucelosil RP_{18}, 7 μm, 52% CH_3OH, 30 mM $NaClO_4$, 30 mM HCOOH) to yield 20.5 mg of **5** ClO_4^- salt (9.1 μmol, 50%) of the major rapidly eluting component and 3 mg of the minor one: ^1H NMR (CD_3CN) δ 7.58 (s, 4 H), 4.40 (br s, 4 H), 3.3, 3.19 (overlapping br m, 47–48 H), 2.89 (s,

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18 H), 1.55–1.95 (br, partly covered by solvated residues), 1.4 (br s, 70–74 H); ^{13}C NMR (fluoride salt, D_2O) δ 136.0, 135.7, 132.5, 132.2, 65.4, 64.2, 63.9, 61.7, 61.0, 51.2, 50.9, 29.9, 29.8, 27.9, 27.7, 23.8, 23.7, 23.6.

The minor component exhibited a ^1H NMR spectrum which was virtually identical with the corresponding spectrum of **5** except for one feature: in addition to the signal of the $N-CH_3$ groups at 2.89 ppm another singlet at 3.03 ppm appeared having one-fifth of the area of the peak at 2.89. We tentatively assign the structure of a mono-in $N-CH_3$ isomer to this compound.

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Effect of Phenyl Substitution on the Photochemistry of Conformationally Restricted Cycloalkanones[1]

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Abstract: The photochemical and photophysical properties of pentacycloundecan-8-one (**1**) and the phenyl derivatives **2** and **3** are described. All three systems are highly photostable in both singlet and triplet manifolds. No fluorescence from the aromatic moieties in **2** and **3** was observed; they appear to undergo rapid intramolecular energy transfer to the carbonyl chromophores. Whereas at 298 K the excited state behavior of the carbonyl group in **2** ($\Phi_f = 0.0033$, $\tau_s = 11.1$ ns, $\tau_T = 12$ ns) is consistent with that of **1** ($\Phi_f = 0.0039$, $\tau_s = 10.9$ ns, $\tau_T = 9.4$ ns), the syn-isomer **3** is nonfluorescent and has a shorter triplet state lifetime (3.6 ns). Rapid internal exciplex formation is believed to be responsible for this behavior.

The photochemical and photophysical behavior of nonconjugated polychromophoric molecules has continued to be the subject of intense investigation by many groups. These studies have revealed novel photochemical phenomena and have provided information on intramolecular energy transfer,[2-5] electron, charge transfer, or exciplex formation,[6-13] and energy migration.[14] Complex behavior is expected in bichromophoric systems not only because of competitions among the above-mentioned processes but also because more than one mechanism may be operative.[6,7,15-19]

For example, it has been known for some time that β-aryl rings "deactivate" both carbonyl singlets and triplets as evidenced by decreased intersystem crossing efficiencies and reduced quantum yields of Norrish type II reaction.[11-13,15-19] In fact, the low efficiency of photoreduction of β-phenylpropiophenone has been recognized for over 40 years.[19] In at least one study it was concluded that chromophoric coupling occurs "through space" rather than "through bonds" and that interaction of both n_{CO} and π_{CO} with the π-aryl system may be of importance.[15] In agreement with this, limitations to conformational mobility (e.g., by inclusion in zeolites) are frequently sufficient to limit severely the efficiency of intramolecular deactivation.[20-22]

In a different context Amrein and Schaffner[4] have rationalized the behavior of isomeric naphthyl indanones in terms of competing through space exciplex formation (endo isomer) and through bond energy transfer (exo and endo isomers). These workers postulated that through σ-bond interaction is of greater importance than through-space orbital overlap in the endo case and that weak intramolecular exciplex formation provides an endo-specific mechanism for radiationless deactivation.

We have been interested in the geometrical aspects of these kinds of long-range phenomena in bichromophoric systems, especially in nonconjugated unsaturated ketone photochemistry.[23] This report deals with intramolecular interactions which control the behavior of nonconjugated phenyl ketones. Earlier studies have dealt with aromatic ring quenching of carbonyl triplet states in intermolecular systems[24-29] and in relatively flexible β-aryl ketones.[11-19] We sought to design molecules with greater molecular rigidity in which exciplex lifetimes might be lengthened. This

Table I. Absorption Spectra of **1–3** in Acetonitrile Solution

substrate	λ_{max} (ϵ)[a]	λ_{max} (ϵ)[a]
1		299 (18)
2	258 (210)	299 (20)
3	262 (246)	301 (33)

[a] λ_{max} in nanometers (±2) and ϵ in units of M^{-1} cm^{-1}.

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