Again AM1-SM1 predicts the $\Delta\Delta G_{g\rightarrow aq}$ values accurately. Interestingly, the rotameric equilibrium between the *E* and *Z* forms of *N*-methylacetamide is unaffected by aqueous solvation, i.e., $\Delta\Delta G_{g\rightarrow aq} = 0.0$, although $\Delta G_S°$, the free energy of solvation for either isomer, is sizable at −10.0 kcal/mol.[22,23] AM1-SM1 predicts $\Delta G_S°$ for the *E* isomer exactly, but yields only −8.5 kcal for the *Z* isomer, giving a $\Delta\Delta G_{g\rightarrow aq}$ of 1.5 kcal.

We conclude that AM1-SM1 has useful chemical accuracy for the effect of hydration on chemical equilibria. We expect that in most cases the dominant error in AM1-SM1 molecular orbital calculations of relative free energies for medium-size organic molecules in aqueous solution will be the error in treating the electronic structure of the solute, not the error in the hydration effect.

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Enantioselective and Diastereoselective Molecular Recognition of Alicyclic Substrates in Aqueous Media by a Chiral, Resolved Synthetic Receptor[1]

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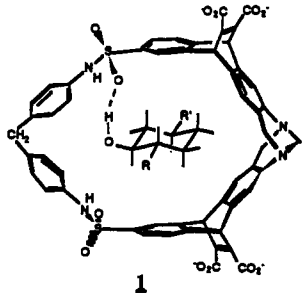
Alkanes have small dipole moments, are of relatively low polarizability, and bear no hydrogen-bonding groups. For this reason, simple alicyclic molecules, when compared to the multiple hydrogen bond forming targets most often studied in contemporary molecular recognition projects, can be characterized as rather reluctant partners in host–guest events. Nevertheless, molecules of this class are often used in natural intraspecies and intracellular communication processes, because alicyclic molecules are especially stable, stereochemically complex, and information-rich.[3] Shape selective receptors for alicyclic molecules could be used in analytical applications, in chromatography, or as agents for the control or catalysis of alicyclic substrate reactivity. Here we describe the synthesis and initial characterization of an optically pure, water-soluble receptor (**1**) that binds stereoselectively to neutral alicyclic targets. The receptor shows immediate promise as a chiral shift reagent for alkanes.



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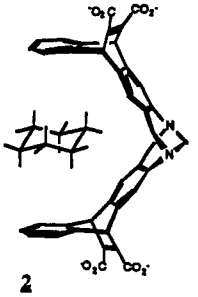

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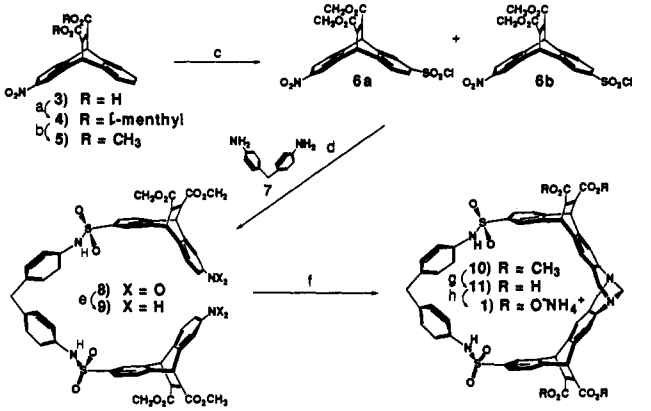
Since the pioneering work of Whitlock, Koga, Tabushi, and Murakami, cyclophanes have become a well-established class of synthetic receptors for neutral organic targets and have very often been used in studies of binding to *aromatic* substrates.[4,5] Much less often, cyclophane hosts have been used for neutral aliphatic and alicyclic guests or prepared in optically pure form.[6g-i,7] A simple rectangular shape is adequate for binding to benzenoid substrates.[4,8] Receptors for even the simplest aliphatic substrates require a larger pocket. For two benzene rings to bracket a cyclohexane ring, the benzene rings should be separated by about 8.5 Å. Chiral molecular tweezers (**2**) prepared in this lab appear to be well suited for alkane binding but have a disadvantage: water-soluble derivatives of these simple chiral clefts dimerize when in solution.[9]

Scheme I[a]



[a] (a) DCC/CH_2Cl_2, (−)-menthol, then separate diastereomers; (b) concentrated H_2SO_4, then CH_3OH, H^+; (c) $ClSO_3H$; (d) **7**, C_5H_5N; (e) Ni (Raney), then H_2/PtO_2; (f) TFA, hexamethylenetetramine; (g) LiOH, $MeOH/H_2O$; (h) NH_4OH/H_2O.

With these thoughts in mind, we undertook the synthesis of a new chiral and conformationally restricted cyclophane (Scheme I). The racemic nitro acid **3** was resolved through formation of the (−)-menthyl diesters. Crystallization (hexane–ethyl acetate) provided pure diastereomer **4** (mp 186–187 °C).[10] The optically pure dimethyl ester **5**($[\alpha]_D$ = 48.2°) was obtained in 21% overall yield from diacid **3**.[10] Chlorosulfonylation of **5** afforded two regioisomeric sulfonyl chlorides (**6**) in approximately equal amounts. Isomer **6a** was treated with diamine **7** to afford the bis(sulfonamide) **8**. Treatment of diamine **9** in trifluoroacetic acid with hexamethylenetetramine created the dibenzodiazocine unit and provided the macrocyclic tetraester **10** in 28% yield.[11-13]

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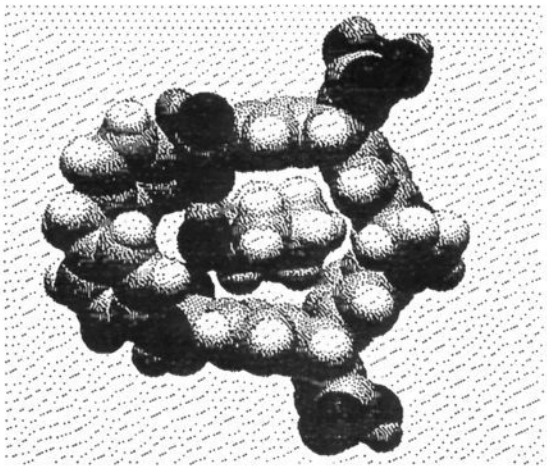
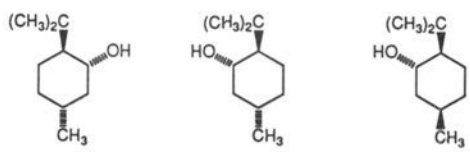


Figure 1. Representation of a molecular complex between synthetic receptor **1** (shown as the tetraacid) and cyclohexanol. The atomic radii used here are not van der Waals type radii, but instead approximate the radii used in CPK models. The profile of the cyclic alkane is well matched by the hexagonal lipophilic pocket enclosed by the receptor.

The terpenes offer a readily available library of defined alkane shapes.[14] Binding of this new receptor to (−)-menthol (**12**), (+)-menthol (**13**), and (+)-isomenthol (**14**) in a $ND_4^+Cl^-/ND_3$ buffer at pD 9.0 in D_2O at 20 °C was evaluated by analysis of NMR titration data.[15] It was found that (−)-menthol and (+)-menthol have association constants of 2500 ± 200 M^{-1} and 2000 ± 200 M^{-1}, respectively. There are no previous reports of binding of such small, partially water soluble alkanes to a synthetic receptor, but this result compares favorably with association constants obtained for much larger and less water soluble aliphatic guests.[7c]



12 **13** **14**

The axial methyl group of (+)-isomenthol was predicted to inhibit binding of this molecule within this carefully shaped cleft. Indeed, the association constant with (+)-isomenthol (1000 ± 200 M^{-1}) is half that observed for (+)-menthol. The limiting chemical shifts for the three methyl groups in each of these substrates indicate differences in the time-averaged binding position of the three isomeric menthols. Chemical shifts of the isopropyl methyl groups in (+)-isomenthol (+1.45/+1.20 ppm) are much larger than those observed for corresponding groups in (−)- and (+)-menthol (+0.66/+0.55 ppm and +0.43/+0.68 ppm, respectively).[16] This supports the idea that the axial methyl group in isomenthol causes the time-averaged position of the receptor to be shifted toward the isopropyl group.

Receptor **1** was designed to be a conformationally rigid molecule that would make intimate contact with an enclosed cyclohexanoid substrate: it was not designed to recognize the two enantiomers of menthol. The observed differences in binding of (+)- and (−)-menthol, though small, are unprecedented in the context of small alicyclic molecular recognition in aqueous media. This success suggests that the receptor–substrate contacts are quite intimate (Figure 1).

The synthesis and initial binding studies that are reported here illustrate that stereoselective binding can be achieved in water by a synthetic receptor without multiple receptor–substrate hydrogen bonds. The results are modest, but in these initial studies, partially water soluble guests were tested, and they were chosen because they were easily available and the association constants could be accurately measured. Less water soluble targets will have higher affinities for this receptor, and other guests will be bound more enantioselectively. Because the synthesis is convergent and capping structures more elaborate and interactive than 4,4′-methylenebis(aniline) can easily be utilized, other, more shape-selective synthetic receptors can be based on this general system.

Acknowledgment. This work was funded by the National Institute of General Medical Sciences (GM-34846) and the Alfred P. Sloan Foundation. Dr. Fu-Tyan Lin provided support and advice in our NMR experiments. Molecular modeling software was obtained through the generosity of Professor W. C. Still (Department of Chemistry, Columbia University; MacroModel software) and Dr. B. Hesp, Ph.D. (ICI Pharmaceuticals; Enigma and Aesop software).

Supplementary Material Available: Preparative procedures and characteristic data (IR, ^1H NMR, ^{13}C NMR, MS) for **4**, **5**, **6a**, and **8–10**, complete binding data for association constants, and plots of calculated and observed chemical shifts for each binding experiment (8 pages). Ordering information is given on any current masthead page.

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Oxidative Ligand Transfer to Alkanes: A Model for Iron-Mediated C–X Bond Formation in β-Lactam Antibiotic Biosynthesis

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Oxidative C–X bond formation reactions are proposed in the biosynthesis of antibiotic β-lactams such as isopenicillin N, cephalosporin, and clavaminate. The respective enzymes, isopenicillin N synthase,[1] deacetoxycephalosporin C synthase,[2] and clavaminate synthase,[3] all require Fe(II) in a non-heme active site and utilize O_2 to effect these transformations; the latter two also require the cofactor, α-ketoglutarate. It has been speculated that the C–X bond forms via an iron–oxo intermediate such as A which abstracts hydrogen from RH and transfers the X group to the caged alkyl radical (see Scheme I).[4] However, examples for such oxidative ligand transfers in simple model systems are lacking. Funtionalized alkanes have been obtained from $Mn^{III}TPP/PhIO$[5] and $Fe(PA)_2/H_2O_2$[6] systems;[7] however, these transformations result from the interception by Mn(TPP)X and

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