were washed with brine (20 mL) and dried. Removal of solvent in vacuo provided 26 mg of a white solid, which was dissolved in methanol-tetrahydrofuran (5 mL/2 mL) and treated with perchloric acid (2 drops). After 15 min, the solution was diluted with pH 8 phosphate buffer (30 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried, the solvent was removed under reduced pressure, and the residue was chromatographed (TLC grade silica gel, 18% ethyl acetate in petroleum ether) to yield 9 mg (43%) of 3-palmitate ester **38** as a white solid and 4 mg (13%) of 3,5-dipalmitate ester **39**.

For **38**: mp 120-125 °C; IR (thin film, cm^{-1}) 3550-3250 (broad), 2920, 2860, 1745, 1695, 1470, 1455, 930, 875; ^1H NMR (300 MHz, C_6D_6) δ 5.75 (d, J = 1.5 Hz, 1 H), 5.39 (t, J = 1.6 Hz, 1 H), 5.23 (s, 1 H), 4.51 (s, 1 H), 4.35 (d, J = 11.5 Hz, 1 H), 3.97 (d, J = 11.5 Hz, 1 H), 3.95-3.85 (m, 2 H), 3.38 (br s, 1 H), 2.44 (br s, 1 H), 2.23 (dd, J = 15.2, 11.7 Hz, 1 H), 2.16 (t, J = 7.6 Hz, 2 H), 1.75 (t, J = 8 Hz, 1 H), 1.67 (d, J = 1.1 Hz, 3 H), 1.62-1.50 (m, 5 H), 1.50-1.15 (m, 26 H), 0.91 (t, J = 6.6 Hz, 3 H), 0.88-0.82 (m, 1 H); MS, m/z (FAB, M^+ + H) calcd 533.3842, obsd 533.3837.

Diesterification of 3. By use of the procedure described above, but with 13 mg (0.032 mmol) of **3**, 16 mg (0.06 mmol) of palmitoyl chloride, and 28 mg (0.154 mmol) of 4-(dimethylamino)pyridine in 1 mL of toluene, there was isolated exclusively the dipalmitate **39** (11.4 mg, 47%) after chromatography (TLC grade silica gel, 12% ethyl acetate in petroleum ether): mp 80-83 °C; IR (thin film, cm^{-1}) 3530, 3420, 2920, 2850, 1740, 1720, 1695, 1470, 1450, 1390, 1170, 1155, 915, 725; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (s, 1 H), 5.76 (s, 1 H), 5.56 (s, 1 H), 5.40 (s, 1 H), 4.00 (s, 2 H), 3.70 (s, 1 H), 2.45-2.20 (m, 5 H), 2.05-1.97 (m, 1 H), 1.81-1.50 (m, 13 H, including CH_3 singlet at 1.68), 1.40-1.20 (br s, 48 H), 1.15-0.93 (m, 2 H), 0.88 (t, J = 6.5 Hz, 6 H); MS, m/z (FAB, M^+ + H) calcd 772, obsd 772.

Acknowledgment. This research was made possible by the generous financial support of the National Institutes of Health (Grant CA-12115). The biological assays were performed at the Eli Lilly Co.

Note Added in Proof. The results of the irritant assays involving **38** and **39** on the mouse ear have now been completed courtesy of Professor Hecker (Heidelberg). Following a standard 24-h wait after administration, no irritant unit with 5 μg/mouse ear was seen with either ester. Thus, the IU^{24} values are necessarily larger, and the $ID_{50}{}^{24}$'s are expected to be even higher. In comparison, the IU^{24} of 3-*O*-hexadecanoylingenol is 0.1 μg/ear and its $ID_{50}{}^{24}$ is 0.050 μg/ear. Although the PKC-binding activity of **38** and **39** and their capability of stimulating Epstein-Barr-Virus synthesis are currently being determined, past correlations would suggest a prognosis that is not favorable.

Supplementary Material Available: Tables containing fractional coordinates, temperature factors, bond distances, and bond angles of **20** (5 pages). Ordering information is given on any current masthead page.

Molecular Recognition in Aqueous Media. Conformationally Restricted Water-Soluble Cyclophanes Derived from 6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine

Marlon D. Cowart, Irving Sucholeiki, Rudolf R. Bukownik, and Craig S. Wilcox*

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received January 13, 1988*

Abstract: Two new water-soluble cyclophanes, which incorporate the Tröger's base structural unit, have been prepared. The two macrocycles are very similar and differ only by two (geminal) methyl groups. NMR data reveal that these macrocycles form complexes in aqueous solution with benzenoid substrates. Analysis of the titration binding curves indicates dissociation constants ranging from 3 to 23 mM. Computer-aided molecular modeling studies of these hosts were carried out, and probable conformations for the macrocycles are discussed. Association energies for the host based on the diphenylmethane structural unit are always stronger (by 0.1-0.4 kcal/mol) than the binding energies measured for the host based on 2,2-diphenylpropane. Although the differences in association energies for the two hosts with a given substrate are small (0.1-0.4 kcal/mol), the average structures of the two complexes are believed to differ. Host-induced changes of guest chemical shifts are larger for the host derived from diphenylmethane and indicate that introduction of the geminal dimethyl group inhibits deep complexation, while shallow host-guest interactions are less affected.

Several water-soluble cyclophanes are known to be effective receptors for small, neutral organic molecules. Pioneering experiments by Koga, Tabushi, and Whitlock have demonstrated that water-soluble cyclophanes prepared from 1,4-disubstituted benzene derivatives can bind to benzenoid and naphthalenoid substrates in aqueous solution.[1] Diederich has carefully investigated a number of new water-soluble cyclophanes based on 4,4-diarylpiperidinium ions.[2] We have shown that derivatives of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (which we refer to as "Tröger's base derivatives") are easily prepared in good yield.[3,4] The bridged dibenzodiazocine ring system is sharply

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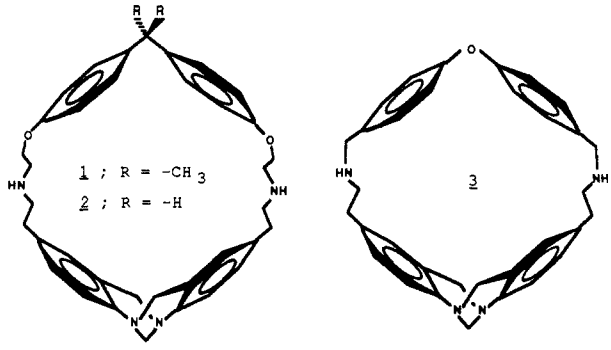


Figure 1. Water-soluble cyclophanes based on the Tröger's base structural unit.

folded and is readily incorporated into a macrocyclic ring.

We were attracted to the dibenzodiazocine structural unit because the two aromatic rings are held in a fixed relative position and, when included in a macrocyclic structure, the rings are not able to rotate in relation to the cavity defined by the macrocycle.

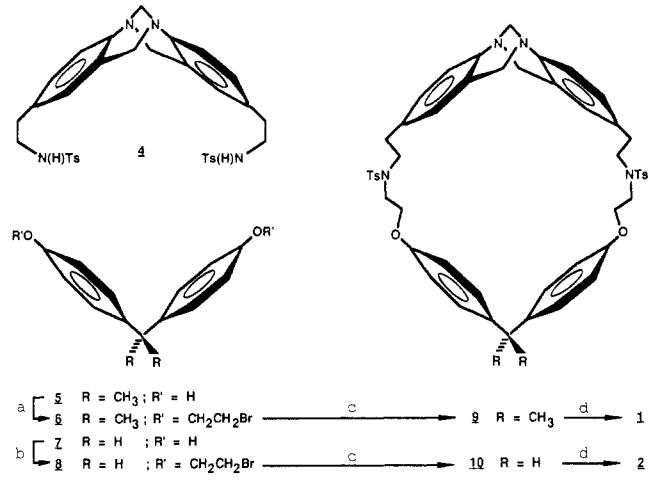
Studies of intermolecular interactions in aqueous solution can illuminate aspects of biological processes. Such studies are a starting point in the rational design of selective organic catalysts and reagents. Interpretations of the results of solution phase binding studies are complicated when the host and guest molecule are flexible. The increased rigidity of host molecules based on dibenzodiazocine is intended to simplify the analysis of host–guest interactions and may also afford tighter binding or more selective hosts, because in comparison with previously reported cyclophanes these new macrocycles are more organized. Good host–guest interactions will result in cases where the host shape is maintained in a shape complementary to the guest.[5] This paper describes the preparation and properties of the first water-soluble macrocyclic dibenzodiazocine-derived hosts and compares diphenylmethane and diphenylpropane as components of water-soluble cyclophanes.[6]

Results

Design and Synthesis. The design of the hosts **1** and **2** (Figure 1) was based both on experience and on computer-based molecular modeling experiments. The general objective was to bridge the dibenzodiazocine unit with a second diaryl component. The dibenzodiazocine unit is chiral and racemic, and therefore, to avoid the complications of diastereomer formation, the second component must be achiral. Readily available candidates included the diphenylamines, diphenyl ethers, diphenylmethanes, and 2,2-diphenylpropanes. Computer-aided molecular modeling suggested that the connecting chains should contain five or six atoms and that chains of four atoms would afford a cavity too small to include a benzenoid substrate.[7] This prediction was borne out in a preliminary study: the host **3** (Figure 1), wherein four atoms separate the dibenzenoid moieties, was found to give no evidence for complex formation with benzenoid substrates in aqueous solution.[8]

The specific synthetic targets (**1** and **2**) were chosen because they could be prepared from readily available starting materials. It was also hoped that insights into the structure of the complexes might be revealed by comparisons of the two closely related hosts.

Chart I



[a] (a) KOH, $BrCH_2CH_2Br$, EtOH–H_2O; (b) NaOH, $BrCH_2CH_2Br$, $Bu_4N^+OH^-$, H_2O–CH_2Cl_2; (c) **4**, $CsCO_3$, DMF, 80–98 °C; (d) Na, anthracene, DME, or THF.

The syntheses (Chart I) were based on combining the bis(sulfonamide) **4** with an appropriate dihalide. Preparations of bis(sulfonamide) **4** have been described previously.[4] The dibromides required for formation of the macrocycle were prepared by alkylation of either 2,2-bis(*p*-hydroxyphenyl)propane (**5**) or bis(*p*-hydroxyphenyl)methane (**7**) by 1,2-dibromoethane. The resulting dibromides were treated with bis(sulfonamide) **4** in DMF in the presence of cesium carbonate to afford the macrocyclic bis(sulfonamides) **9** and **10** in 52% or 43% yields, respectively. Deprotection of these macrocyclic bis(sulfonamides) afforded diamines **1** and **2** as analytically pure hydrochloride salts. In order to verify that the macrocyclic structure of these hosts was required for substrate binding, a control compound (**12**) was also prepared.

11 ; R = Ts
12 ; R = H

Evaluation. The dissociation constants (K_d) for these new host–guest systems were determined by NMR spectroscopy. The experiment consisted of holding one component (usually the guest) at constant concentration and varying the concentration of the second component. The solvent was D_2O, and the pD was 1.9 ± 0.1 (KCl/DCl buffer, 100 mM). At this pD, three of the four nitrogens are protonated and plots of host proton positions as a function of concentration indicated that aggregation did not occur at concentrations up to 50 mM. One diazocine nitrogen remains unprotonated. In separate experiments we found that the dissociation constants were unchanged over the range from pD 1.7 to 2.4. Chemical shifts (external standard) for protons on the first component were plotted against the concentration of the second component to give a typical titration curve (Figures 2 and 3). Because of the approximation made by Benesi and Hildebrand in deriving their linear expression, use of the Benesi–Hildebrand method to analyze this NMR binding data is not appropriate.[9] Bergeron illustrated that the Benesi–Hildebrand method will lead to large errors in K_d whenever the concentration of the minor component is greater than one-tenth of the true K_d.[10] This is so without regard to the ratio of components. Because many data points must be taken for each binding experiment a practical

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Table I. Dissociation Constants (K_d) and Extrapolated Maximum Chemical Shifts ($\Delta\delta_{max}$)[a]

substrate	K_d, M/ΔG, kcal/mol		$\Delta\delta_{max}$, ppm	
	2 (R = H)	**1** (R = CH_3)	**2** (R = H)	**1** (R = CH_3)
2,4,6-trimethylphenol	0.010/2.7	0.014/2.5	–; H3, 2.44	–; H3, 2.24
4-methoxyphenol	0.017/2.4		H2, 1.50; H3, 2.54	
4-toluenesulfonic acid	0.003/3.4	0.004/3.3	H2, 1.53; H3, 2.44	H2, 1.48; H3, 2.26
4-methylphenol	0.019/2.3	0.023/2.2	H2, 1.18; H3, 2.24	H2, 1.39; H3, 1.83
4-cyanophenol	0.006/2.9	0.015/2.5	H2, 1.35; H3, 2.58	H2, 1.30; H3, 2.34
4-nitrophenylacetate[b]	0.007/2.9		H2, 1.42; H3, 2.19	
1,3-dihydroxynaphthalene[c]	0.003/3.4	0.005/3.1	H5, 2.04; H6, 1.37	H5, 1.41; H6, 1.29
			H7, 1.21; H8, 2.01	H7, 1.21; H8, 1.55

[a] The guest concentration was 3–4 mM. Unless indicated otherwise, the solvent was D_2O (pD 1.9 ± 0.1; 0.1 M KCl–DCl buffer). [b] Solvent was 9:1 D_2O–CD_3OD. [c] pD 2.3 ± 0.1, 0.1 M KCl–DCl buffer.

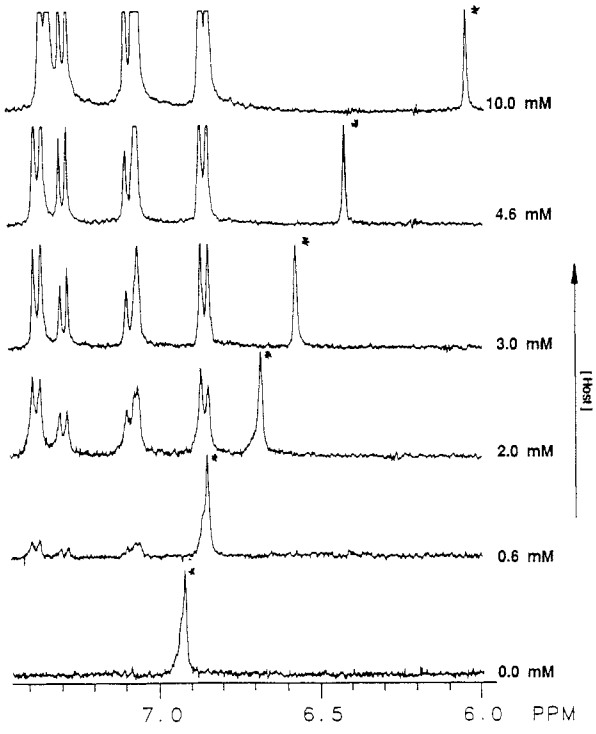

Figure 2. Effect of increasing host concentration on aryl protons of trimethylphenol (3 mM). Host concentration (mM) is indicated on the right.

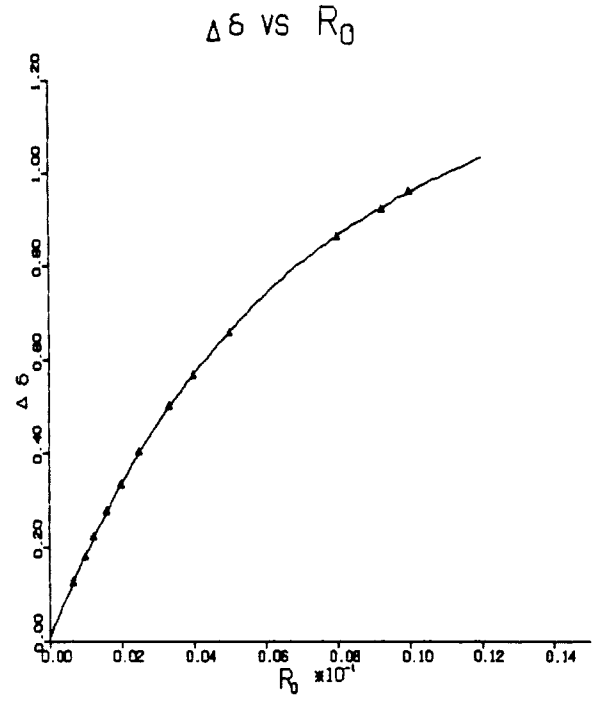

Figure 3. Plot of calculated (—) and measured (Δ) chemical shifts for 1,3-dihydroxynaphthalene (3 mM) titrated with host **1** (0–10 mM).

minimum concentration in this case for NMR experiments is about 10^{-3} M, and the Benesi–Hildebrand technique is therefore not routinely applicable to NMR data for systems where K_d is less than 10^{-2} M.

Titration curves for NMR binding experiments are best analyzed by an exact curve-fitting procedure. Experiments in this lab have been analyzed by using a nonlinear curve-fitting procedure.[4] At present we prefer a linear fit algorithm that was developed about 25 years ago and has recently been applied to the analysis of solute–solute interactions.[11] Results afforded by such an analysis are illustrated in Figure 3. It has been pointed out that in determining dissociation constants from titration data, it is important that the experiment cover a region of saturation with as large a range as possible.[12] Our experiments were designed to cover the range from 5% saturation to more than 60% saturation. Dissociation constants were determined for each proton observed. For a given proton, precision and reproducibility were good, and four independent K_d determinations made on the same system fell in a range within ±15% of the mean. Reproducibility and accuracy are better for tighter binding systems, where a greater range of saturation values can be examined and where the magnitude of the shifts is large compared with uncertainties in peak positions.

An advantage of the NMR method for determining dissociation constants is that each proton in the host or guest can be monitored during the titration experiment. Discrepancies among the dissociation constants determined for the different protons can be an important source of information. Discrepancies larger than the expected reproducibility of the analysis indicate that the observed titration curve may not be the result of a simple 1:1 equilibrium binding process. In the present work dissociation constants as determined for the several protons in each guest agreed to within ±15% of the mean. This corresponds to an uncertainty in free energy of association (ΔG_{assoc}) of less than 100 cal/mol.

Hosts **1** and **2** bind to benzenoid substrates in aqueous solution with binding energies that range from 2.1 to 3.3 kcal/mol. Dissociation constants for the two host molecules with several benzenoid guests are presented in Table I. Both of the macrocyclic hosts induced strong upfield shifts for guest protons, and the titration curves revealed saturation phenomena. In contrast, the control molecule (**12**) induced very little change (<0.1 ppm) in the spectra of the guests even at the highest concentrations, and the plot of these small shifts vs concentration of the control was linear.

Discussion

Molecular Modeling Studies. Conformational analysis of macrocycles of this type is a challenging task and should not be

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(12) (a) Person, W. B. *J. Am. Chem. Soc.* **1965**, *87*, 167–170. (b) Deranleau, D. A. *Ibid.* **1969**, *91*, 4044–4054.

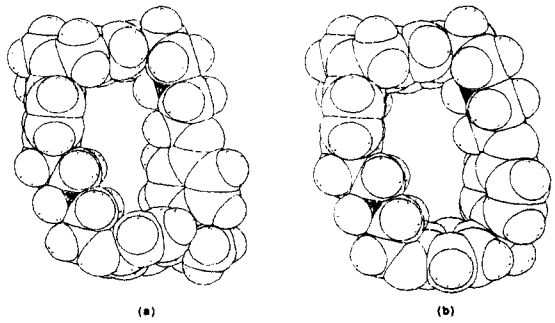
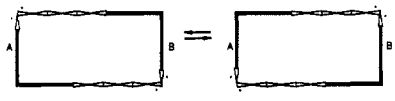


Figure 4. (a) Space-filling representation of a low-energy conformer located for host **1**. (b) Representation of a similar conformational minimum located for host **2**. The effect of the diazocine unit, which helps define the rectilinear outline of these hosts, is clearly revealed.

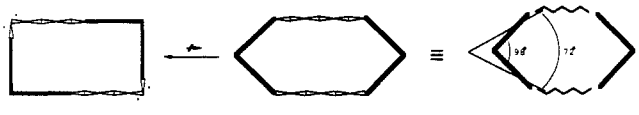
treated superficially. We have examined more than 50 conformers (all of which were local conformational minima) of macrocycle **2**.[7] The results indicate that one important family of conformers for these macrocycles is as illustrated in Figure 4a.

It is interesting that no low-energy conformations were located corresponding to a molecule that had a C_2 axis of symmetry. The conformations illustrated in Figure 4 are representative of all our results of modeling tetraarylcyclophanes and is similar to the structure of a related host synthesized by Diederich.[13]

It was observed that, in general, the preferred conformations for these systems maintain a series of anti torsional angles and two gauche torsional angles (a typical "corner" as described by Dale[15]) in each connecting chain. The corners, or gauche bonds, on each side of the macrocycle are not related by a C_2 symmetry operation: such conformers were found to be quite unstable and/or to have no cavity sufficiently large or appropriate in shape for binding of a benzenoid guest. In a typical low-energy conformer, one corner is positioned adjacent to the Tröger's base unit and the corner in the other connecting chain is adjacent to the diphenylmethane unit. The results of these modeling studies may be summarized pictorially (the asterisk (*) indicates the position of a gauche torsional angle and A and B represent the two diaryl units):[14-16]



The reason that the connecting chains contain at least one gauche bond is obvious for cases that include an even number of atoms in the connecting chains. A macrocyclic structure cannot be prepared if the connecting chains contain an even number of atoms and only anti torsional angles: the terminal bonds in such a system would be antiperiplanar and not convergent, as required for a reasonably accessible macrocyclic structure.[15] Modeling results indicate that for systems similar to **1** but that have only five atoms in the connecting chain, gauche bonds are also required.



Unstrained connecting chains composed of an odd number of atoms and only anti torsional angles would require the bis(aryl) units to subtend an angle of just 72°. Available bis(aryl) units subtend angles of from 92 to 112°. The mismatch is best accomodated by introducing one gauche torsional angle into each chain

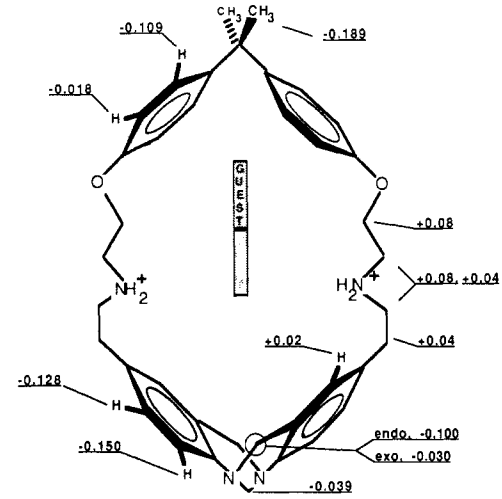


Figure 5. Changes in host chemical shift induced by *p*-cyanophenol (guest, 20 mM; host, 3 mM). Negative signs indicate downfield shifts.

and allowing the other torsional angles to remaian near the optimum. The gauche effect is probably not important here as these calculational results and geometrical analyses are similar for connecting chains composed of only carbon atoms.[17]

Observed Chemical Shifts. The chemical shifts induced in the hosts and guests during complexation can help define allowable structures for the host–guest complex. Typical shifts observed for guests are illustrated in Table I. It is revealing that for the 1,4-disubstituted benzene derivatives the protons ortho to the more lipophilic substituent are more affected by complexation than are the protons ortho to the less lipophilic substituent. Some of this difference may be due to the intrinsic susceptibility of the guest protons, but the fact that the difference persists in the case of *p*-methoxyphenol, where the intrinsic susceptibility of the aryl protons should be very similar, indicates that differences between the protons per se are likely to be negligible.

It is most likely that the differences indicate that the more lipophilic substituent is, on average, more often bound in the cleft and the time-averaged position of protons adjacent to the more lipophilic substituent is closer to the shielding regions of the host aryl groups than the time-averaged position of the protons next to the hydrophilic substituent.

The effect of complex formation on host chemical shifts is illustrated in Figure 5. The upfield shift of protons in the connecting chains and downfield shifts for protons at the ends of the hosts indicate that the time-averaged position of the guest is as shown in the figure. Of course such an average might be achieved either by docking to a host conformation that has a C_2 axis of symmetry or by rapid interchange and docking to host conformers similar to that shown in Figure 4. The molecular modeling results described above support the latter interpretation.

It is at first surprising that the geminal methyl groups of **2** are shifted to such a large extent (0.19 ppm downfield). It is observed, however, that in most conformers of **2** (due to a twisting of the benzene rings in the 2,2-diphenylpropane unit, vide infra) the geminal methyl groups are, on average, as close to the cavity as are the protons ortho to the 2-propyl group. This is illustrated in Figure 4b.

The endo protons of the dibenzodiazocine unit are affected more by the guest than are the exo protons. This is consistent with an inclusion type complexation. The endo protons resonate at higher field than the exo protons and are also identified by the absence of an NOE enhancement on irradiation of the bridging methylene group protons (the exo protons are enhanced in the same experiment) and by a small *W* coupling with the bridging methylene protons. Such coupling is not observed for the exo protons.

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(14) Conformations of the connecting chains are graphically illustrated with the wedge-type "bird's-eye" representations preferred by Dale and recently used by Masek et al. in the context of cyclophane conformational analysis.[15,16] The diagrams are meant to illustrate only the conformation along the connecting chains and do not accurately represent the orientation of the connecting chains relative to the aromatic groups.
(15) Dale, J. *Top. Stereochem.* **1976**, *9*, 199–270.
(16) Masek, B. B.; Santarsiero, B. D.; Dougherty, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 4373–4379.
(17) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102–111. The gauche effect is not the reason that gauche bonds are preferred in the side chains of these macrocycles; however, gauche interactions of polar bonds noticably affect the relative ordering of otherwise similar conformers.

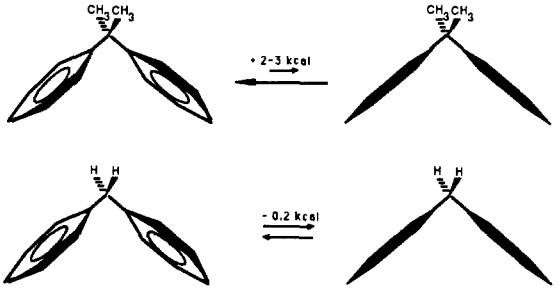

Figure 6. Comparison of C_{2v} and C_2 conformers of diphenylmethane and diphenylpropane.

Comparison of the Guests. It is obvious that lipophilicity does not alone determine the strength of the host–guest interaction. For both hosts, the most tightly bound benzenoid guest was *p*-toluenesulfonate anion. A similar result was observed by Koga, who also found that cationic hosts bind anionic guests strongly.[18] Among the neutral substrates, the two that bear electron-withdrawing groups were most tightly bound. For example, 4-cyanophenol was bound more tightly than 4-methylphenol or 2,4,6-trimethylphenol, despite the fact that the latter are more lipophilic and less water-soluble than 4-cyanophenol. This enhanced affinity for substrates bearing electron-withdrawing groups suggests two possibilities. First, an important energetic component of the docking interaction may be a charge-transfer or donor–acceptor interaction. Diederich has suggested the importance of such interactions in nonaqueous systems.[19] Second, it may reasonably be surmised that an electron-withdrawing group would enhance the edge–face interactions described by Burley and Petsko as an important intermolecular force between aromatic rings.[20] The stronger binding of 4-cyanophenol would then be a consequence of enhanced polar interactions between the protons of the electron-deficient aromatic guest and the π-electrons of the host. The data here do not allow a choice between these two possibilities, and the two explanations are not mutually exclusive.

Comparison of the Hosts. The two hosts differ only in the presence of the geminal methyl groups on the carbon connecting the two aryl rings. These methyl groups have a substantial effect on available conformations for the diaryl unit. Mislow has examined preferred conformations for diphenylmethanes and found that both force field and MINDO calculations predicted the C_{2v} or gable conformation of diphenylmethane to be preferred in comparison with the C_2 or propeller conformer.[21] In contrast, molecular mechanics calculations on 2,2-diphenylpropane indicate that the C_2 conformer is preferred by nearly 3 kcal/mol (Figure 6).

These considerations suggest that if the gable conformation of the diphenyl unit is required for formation of the complex, then host **2**, in which the diphenyl unit can easily take up a gable conformation, should differ detectably from host **1**, in which the diphenyl unit is probably more restricted to a propeller conformation.

As revealed in Table I, host **2** is, indeed, a consistently better receptor than host **1**. The differences, however, are quite small. It is likely that for most of these guests effective host conformations do not require that the diphenyl unit adopt a rigid gable conformation. Computer-aided modeling experiments indicate that there are several ways that the guests can approach the cavity and make contact with a concave surface of the host without requiring the diphenyl units to adopt a gable conformation. Because of this the differences in binding interactions involving the two hosts will not approach the magnitude of the conformational differences illustrated in Figure 6.

It should also be noted, however, that introduction of the two methyl groups can lead to changes in the average structure of the complex as well as changes in the free energies of association. Small changes in free energy of association do not necessarily correspond to small structural differences, and it is possible for the average structure of two complexes to be quite different while at the same time the free energies of association are nearly identical. Hammond's postulate has no place in this context.

The magnitude of the shifts induced by host **2** is always larger than shifts induced by host **1**, and this difference is greatest for the largest guest. This suggests that, in comparison with host **1**, host **2** forms complexes in which the time-averaged position of a given guest is deeper in the pocket (closer to the host aromatic rings). This interpretation is quite consistent with molecular modeling results. Comparison of Figure 4, parts a and b, reveals the effect that introduction of the geminal methyl groups has upon the shape of the host.

Conclusion

Dibenzodiazocines, diphenylpropane, and diphenylmethane are useful components for constructing water-soluble cyclophanes. This article compares the diphenylpropane and the diphenylmethane structural units. The diphenylmethane unit provided a host (**2**) with consistently better guest binding properties than the comparable host (**1**) derived from diphenylpropane. It can be concluded that the geminal dimethyl group in host **1** destabilizes the occupied host (and in particular, deeply bound complexes with that host) more than it destabilizes the unoccupied host. Molecular modeling results indicate that the diphenylmethane host (Figure 4a) is more open than the diphenylpropane-derived host (Figure 4b). The diphenylmethane-derived host will allow docking of the guest deeper in the cavity than a diphenylpropane host. Host-induced substrate chemical shift changes are consistent with this conclusion because the host bearing the geminal methyl groups forms complexes, which show smaller chemical shift changes than the host not having those methyl groups.

Although the differences in association energies for the two hosts with a given substrate are small (0.1–0.4 kcal/mol), it does not necessarily follow that the average structures of the two complexes are similar. While energetic differences of this magnitude may be relatively unimportant, struetural differences will be very important if these hosts are to be used as binding sites for the construction of selective organic catalysts.

Studies of molecular recognition in water are important sources of information relevant to biomolecular docking processes. The information obtained in this study can be used to test current theories of molecular association or to aid in the definition of parameters for empirical intermolecular and intramolecular force fields. Predictions of results presented here might serve as a challenging goal for theoreticians interested in quantitative determinations of solvent–solute and solute–solute interactions.

These studies were carried out in D_2O at pD 1.9. New hosts that may be soluble at physiological pH are desirable, and approaches to such hosts are being evaluated.

Experimental Section[22]

2,2-Bis[*p*-(2-bromoethoxy)phenyl]propane (6). To 30 mL of 50% ethanol in a round-bottomed flask was added 4.56 g (20.0 mmol) of bisphenol A (**5**) and 18.7 g (100 mmol) of 1,2-dibromoethane. The mixture was heated at reflux, and a solution of 3.70 g (66.0 mmol) of KOH in 50% ethanol was added dropwise over 3 h. The reaction mixture was concentrated in vacuo to about half the original volume, and the residue was poured into 75 mL of CH_2Cl_2, washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a colorless oil. The oil was purified by flash chromatography (40 × 160 mm column of silica gel, CH_2Cl_2) to give a colorless oil, which crystallized upon standing and was recrystallized from absolute ethanol to give 2.83 g (32%) of **6** as colorless prisms: mp 92–94 °C; R_f 0.21 (SiO_2, CH_2Cl_2); IR ($CHCl_3$) 3020, 3005, 2960, 1605, 1510, 1440, 1200, 1015 cm^{-1}; 360-MHz ^1H NMR ($CDCl_3$) δ 7.14 (dd, 2 H, J = 8.6, 2.2 Hz), 6.81 (dd, 2 H, J = 8.6,

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2.2 Hz), 4.26 (t, 2 H, J = 6.1 Hz), 3.62 (t, 2 H, J = 6.1 Hz), 1.63 (s, 3 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ 131.9, 123.5, 112.3, 103.0, 70.8, 52.5, 45.7, 45.0. Anal. Calcd for $C_{19}H_{22}O_2Br_2$: C, 51.61; H, 5.01. Found: C, 51.75; H, 5.09.

Bis[*p*-(2-bromoethoxy)phenyl]methane (8). To 300 mg (1.5 mmol) of bis(4-hydroxyphenyl)methane (**7**) in 15 mL of CH_2Cl_2 was added 3.9 mL (5.9 mmol) of 40% tetrabutylammonium hydroxide, 15 mL of 0.56 N NaOH solution, and 3.9 mL (45.2 mmol) of 1,2-dibromoethane. The mixture was vigorously stirred at room temperature for 24 h. The organic layer was separated, and the aqueous layer was extracted with 50 mL of CH_2Cl_2. The combined organic layers were washed with 100 mL of 1 N NaOH and 100 mL of H_2O, and dried over $MgSO_4$. Removal of the volatile components under reduced pressure afforded a white solid/oil mixture, and chromatography (SiO_2, 30% SkB–CH_2Cl_2) afforded 248 mg (40%) of **8** as a white crystalline solid: R_f 0.63 (SiO_2, 30% hexane–CH_2Cl_2); mp 82–83 °C; IR (CH_2Cl_2) 3020, 2932, 1751, 1610, 1509, 1242, 1018, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 4 H, J = 7.7 Hz), 6.81 (d, 4 H, J = 7.7 Hz), 4.32 (t, 4 H, J = 5.7 Hz), 3.85 (s, 2 H), 3.59 (t, 4 H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 156.5, 134.4, 129.8, 114.9, 68.0, 40.1, 29.0; MS, m/e calcd for $C_{17}H_{18}O_2Br_2$ 411.96735, measured 411.96677. Anal. Calcd for $C_{17}H_{18}O_2Br_2$: C, 49.29; H, 4.34. Found: C, 49.20; H, 4.35.

26,26-Dimethyl-16,36-bis(*p*-tolylsulfonyl)-6*H*,12*H*-2,8-(ethaniminoethanoxy[1,4]benzenomethano[1,4]benzenoxyethaniminoethano)-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (9). To a vigorously stirred suspension of 1.1 g (3.4 mmol) of Cs_2CO_3 in 10 mL of DMF at 98 °C was added a mixture of 336 mg (0.546 mmol) of disulfonamide **4** and 241 mg (0.546 mmol) of dibromide **6** in 10 mL of DMF at 0.96 mL/h via syringe pump. After the entire solution had been added, the reaction mixture was stirred for an additional 3 h at 98 °C, cooled to room temperature, poured into 150 mL of CH_2Cl_2, and washed with 100 mL of water. The organic phase was washed with water (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a clear tan oil, which was purified by flash chromatography (20 × 200 mm column of SiO_2, 20% CH_3CN–CH_2Cl_2) to give 252 mg (52%) of **9** as a colorless syrup: R_f 0.29 (SiO_2, 20% CH_3CN–CH_2Cl_2); IR ($CHCl_3$) 2960, 2940, 1750, 1505, 1495, 1330, 1160, 1090 cm^{-1}; 360-MHz ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2 H, J = 8.3 Hz), 7.27 (d, 2 H, J = 8.3 Hz), 7.01 (d, 2 H, J = 8.6 Hz), 6.96 (d, 1 H, J = 7.9 Hz), 6.85 (dd, 1 H, J = 7.9, 1.8 Hz), 6.67 (d, 1 H, J = 1.8 Hz), 6.59 (d, 1 H, J = 8.6 Hz), 4.60 (d, 1 H, J = 15.8 Hz), 4.23 (s, 1 H), 4.04 (br s, 2 H), 4.02 (d, 1 H, J = 15.8 Hz), 3.61 (m, 2 H), 3.33 (m, 2 H), 2.73 (m, 2 H), 2.41 (s, 3 H), 1.63 (s, 3 H), 1.58 (s, 3 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ 156.0, 146.5, 143.7, 143.2, 137.3, 134.1, 129.6, 127.7, 127.1, 125.0, 114.0, 67.5, 67.1, 58.7, 50.5, 47.6, 41.6, 34.9, 30.6, 21.4.

16,36-Bis(*p*-tolylsulfonyl)-6*H*,12*H*-2,8-ethaniminoethanoxy[1,4]benzenomethano[1,4]benzenoxyethaniminoethano)-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (10). To a vigorously stirred suspension of 1.08 g (3.3 mmol) of Cs_2CO_3 in 20 mL of dry DMF under nitrogen at 80 °C was added a mixture of 431 mg (0.69 mmol) of **4** and 287 mg (0.69 mmol) of dibromide **8** in 20 mL of dry DMF over a period of 6 h via syringe pump. Heating was continued for another 1.5 h and then cooled to room temperature. The DMF was vacuum distilled off, leaving a brown residue. To the residue was added 45 mL of H_2O, and the mixture was stirred for 12 h. The solid was filtered and placed under pump vacuum. The resulting white solid was purified by flash chromatography (SiO_2, 15% diethyl ether–CH_2Cl_2) to give 266 mg (43%) of **10**, a light yellow foam, which crystallized as a white solid upon heating with alcohol: R_f 0.20 (SiO_2, 15% diethyl ether–CH_2Cl_2); mp 230–235 °C dec; IR ($CHCl_3$) 3024, 2931, 1736, 1602, 1492, 1340, 1225, 1113, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 4 H, J = 7.8 Hz), 7.27 (d, 4 H, J = 7.8 Hz), 6.97 (d, 4 H, J = 8.4 Hz), 6.94 (d, 2 H, J = 8.4 Hz), 6.84 (d, 2 H, J = 8.4 Hz), 6.64 (s, 2 H), 6.61 (d, 4 H, J = 8.4 Hz), 4.57 (d, 2 H, J = 16.8 Hz), 4.15 (s, 2 H), 4.03–3.96 (m, 6 H), 3.78 (s, 2 H), 3.60 (t, 4 H, J = 3.9 Hz), 3.29 (t, 4 H, J = 8.2 Hz), 2.70 (t, 4 H, J = 8.2 Hz), 2.40 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 156.5, 146.6, 146.5, 143.2, 137.3, 134.6, 134.0, 129.6, 127.8, 127.7, 127.1, 127.0, 125.0, 114.6, 67.4, 66.9, 58.6, 50.4, 47.6, 40.3, 35.0, 21.4; MS, m/e calcd for $C_{50}H_{52}N_4S_2O_6$ 868.33282, measured 868.33472. Anal. Calcd for $C_{50}H_{52}N_4S_2O_6$: C, 69.09; H, 6.03; N, 6.45. Found: C, 68.84; H, 6.08; N, 6.37.

***N*,*N*'-6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diyldi-2,1-ethanediylbis(phenylmethyl)bis[4-methylbenzenesulfonamide] (11).** To a suspension of 1.17 g (3.60 mmol) of Cs_2CO_3 in 20 mL of DMF was added 370 mg (0.60 mmol) of disulfonamide **4** and 167 mg (1.32 mmol) of benzyl chloride. The mixture was heated with stirring at 80 °C for 2 h, cooled, and then poured into 150 mL of rapidly stirred water containing 3 g of Celite. The suspension was filtered, and the solid filter cake washed with 100 mL of CH_2Cl_2. The organic phase was washed with 100 mL of water and dried ($MgSO_4$), and the solvent was removed to give a colorless oil that was purified by flash chromatography (40 × 180 mm column of silica gel, 20% EtOAc–CH_2Cl_2) to give 322 mg (40%) of **11** as a colorless oil: R_f 0.23 (SiO_2, 20% EtOAc–CH_2Cl_2); IR ($CHCl_3$) 2960, 2940, 1700, 1600, 1500, 1420, 1340, 1240, 1160, 1095 cm^{-1}; 360-MHz ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2 H, J = 7.9 Hz), 7.27 (d, 2 H, J = 7.9 Hz), 7.17–7.24 (m, 5 H), 6.94 (d, 1 H, J = 8.3 Hz), 6.72 (dd, 1 H, J = 8.3, 1.4), 6.41 (d, 1 H, J = 1.4 Hz), 4.53 (d, 1 H, J = 16.6 Hz), 4.24 (d, 2 H, J = 4.2 Hz), 4.2 (s, 1 H), 3.97 (d, 2 H, J = 16.6 Hz), 3.15 (m, 2 H), 2.46 (t, 2 H, J = 7.9), 2.41 (s, 3 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ 186.8, 146.5, 143.2, 137.2, 136.3, 134.1, 129.6, 128.5, 128.4, 127.7, 127.6, 127.1, 126.9, 125.0, 66.9, 58.5, 52.3, 49.4, 34.7, 21.4.

***N*,*N*',6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine-2,8-diyldi-2,1-ethanediylbis[phenylmethane] (12).** To a solution of 240 mg (0.302 mmol) of disulfonamide **11** in 0.5 mL of 1,2-dimethoxyethane at 0 °C was added 12.1 mL (1.208 mmol) of a freshly prepared 0.1 M solution of sodium anthracene in 1,2-dimethoxyethane. After 2 min at 0 °C, the reaction was poured into 25 mL of 0.25 M NaH_2PO_4 and 100 mL of water and washed with 100 mL of ether. The aqueous phase was diluted with an equal volume of water, basified with 20 mL of 2 N NaOH, and extracted with 4 × 25 mL of chloroform. The combined organic phase was washed with 100 mL of water containing 1 mL of 2 N NaOH, dried (Na_2SO_4), and concentrated in vacuo to give 48 mg of a tan oil, which was purified by flash chromatography (20 × 180 mm column of silica gel, 80% EtOH–10% H_2O–10% Et_3N) to give 41 mg (28%) of **12** as a thick colorless oil: R_f 0.64 (SiO_2, 80% EtOH–10% H_2O–10% Et_3N); IR ($CHCl_3$) 3200–3400, 2960, 1600, 1500, 1245, 1210 cm^{-1}; 360-MHz ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1 H, J = 8.3 Hz), 7.44–7.31 (m, 6 H), 7.09 (s, 1 H), 5.05 (s, 1 H), 5.02 (d, 1 H, J = 16.6 Hz), 4.55 (d, 1 H, J = 16.6 Hz), 4.16 (d, 1 H, J = 13.0 Hz), 4.11 (d, 1 H, J = 13.0 Hz), 3.21 (t, 2 H, J = 7.9), 2.97 (t, 2 H, J = 7.9 Hz); 90-MHz ^{13}C NMR (the dihydrochloride salt in D_2O) δ 137.7, 137.1, 130.3, 129.6, 129.2, 127.8, 124.5, 67.2, 56.9, 50.8, 47.0, 30.8. A portion of the free amine was converted to the salt by treatment with excess aqueous HCl and subsequent lyophilization to give the trihydrochloride salt of **12**. Anal. Calcd for $C_{33}H_{38}Cl_3N_4 \cdot 1.75H_2O$: C, 63.05; H, 6.65; N, 8.91. Found: C, 63.07; H, 6.68; N, 8.62.

26,26-Dimethyl-6*H*,12*H*-2,8-(ethaniminoethanoxy[1,4]benzenomethano[1,4]benzenoxyethaniminoethano)-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (1). To a solution of 206 mg (0.229 mmol) of macrocycle **9** in 8 mL of 1,2-dimethoxyethane at 0 °C was added 9.2 mL (0.916 mmol) of a freshly prepared 0.1 M solution of sodium anthracenide in 1,2-dimethoxyethane. After 2 min at 0 °C, the deep blue solution was treated with 1 mL of saturated sodium chloride solution. The mixture was poured into 100 mL of 0.25 M NaH_2PO_4 and washed with ether (2 × 100 mL). The aqueous layer was diluted with an equal volume of saturated sodium chloride solution and basified with 10 mL of 2 N NaOH solution. This was extracted with $CHCl_3$ (5 × 30 mL), and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a viscous residual oil, which was purified by ion-exchange chromatography (5 × 55 mm of BioRex-70 gel, 0.5–1% NH_4Cl in 50% MeOH) to yield 77 mg (45%) of **1** as a colorless oil: R_f 0.67 (SiO_2, 80% EtOH–10% Et_3N–10% H_2O); IR ($CHCl_3$) 3100–3500, 3000, 2930, 1610, 1510, 1495, 1300, 1245, 1180 cm^{-1}; 360-MHz ^{1}H NMR ($CDCl_3$) δ 7.08 (d, 2 H, J = 9.0 Hz), 6.96 (d, 1 H, J = 7.9 J = Hz), 6.84 (dd, 1 H, J = 7.0, 1.8 Hz), 6.69 (d, 1 H, J = 1.8 Hz), 6.70 (d, 2 H, J = 9.0 Hz), 4.63 (d, 1 H, J = 16.6 Hz), 4.23 (s, 1 H), 4.09 (br s, 2 H), 4.07 (d, 1 H, J = 16.6 Hz), 2.88–3.05 (m, 2 H), 2.80–2.86 (m, 2 H), 2.62 (t, 2 H, J = 7.2 Hz), 1.67 (s, 3 H), 1.25 (s, 1 H); 90-MHz ^{13}C NMR ($CDCl_3$) δ 156.3, 146.4, 143.6, 135.4, 127.8, 127.6, 127.4, 126.8, 125.1, 114.6, 67.1, 66.9, 58.4, 49.5, 47.8, 41.5, 35.4, 30.4; MS, calcd for $C_{38}H_{44}N_4O_2$ 588.3464, found 588.3485. A sample of the free amine was converted to the dihydrochloride salt by treatment with 2 equiv of 0.0941 N aqueous HCl and subsequent lyophilization to give the dihydrochloride salt of **1** as a fluffy white foam, which did not noticably absorb water from the atmosphere. Anal. Calcd for $C_{38}H_{46}Cl_2N_4O_2 \cdot 2.5H_2O$: C, 64.58; H, 7.27; N, 7.93. Found: C, 64.73; H, 7.17; N, 7.93.

6*H*,12*H*-2,8-(Ethaniminoethanoxy[1,4]benzenomethano[1,4]benzenoxyethaniminoethano)-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (2). To a stirred solution of 200 mg (0.23 mmol) of **10** in 50 mL of dry THF under nitrogen at 0 °C was added over a period of 3 min 5 mL of a 0.43 M solution of sodium anthracene. The blue solution was allowed to stir at 0 °C for an additional 2 min and then quenched with 40 mL of 0.5 M H_2SO_4. The acidic aqueous mixture was washed with 3 × 50 mL of diethyl ether and then basified with concentrated ammonium hydroxide. The aqueous mixture was extracted with 3 × 80 mL of CH_2Cl_2. The combined organics were dried over Na_2CO_3 and filtered, and volatile components were removed under reduced pressure to give 57 mg of a yellow foam, which was purified by flash chromatography (SiO_2, 10% methanol–CH_2Cl_2) to give 30 mg (23%) of **2** as a light yellow foam: R_f 0.06 (SiO_2, 10% methanol–CH_2Cl_2); IR ($CHCl_3$) 2934, 2869, 1750, 1600, 1510, 1466, 1250, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.05 (d, 4 H, J

= 8.4 Hz), 6.92 (d, 2 H, J = 8.1 Hz), 6.8 (d, 2 H, J = 8.1 Hz), 6.73 (d, 4 H, J = 8.4 Hz), 6.67 (s, 2 H), 4.61 (d, 2 H, J = 16.8 Hz), 4.23 (s, 2 H), 4.08-4.00 (m, 6 H), 3.81 (s, 2 H), 3.05-2.90 (m, 4 H), 2.81 (t, 4 H, J = 6.0 Hz), 2.59 (t, 4 H, J = 6.7 Hz), 1.97 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.9, 146.3, 135.3, 134.6, 129.6, 127.7, 127.3, 126.7, 125.1, 115.2, 67.0, 66.9, 58.4, 49.4, 47.8, 40.4, 35.3; MS, m/e calcd for $C_{36}H_{40}N_4O_2$ 560.31513, measured 560.31306. A portion of the free amine was converted to the trihydrochloride salt by treatment with excess aqueous HCl and subsequent lyophilization to give the trihydrochloride salt of **2**. Anal. Calcd for $C_{36}H_{43}Cl_3N_4O_2 \cdot 3H_2O$: C, 59.71; H, 6.82; N, 7.74. Found: C, 59.32; H, 6.77; N, 7.40.

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Structural and Synthetic Studies of the Spore Germination Autoinhibitor Gloeosporone

Stuart L. Schreiber,* Sarah E. Kelly, John A. Porco, Jr., Tarek Sammakia, and Edward M. Suh

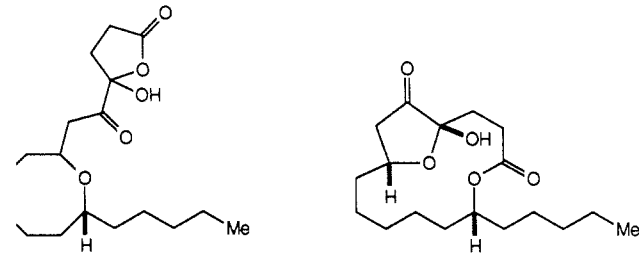
Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received February 26, 1988*

Abstract: Gloeosporone **1** is an autoinhibitor of spore germination that was recently isolated from conidia of *Colletotrichum gloeosporioides*. The structure initially proposed by Meyer et al. contained an unusual oxocane ring system (**1a**). A stereoselective synthesis of one of the two possible stereoisomeric forms of the oxocane structure that cast doubt on the structural proposal is described. Reinvestigation of the natural product resulted in the formulation of a structure that contains a 14-membered macrolide. Two syntheses of this compound are described which confirmed the new proposal and established the relative and absolute configuration of gloeosporone (**1b**). The asymmetric synthesis was achieved with use of an asymmetric reduction catalyst recently reported by Noyori et al. The reassignment of structure suggests that related macrolide natural products such as grahamimycin A_1 (**23**) and colletodiol (**24**) may exhibit similar spore germination inhibitory properties.

Germination regulatory agents have been identified from conidia of several species of fungi.[1] These compounds are autoinhibitors of spore germination and are believed to promote a favorable spatial distribution of the fungal species. Thus, many fungal spores will germinate efficiently only when their density is low. Self-inhibition to germination occurs under high-density conditions by a structurally specific spore response to the endogeneous autoinhibitors. These observations led to a proposed strategy for the development of fungistatic compounds.[2] The natural autoinhibitors or nonnatural analogues may be expected to mimic the conditions of crowding and result in inefficient spore germination.

In 1982, Lax et al. reported the isolation, biological activity,[3] and structure elucidation[4] of an autoinhibitor of spore germination from conidia of *Colletotrichum gloeosporioides*. The potency of this compound toward several *Colletotrichum* spp., including a pathogenic *Fusarium* species, and the novelty of the proposed structure **1a** are striking. The saturated eight-membered cyclic ether is rare in nature and unique among the known autoinhibitors of spore germination. Gloeosporone serves as a model compound for the development of species-specific fungistats and a biological probe molecule for investigations of the mechanism(s) of germination regulation.

The first report describing the spectroscopic properties of crystalline gloeosporone left a degree of uncertainty concerning the purported structure.[4] Our studies in this area were launched with (inter alia) the intention of clarifying the issue of structure. As will be described shortly, this research prompted a reinvestigation of the structure of gloeosporone, which, through an international effort, resulted in the reassignment of structure **1a** to the macrolide **1b**.[5] In the course of our research several issues that are relevant to the stereocontrolled synthesis of eight-membered ring ethers were probed and several syntheses of **1a** and **1b** were achieved.[6] Herein, we report on these findings.



1a 1b

Gloeosporone: The Oxocane. The original report concerning the oxocane structure of gloeosporone included the finding that a one-hydrogen resonance in the ^{1}H NMR spectrum appeared at δ 5.06.[4] This signal was assigned to the oxocane ring methine of the carbon bearing the pentyl side chain. Although more indicative of a methine bearing an acyloxy than alkoxy group, an anomalous deshielding effect could not be ruled out. Accordingly, a synthetic effort toward the oxocane **1a** was initiated.

The stereochemistry of **1a** was not addressed in the original report, and no data was presented that could distinguish between, for example, ring isomers (i.e., NOEDS). Our initial target was the cis isomer of **1a**, and our plan entailed the utilization of the stereoselective synthesis of cis oxocenes developed earlier in our laboratories in synthetic studies directed toward marine natural

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