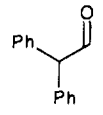
of the phenyl group on the ionization of 2-indanone. This effect must be due in large part to interactions in the enolate ion, inasmuch as the phenyl group is fairly well insulated from the carbonyl function in the ketone. Phenyl substituents are known to stabilize carbon–carbon double bonds, but the value assigned to this interaction, D = 4.9 kcal mol^{-1},[10] is much less than the substituent effect of 9.5 kcal mol^{-1} determined here. This suggests that there is an additional stabilizing effect in the present system produced by interaction of the phenyl and O^- groups through the enolate double bond. A similar interaction, weakened by noncoplanarity, might be expected to operate in the acid ionization of diphenylacetaldehyde, **6**, and comparison of the pK_a of that



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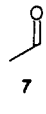

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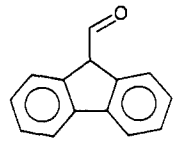

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substance (10.42)[11] with that of acetaldehyde, **7** (16.73),[12] gives $\delta\Delta G$ = 4.3 kcal mol^{-1} as the effect per phenyl group. It is interesting in this connection that comparison of 9-formylfluorene, **8** (pK_a = 6.2),[13] where coplanarity is forced upon the system, with acetaldehyde gives $\delta\Delta G$ = 14.4 kcal mol^{-1}: this is still short of twice the effect of the single ring in 2-indanone despite the fact that ionization of 9-formylfluorene generates a new aromatic ring.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We are grateful to Professors Ralph M. Pollack and Dale L. Whalen for communicating the results of their work to us prior to publication and for helpful discussions.

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Molecular Recognition in Aqueous Media: Donor–Acceptor and Ion–Dipole Interactions Produce Tight Binding for Highly Soluble Guests

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Molecular recognition studies in aqueous media[2a] using synthetic receptors of the cyclophane type[2-6] have revealed two major binding forces.[7] The first is a hydrophobic effect, in which relatively water-insoluble guests associate with a hydrophobic cavity of the host.[2,3] Guests that can fit into the host binding site show trends in association constants (K_a) which correlate well with the water insolubility of the guest. Quite large values for K_a can be obtained with highly insoluble guests.[2] The second factor, generally seen in combination with the first, is an electrostatic effect in which, for example, cationic, water-solubilizing groups on the host come into close contact with anionic substructures in the guest. Studies in several host systems have shown that such direct electrostatic interactions can be quite favorable.[2-4]

Table I. Binding Parameters for P and C with Guests 1–9

guest	solubility[a] (M)	host P $-\Delta G°$ [b]	host P K (M^{-1})	host C $-\Delta G°$ [b]	host C K (M^{-1})
1	0.078	5.4	10 000	5.9	22 000
2	0.023	5.5	11 000	5.8	20 000
3	0.014	6.2	38 000	6.0	30 000
4	0.037	6.3	47 000	6.3	46 000
5	0.030	6.4	55 000	6.7	100 000
6	0.016	4.2	1 400	4.3	1 600
7	0.0032	4.5	2 100	4.8	3 800
8	0.52	7.6	400 000	6.3	47 000
9	0.45	7.2	200 000	6.0	27 000

[a] Solubility of the guest determined in the operating buffer pD ≈ 9. [b] In kcal/mol at 295 K; values listed are accurate to ±200 cal/mol.

We demonstrate herein that donor/acceptor (D/A) π-stacking interactions[8,9] and ion–dipole attractions can also contribute significantly to aqueous binding.[9] Hosts P and C,[10] (Figure 1) were chosen as a pair with very similar binding site dimensions and comparable degrees of preorganization.[11] The rigid macrocyclic framework prevents the charged groups from achieving close contacts with encapsulated guest molecules. Certainly, any *differences* between P and C could not be ascribed to electrostatic effects. In fact, any such differences can confidently be ascribed to the different natures of the "linker" (⊗) group. If the hydrophobic effect is dominant, C should be the stronger binder, since cyclohexyl is generally considered to be more hydrophobic than phenyl.[2,4,12] On the other hand, P should be the better host

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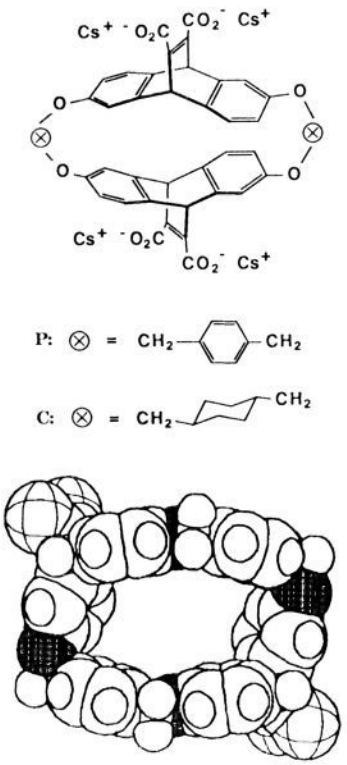
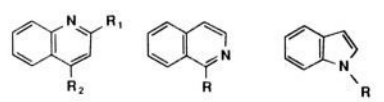


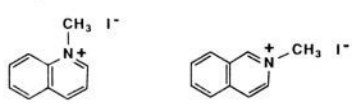
Figure 1. Top: (R,R,R,R) host structure. Enantiomerically pure hosts were used in all binding studies. Bottom: space-filling representation of the rhomboid conformation of P. Oxygen atoms in the macrocyclic ring are shaded; the carboxylates are represented as hatched spheres for clarity.

if specific aromatic ring effects are important. Note that by varying host structure one can factor out guest solubility effects.

Modeling studies suggested the hosts can adopt a C_2, rhomboid shape (Figure 1).[13] This produces a cavity well-suited for π-stacking with guests comparable in size to a naphthalene. Distinctive and characteristic NMR shift patterns in both hosts and guests (**1**–**9**) provide compelling evidence for this arrangement.



1: R1 = R2 = H **4:** R = H **6:** R = H
2: R1 = CH3; R2 = H **5:** R = CH3 **7:** R = CH3
3: R1 = H; R2 = CH3



8 **9**

Importantly, these NMR shift studies clearly indicate that both P and C bind all guests in the same conformation. In the rhomboid conformation, one of the two rings of each ethenoanthracene unit and both rings of the "linker" can stack with the guest.

Table I summarizes binding studies on a series of quite water-soluble guests.[16] Hosts P and C are constructed from electron-rich π systems and should preferentially bind electron-deficient π systems if D/A interactions are important. Indeed both P and C bind the electron-deficieint[17] quinoline and isoquinoline systems (**1**–**5**) more tightly than the electron-rich[17] indole systems (**6** and **7**), even though the indoles are the significantly less soluble compounds (Table I). Modeling studies and the various "methylation" studies (**1** versus **2** or **3**, etc.) clearly show that this is not a consequence of steric fit. The effect is substantial, being worth ca. 1.5 kcal/mol in $\Delta G°_{295}$. The especially electron-rich oxygen-substituted rings of the ethenoanthracenes apparently dominate the D/A effects, and so differences between P and C are small.[18]

Alkylation at N to produce quinolinium (**8**) and isoquinolinium (**9**) should further enhance D/A interactions. Methylation also greatly increases the water solubility of the guests, and so the relative constancy of $\Delta G°_{295}$ for C in the **1**/**8** and **4**/**9** pairs in fact indicates a substantial enhancement in attractive host/guest interactions for the cationic guests.[19]

Host P binds the charged guests (**8** and **9**) much more strongly than C. The K_a values obtained are remarkably large for such freely water-soluble guests. Studies with "isostructural" guest pairs (**8**/**3**, **8**/**5**, and **9**/**2**) show that the effect is due to the charge, not to steric or hydrophobic effects. The enhanced binding could be a consequence of D/A effects in the linker, which become more pronounced with the more electron-deficient guests. However, previous work[14] and more recent studies[15] demonstrate that P has a general, strong affinity for quaternary ammonium compounds, even fully aliphatic ones. Thus, we interpret the enhanced binding of **8** and **9** as indicative of the polarization of the host P in response to the positive charge of the guest.[20] Such ion–dipole effects are apparently important in stabilizing the secondary structure of proteins, in that there is a strong tendency for positively charged amino acid side chains (Lys, Arg, Asn,and Gln) to position the positive charge directly over the face of an aromatic residue (Phe, Tyr, and Trp).[21]

We believe this study provides the most clear-cut evidence to date for the operation of substantial host/guest D/A interactions in an aqueous environment. We also propose that with a highly polarizable host such as P, ion–dipole attractions[21] can contribute substantially to the binding. With proper electronic matching of

(13) Both CPK models and molecular mechanics calculations indicate that both the rhomboid conformation and the previously described[14] toroidal form are feasible and apparently close in energy. We have no evidence concerning which form is preferred in the absence of guest. Further discussion will be presented elsewhere.[15]

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(16) All binding studies were performed in a 10 mM cesium borate buffer at pD ≈ 9. Typically, [Host] = 25–250 μM (always below the CMC) and [Guest] = 150–1000 μM. Control experiments with 2,6-diethoxy-9,10-dihydro-9,10-(1,2-dicarboxy)ethenoanthracene dicesium salt[10] showed no significant complexation with these guests. Binding constants were calculated by using a newly developed nonlinear least-squares, Levenberg–Marquardt procedure[15] (MULTIFIT) in which K_a was simultaneously fit to the chemical shift changes for *all* the observable protons of the guest. It can be shown[15] that this approach gives the best (in a least-squares sense) binding constant for a given data set. Of course, when fitted individually all protons should yield the same value for K_a. In practice, this is generally the case (within reasonable error bars), but occasionally an individual fit deviates significantly from the others. The MULTIFIT approach is superior to a simple averaging of individual fits for treating such cases.

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host and guest, even quite water-soluble guests can experience strong "hydrophobic" binding.

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Total Synthesis of Glycinoeclepin A

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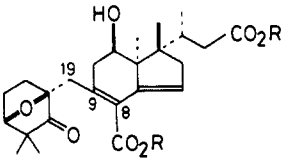
Our recent isolation[1] and structural elucidation[2] of glycinoeclepin A has revealed that this compound possesses an unusual molecular structure (**1**) and shows significant hatch-stimulating activity for the soybean cyst nematode. These characteristics, combined with the lack of a satisfactory natural source, render the title compound an attractive and challenging synthetic target. We describe herein the first total synthesis of **1**.

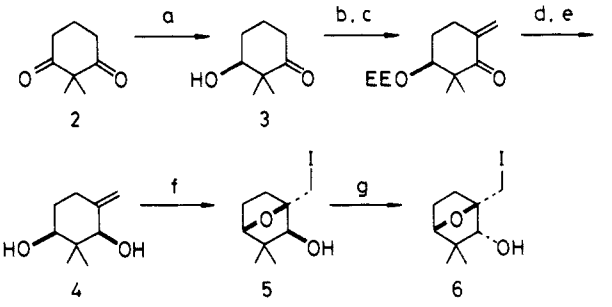


1. R=H
1a. R=CH_2CO-p-C_6H_4Br

The chiral synthesis of the A-ring of **1** started with enzymatic reduction of 2,2-dimethylcyclohexane-1,3-dione (**2**), which was performed with Baker's yeast, giving (*S*)-2,2-dimethyl-3-hydroxycyclohexan-1-one (**3**)[3] (Scheme I). The keto alcohol **3** (94.3% ee) was converted into an olefinic *cis*-glycol **4** in a five-step process involving formation of an α,β-unsaturated ketone,[4] followed by stereoselective reduction. The compound **4**, when treated with *N*-iodosuccinimide in acetonitrile (MeCN) in the dark, underwent smooth halocyclization to yield (1*R*,2*S*,4*S*)-1-iodomethyl-3,3-dimethyl-7-oxabicyclo[2.2.1]heptan-2-ol (**5**), which on simple recrystallization gave an *optically pure* sample, mp 99–101 °C (100% ee). Jones oxidation and hydride reduction of the pure alcohol (**5**) afforded exclusively the isomeric (2*R*)-alcohol **6**, mp 80–81 °C.

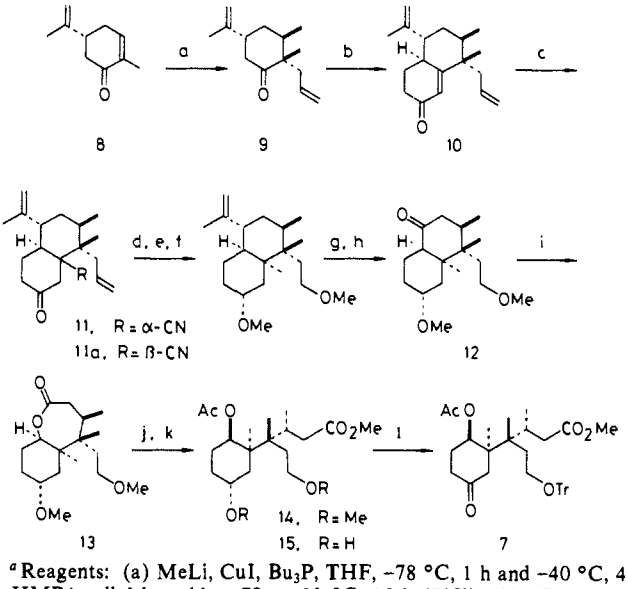
The synthesis of another fragment **7**, corresponding to the C and D ring moiety of **1**, started with (*R*)-(−)-carvone (**8**) and involved stereoselective construction of four successive chiral centers as the key steps (Scheme II). Nucleophilic/electrophilic carba-condensation[5] of **8** proceeded smoothly with high stereoselectivity, giving a dialkylated compound **9**, which underwent annelation[6] to yield an α,β-unsaturated octalone **10**, mp 53–55 °C. Hydrocyanation of **10** under kinetic conditions[7] effected predominant formation (63%) of the desired *cis*-cyano ketone **11**,

Scheme I[a]



[a] Reagents: (a) Baker's yeast, D-glucose, KH_2PO_4, $MgSO_4$, DMF–H_2O (1:38), 24 °C (67%); (b) $EtOCH{=}CH_2$, PPTS (97%); (c) DMF–dimethyl acetal, 110 °C, 2 days; DIBAH (63%); (d) $NaBH(OMe)_3$ (87%); (e) HCl (99%); (f) NIS, MeCN, 20 °C, 16 h (79%); (g) Jones oxidation; $NaBH_4$ (92%).

Scheme II[a]



[a] Reagents: (a) MeLi, CuI, Bu_3P, THF, −78 °C, 1 h and −40 °C, 4 h; HMPA, allyl bromide, −78 → 23 °C, 15 h (78%); (b) LDA, Me-COC(TMS)$=CH_2$; NaOMe (74%); (c) HCN, Et_3Al, THF, 23 °C, 30 h; (d) OsO_4, NMO (80%); (e) $NaIO_4$; $NaBH_4$; MeI, NaH (61%); (f) DIBAH; $NH_2NH_2{\cdot}H_2O$, $NH_2NH_2{\cdot}2HCl$, triethylene glycol, 120 °C, 3.5 h; KOH, 200 °C, 6.5 h (82%); (g) O_3; Me_2S; CF_3CO_3H (55%); (h) $LiAlH_4$; Jones oxidation (93%); (i) CF_3CO_3H (72%); (j) KOH; CH_2N_2; Ac_2O, DMAP, Et_3N (57%); (k) $AlCl_3$, NaI, MeCN, 0 → 20 °C, 6 h; CH_2N_2 (85%); (l) TrCl, DMAP, Et_3N; PDC (91%).

mp 180–182 °C, accompanied by its trans isomer **11a**, mp 148–149 °C (30%).[8] The configuration of these ketones was confirmed by the X-ray crystallographic analysis of **11**,[9] indicating that stereoselective introduction of the four asymmetric centers has been completed as anticipated. The compound **11** was transformed by a usual several-step sequence into decalone **12**, which was oxidized with peroxytrifluoroacetic acid into ϵ-caprolactone **13** and then submitted to ring opening in a three-step process to give methoxycarbonyl acetate **14**. Cleavage of the two methoxyl groups of **14** was effected according to the Fuji procedure[10] to yield triol monoacetate **15**, which on tritylation and oxidation[11] afforded acetoxycyclohexanone trityl ether **7**.

The next phase of synthesis was the combination of the two fragments **6** and **7**, one of the most critical steps of the synthesis.

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(8) Treatment of compound **11a** with *t*-BuOK (1.5 equiv) in *t*-BuOH under reflux for 1.5 h led to recovery of **10** in 81% yield.

(9) The intensity measurements were performed by Dr. A. Furusaki, Hokkaido University, at the High Brilliance X-ray Laboratory of Hokkaido University.

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