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Solvent Effects on the Binding Equilibria between the Guests Indole and Catechol and the Host Cyclobis(paraquat-*p*-phenylene)

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Introduction

Originally synthesized by Stoddart and co-workers,[1] the redox-active host cyclobis(paraquat-*p*-phenylene) (**1**$^{4+}$) has gained a prominent position in supramolecular chemistry as a fundamental component in a large number of rotaxanes and catenanes.[2] When combined with a variety of π-donor guests, this cyclophane host forms stable inclusion complexes characterized by well-defined charge-transfer absorption bands in the visible region.[3] Although the development of charge transfer interactions between the host's π-acceptor bipyridinium groups and the included π-donor guest is expected to contribute to the overall stability of the inclusion complex, charge transfer does not seem to be the predominant factor controlling the overall binding affinity between the host and a given guest. This is clearly evidenced by the fact that the binding constant between host **1**$^{4+}$ and the guests tetrathiafulvalene,[4] *p*-phenylenediamine,[3] and benzidine[5] increases with their oxidation potential, i.e., as their π-donor character decreases. It is indeed well-known that $\pi-\pi$ stacking forces cannot be understood only in terms of charge transfer or electron donor−acceptor interactions.[6] Therefore, we are currently performing detailed computational studies to better define all the factors that determine the stability of the complexes formed between this host and electron-rich aromatic guests.[7]

Most of the binding constants involving host **1**$^{4+}$ have been measured in acetonitrile solution. In this solvent, simple aromatic guests[8] are bound with *K* values typically below 200 M^{-1}. As the only exception to this trend, benzidine exhibits a larger binding constant of 1 040 M^{-1}, a fact which has been useful in the design of molecular devices based on the rotaxane framework.[9] Our group has measured several binding constants between **1**$^{4+}$ and electron-rich aromatic guests in aqueous media,[10] and the values were found to be substantially larger than related values measured in acetonitrile. These findings may reflect the importance of solvation effects on the host−guest binding equilibria, as reported by Diederich and co-workers for structurally different cyclophane hosts.[11] Therefore, we decided to investigate in detail the effect of solvent nature on the binding of electron-rich aromatic guests to host **1**$^{4+}$ (see Scheme 1). Due to their favorable solubility in the solvents surveyed, we selected indole and catechol as the guests of choice to carry out this investigation.

Scheme 1. Binding Equilibrium between Host 1^{4+} and Indole

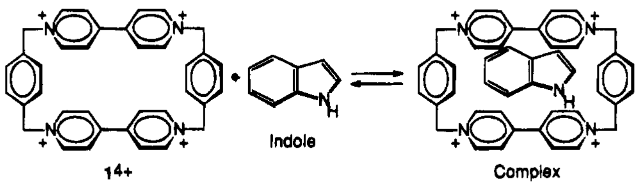

Table 1. Binding Constants and Spectroscopic Data for the Complexes of Host 1^{4+} and the Guests Indole and Catechol Measured in Several Solvents at 25 °C

	indole			catechol		
solvent (ϵ)	*K* (M^{-1})	$\Delta\epsilon$ (M^{-1} cm^{-1})	λ_{max} (nm)	*K* (M^{-1})	$\Delta\epsilon$ (M^{-1} cm^{-1})	λ_{max} (nm)
acetone (20.7)	100	903	460	68	845	460
nitromethane (35.9)	190	973	472	*b*	*b*	*b*
acetonitrile (37.5)	150	1028	460	130	891	446
DMSO (46.7)	110	943	446	110	803	438
formamide (111)	420	865	468	420	722	458
water[a] (80.2)	10 600	682	464	5900	872	446

[a] Also containing 0.1 M phosphate buffer (pH = 7). [b] Not measured.

Results

The selection of solvents for this work is limited by the tetracationic nature of the host which decreases its solubility in highly nonpolar solvents to exceedingly low levels. However, the hexafluorophosphate form of the ligand is sufficiently soluble in acetone while the tetrachloride salt is very soluble in water. It was thus possible to cover a wide range of solvent polarities, from acetone (dielectric constant, ϵ = 20.7), in the low polarity end, to water (ϵ = 80.2) or formamide (ϵ = 111), in the high polarity end. Our experimental results are summarized in Table 1.

Several trends are revealed upon inspection of the experimental data. First, the stability of either the indole or the catechol complexes generally tends to increase as

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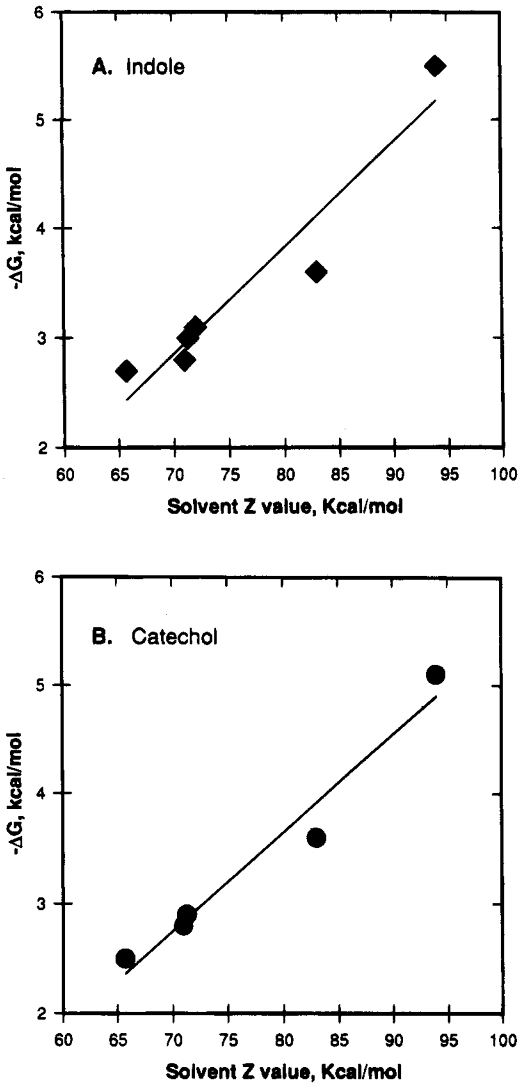

Figure 1. Dependence of the free energy of complex formation at 25 °C on the polarity of the solvent as measured by its *Z*-value. (A) Indole complexes of host $\mathbf{1}^{4+}$. (B) Catechol complexes of host $\mathbf{1}^{4+}$.

the solvent polarity increases. Thus, the largest binding constants measured correspond to the two most polar solvents, formamide and water, while the lowest values are those determined in acetone. However, the binding constants do not correlate directly with the dielectric constants as demonstrated by the *K* values measured in solvents of intermediate polarity (nitromethane, acetonitrile, and DMSO). The magnitude of the solvent effect is strikingly large; for instance, the indole complex of $\mathbf{1}^{4+}$ exhibits a binding constant 100-fold greater in aqueous media than in acetone. A second trend revealed by the data is that the indole complex is at least equally or more stable than the catechol complex in all solvents surveyed in this work. Since catechol has a lower oxidation potential than indole,[12] our data clearly indicate that the best π-donor is not necessarily the best substrate for binding to host $\mathbf{1}^{4+}$, suggesting the limited importance of charge transfer interactions in the overall stability of the inclusion complex. The binding selectivity of the host for indole *vs* catechol can be understood by considering the larger aromatic surface of indole, which probably hinders its solvation in most of the solvents surveyed, therefore rendering its complexes relatively more stable than those of catechol.

The lack of a direct correlation between the stability of the inclusion complexes investigated in this work and the solvent's dielectric constant is not surprising as it is well documented that the dielectric constant is a poor measure of solvent polarity, especially when a large polarity range is covered. Nonetheless, the stability of the indole and catechol complexes of host $\mathbf{1}^{4+}$ correlates satisfactorily with other empirical parameters reflecting solvent polarity, such as *Z*-values. Introduced by Kosower in 1958,[13] the *Z*-values constitute a spectroscopic measurement of solvent polarity which takes advantage of the solvatochromism of the intermolecular charge transfer band observed in solutions of 1-ethyl-4-(methoxycarbonyl)pyridinium iodide. The *Z*-value in a particular solvent is calculated as the transition energy (in kcal/mol) at the wavelength of maximum absorption for the charge transfer band of a solution of this salt in the solvent of choice. The calculated *Z*-value increases with increasing stabilization by solvent molecules to the ground state of the absorbing ion pair between the 1-ethyl-4-(methoxycarbonyl)pyridinium cation and the iodide anion. Therefore, *Z*-values increase with solvent polarity. Figure 1A shows a plot of the free energy of complexation ($\Delta G = -RT \ln K$) for the indole complexes of $\mathbf{1}^{4+}$ as a function of the solvent's *Z*-value. A similar linear free energy plot for the catechol complexes is shown in Figure 1B. In both cases the observed plots are linear, with correlation coefficients of 0.9166 and 0.9632 for indole and catechol, respectively. Our free energies of complexation exhibit similarly good correlations against related parameters of solvent polarity, such as $E_T(30)$ values[14] (data not shown).

Diederich and co-workers also observed a very good correlation between stability of the inclusion complexes formed by structurally different cyclophanes and solvent's $E_T(30)$ values.[11a] They concluded that complex stability increases with solvent polarity because polar solvents exhibit large cohesive forces and low molecular polarizabilities. The complexation processes surveyed here (see Scheme 1) are associated with a large decrease in the aromatic surface exposed to solvent molecules and, therefore, our experimental findings are perfectly consistent with Diederich's arguments.

We also determined the binding constants for the catechol and indole complexes of $\mathbf{1}^{4+}$ in aqueous media (0.1 M pH = 7 phosphate buffer) containing 8 M urea. This large concentration of urea causes the effective denaturing (unfolding) of globular proteins.[15] Recent computational[16] and experimental evidence[17] strongly suggest that urea molecules interact specifically with aromatic surfaces. This is believed to be an important factor in its protein denaturing action. In excellent agreement with this hypothesis, we determined *K* values of 2500 and 430 M^{-1} for the complexes of $\mathbf{1}^{4+}$ with indole

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[12] The voltammetric oxidations of both indole and catechol in acetonitrile solution are irreversible but their oxidation peak potentials are +1.4 and +0.55 V vs SCE, respectively.

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Table 2. Effects of 8 M Urea on the Stability of Inclusion Complexes in Aqueous Media at 25 °C

			K (M^{-1})		
host	guest	medium	[urea] = 0 M	[urea] = 8 M	ΔK (%)
1^{4+}	indole	*a*	10 600	2500	−76
1^{4+}	catechol	*a*	5900	430	−93
β-CD	BNS[c]	*b*	38 000	16 000	−58

[a] 0.1 M phosphate buffer (pH = 7). [b] Pure H_2O, see ref 17b. [c] 6-(4-*tert*-Butylanilino)naphthalene-2-sulfonate sodium salt.

and catechol, respectively, in 8 M urea/0.1 M phosphate buffer (pH = 7). These binding constant values are much lower than those obtained in the absence of urea (see Table 2). For comparison, Breslow and co-workers measured a similar urea-driven effect on the stability of a β-cyclodextrin complex.[17b] However, the relative decrease in the binding constant induced by the presence of 8 M urea was smaller in their case, a result which might be associated with the nonaromatic nature of the cyclodextrin receptor. This quantitative difference is consistent with the improved solvation for aromatic surfaces which is proposed to result from the presence of large concentrations of urea in the medium.

Conclusions

The binding constants between the host 1^{4+} and the guests indole and catechol exhibit a strong solvent dependence. Both binding constants increase with increasing solvent polarity. With both guests, the measured free energy of complexation correlates linearly with the solvent's Z-value (as a quantitative measure of solvent polarity). Both binding constants undergo a substantial decrease in the presence of 8 M urea compared to the values measured in urea-free aqueous media.

Experimental Section

Host 1^{4+} was synthesized as the tetrakis(hexafluorophosphate) salt according to published procedures.[2a] The hexafluorophosphate form of the host was used in all solvents surveyed but water. The tetrachloride salt was prepared by counterion exchange for use in aqueous media. Indole and catechol were purchased from Aldrich and used without further purification. Acetone (Analytical Reagent) was purchased from Mallinckrodt, acetonitrile (GC quality) was from EM Science, dimethyl sulfoxide (99.9%, HPLC grade), nitromethane (95+%, ACS reagent), and formamide (99+%, spectrophotometric grade) were supplied by Aldrich. Deionized water was further purified by passage through a pressurized Barnstead Nanopure system. All other reagents were of the best quality commercially available. The binding constants were measured by monitoring the development of the complex charge transfer absorption band using a Shimadzu UV-vis spectrophotometer and methods already described in detail.[2d] The binding constants and molar absorptivities determined from our experiments are affected by error margins typically lower than +10%.

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