at R_f 0.25 was the desired product contaminated with *N*-methylmaleimide. An analytical sample was obtained by HPLC (1:9 EtOAc/hexane). The first band to elute was the desired product: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, J = 7 Hz, 3 H), 1.30–1.81 (m, 4 H), 2.53 (m, 1 H), 2.93 (s, 3 H), 3.18 (dd, J = 8.5, 6 Hz, 1 H), 3.65 (d, J = 8.5 Hz, 1 H), 5.20 (s, 1 H), 5.45 (s, 1 H), 5.83 (dd, J = 10, 4 Hz, 1 H), 6.20 (dd, J = 10, 2 Hz, 1 H); IR (CCl_4) 2980, 2950, 2890, 1795, 1730, 1455, 1405, 1305, 1130, 1040, 990 cm^{-1}; MS, M$^+$ 219.1259, calcd for $C_{13}H_{17}NO_2$ 219.1255.

N-Methyl-6-ethylidene-3-propyl-4-cyclohexene-1,2-dicarboximide: (*E*)-(1α,2α,3α) isomer: ^{1}H NMR (C_6D_6, 500 MHz) δ 0.87 (t, J = 7.2 Hz, 3 H), 1.28 (m, 2 H), 1.52 (dd, J = 7.2, 1.0 Hz, 3 H) 1.63 (dtd, J = 13, 9, 6 Hz, 1 H), 1.88 (ddt, J = 13, 9.5, 7 Hz, 1 H), 2.09 (tdd, J = 9, 6.5, 3.5 Hz, 1 H), 2.44 (dd, J = 8, 6 Hz, 1 H), 2.61 (s, 3 H), 3.01 (dt, J = 8.5, 1.5 Hz, 1 H), 5.58 (ddd, J = 10, 3.5, 1.5 Hz, 1 H), 5.89 (qqd, J = 7.2, 1.5, 0.8 Hz, 1 H), 6.22 (dm, J = 10 Hz, 1 H); IR (CCl_4) 2950, 2920, 2860, 1770, 1705, 1430, 1380, 1285, 1105, 975 cm^{-1}; MS, M$^+$ 233.1416, calcd $C_{14}H_{19}NO_2$ 233.1411.

Also, two minor isomers were detected δ 3.07 (dt, J = 10, 2.5 Hz) and δ 3.31 (dm, J = 10 Hz) in a 95.1:2.6:2.3 ratio.

(1α,2α,3α)-N-Methyl-6-isopropylidene-3-propyl-4-cyclohexene-1,2-dicarboximide: ^{1}*H* NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, J = 7.2 Hz, 3 H), 1.43–1.89 (m, 4 H), 1.91 (s, 3 H), 2.00 (s, 3 H), 2.29 (m, 1 H), 2.79 (s, 3 H), 3.18 (dd, J = 8.5, 6 Hz, 1 H), 4.02 (d, J = 8.2 Hz, 1 H), 5.65 (dd, J = 10, 3.5 Hz, 1 H), 6.35 (dd, J = 10, 2 Hz, 1 H); IR (CCl_4) 2950, 2920, 2965, 1770, 1705, 1430, 1380, 1285, 1260, 1105, 1005, 965 cm^{-1}; MS, M$^+$ 247.1556, calcd for $C_{15}H_{21}NO_2$ 247.1567.

(1α,2α,3α)-N-Methyl-5-(*tert*-butyldimethylsiloxy)-6-ethylidene-3-propyl-4-cyclohexene-1,2-dicarboximide: ^{1}H NMR ($CDCl_3$, 200 MHz) δ –0.04, 0.00 (2 s, 6 H), 0.82 (s, 9 H), 0.91 (t, J = 7 Hz, 3 H), 1.30–1.82 (m, 4 H), 1.88 (d, J = 7.2 Hz, 3 H), 2.25 (m, 1 H), 2.87 (s, 3 H), 3.06 (dd, J = 8.5, 5.5 Hz, 1 H), 3.50 (d, J = 8.5 Hz, 1 H), 4.80 (d, J = 3 Hz, 1 H), 5.74 (q, J = 7.2 Hz, 1 H); IR, 2950, 2920, 2850, 1770, 1700, 1610, 1435, 1380, 1285, 1260, 1200, 1170, 1110, 970, 925, 905, 840, 790, 735 cm^{-1}; MS, *m/e* 364, 320, 308, 211.

(1α,2α,3α)-N-Methyl-5-(*tert*-butyldimethylsiloxy)-6-isopropylidene-3-propyl-4-cyclohexene-1,2-carboximide: ^{1}H NMR ($CDCl_3$, 200 MHz) δ –0.09, –0.04 (2 s, 6 H), 0.84 (s, 9 H), 0.94 (t, J = 7.3 Hz, 3 H), 1.30–1.86 (m, 4 H), 1.96 (s, 3 H), 2.13 (m, 1 H), 2.86 (s, 3 H), 3.06 (dd, J = 8.2, 5 Hz, 1 H), 4.00 (d, J = 8.2 Hz, 1 H), 4.75 (d, J = 3.4 Hz, 1 H); IR, 2950, 2920, 2850, 1775, 1700, 1610, 1470, 1465, 1430, 1385, 1340, 1285, 1260, 1200, 1110, 980, 930, 905 cm^{-1}; MS, M$^+$ 377.2387, calcd for $C_{21}H_{35}NO_3Si$ 377.2377.

Acknowledgment. We thank the National Science Foundation and PPG Industries for generous support of this work.

Solvent and Salt Effects on Binding Constants of Organic Substrates in Macrocyclic Host Compounds. A General Equation Measuring Hydrophobic Binding Contributions[1]

Hans-Jörg Schneider,* Rüdiger Kramer, Svetlana Simova, and Ulrich Schneider

Contribution from the Fachrichtung Organische Chemie der Universität des Saarlandes, D-6600 Saarbrücken 11, West Germany. *Received April 20, 1987*

Abstract: The variation of association constants K_A is investigated with an azoniacyclophane **1**, binding, e.g., negatively charged fluorescence dyes, both by lipophilic and polar interactions, with α-cyclodextrin **2**, showing extremely large lipophilic contributions, and with a macrocyclic tetraphenolate **3**, characterized by almost entirely electrostatic binding mechanisms with ammonium compounds. For a series of aqueous organic solvent mixtures, all log K_A values correlate linearly with solvophobicity parameters S_p of the corresponding medium; the sensitivity a, expressed as the change in K_A between water ($S_p \equiv 1.0$) and hydrocarbon ($S_p \equiv 0.0$) ranges from $10^{1.2}$ (with **3**) to 10^7 (with **2**). The slope a and the ordinate log K_A^0 (for $S_p = 0.0$) from seven very different systems again correlate linearly, showing that both a and K_A^0 can be used as a measure of hydrophobic contributions to binding; both parameters indicate, e.g., for cyclodextrin, an extremely hydrophobic binding mechanism. Salt effects are found to be large only for ion–ion combinations of hosts **1** and **3** with guest compounds bearing opposite charges; they show surprisingly linear correlations as a Debye–Hückel type function of the ionic strength and allow predictable K_A variation by added salts. The decrease of K_A by an organic salt competing with the observed guest, however, can amount to a factor of ~70 with a commonly used glycine buffer. Improved methods for the optimal planning and evaluation of experiments for the K_A determinations are described.

Several aspects make the investigation of solvent and salt effects on organic host–guest equilibria to a timely subject: the use of such systems as synthetic receptor and enzyme analogues[2] requires a sufficient concentration of complexed material; this can be drastically lowered either by organic solvents, which may be necessary for solubility enhancement, or by salts, which are needed as buffer, or as reagents, or as cosubstrates. Furthermore, a predictable change of complexation constants is also useful for investigations of equilibria and rates under varied conditions dictated by the suitable spectroscopic or kinetic method. Besides these practical aspects, which were an incentive for the present study, solvent and salt effects are expected to shed light on the complex binding mechanisms, which are also relevant for the understanding of analogous biological systems.

Detailed studies along these lines have been undertaken largely with crown ethers and cryptands complexing mostly smaller cations.[3a] The full understanding of medium effects on complex

(1) Host-Guest Chemistry, part 14; part 13: Schneider, H.-J.; Sangwan, N. K. *Angew. Chem.* **1987**, *99*, 924; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 896.

(2) For recent reviews, see: (a) Breslow, R. *Science (Washington, D.C.)* **1982**, *218*, 532. (b) Lehn, J.-M. *Ibid.* **1985**, *227*, 849. (c) Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* **1983**, *113*, 145. (d) Murakami, Y. *Ibid.* **1983**, *115*, 107. (e) Cram, D. J.; Trueblood, K. N. *Ibid.* **1981**, *98*, 43. (f) Franke, J.; Vögtle, F. *Ibid.* **1986**, *132*, 171. (g) Schmidtchen, F. P. *Ibid.* **1986**, *132*, 101. (h) Odashima, K.; Koga, K. In *Cyclophanes*; Academic: New York, 1983; Vol. II, p 629 ff. (i) Sutherland, I. *Ibid.* p 679 ff. (j) Schneider, H.-J.; Busch, R.; Kramer, R.; Schneider, U.; Theis, I. *Adv. Chem. Ser.* **1987**, *215*, 457. (k) Kellog, R. M. *Angew. Chem.* **1984**, *96*, 769; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 782. (l) Diederich, F. *Angew. Chem.* **1988**, *100*, 372; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362.

(3) (a) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271 and references cited therein. (b) DeJong, F.; Reinhoudt, D. N. *Adv. Phys. Org. Chem.* **1980**, *17*, 279.

0002-7863/88/1510-6442$01.50/0

equilibria requires a quantitative evaluation of the whole thermodynamic cycle involving solvation and desolvation of host and guest.[3a,b] Cryptand solvation has been shown, e.g., by Abraham et al.,[4] to contribute significantly to corresponding sodium complex variations in water–methanol mixtures. Generally, the stability of crown ether and cryptand complexes increase from water to methanol and to less polar solvents,[3a,b,5-8] but exceptions were found that were attributed to nonintracavity inclusion.[7] Counteracting enthalpy and entropy contributions[9-12] can furthermore complicate predictions. Gelb and Zompa et al. have carried out detailed thermodynamic, spectroscopic, and structural studies on complexes between different anions and protonated macrocyclic polyamines,[13] which can be considered to be the positively charged counterpart to a smaller negatively charged host investigated in the present paper. They conclude[13] that solvent release and ordering and not the steric fit of the anion guest to the host cavity is dominating the interactions. Sigel et al. have reported on opposing polar and hydrophobic solvent effects on stabilities of mixed-ligand metal ion complexes involving aromatic ring stacking.[14]

Medium and salt effect investigations with hosts having large and lipophilic cavities for complexation of organic substrates have so far been largely restricted to cyclodextrins.[15] That addition of lipophilic solvents to the necessarily aqueous solutions here leads to a decrease of binding constants is a consequence of the hydrophobic driving force and has been observed in several instances.[16-18] A quantitative correlation with corresponding solvent properties, however, has until now not been demonstrated, also due to the lack of suitable solvent parameters, and is one aim of the present work. The presence of inorganic salts can lead to a decrease of binding,[19-21] in particular if the anion is competing with substrate binding in the cavity, or to increased constants,[20,22] which relates to salting in and out effects[22] by change of activity coefficients and water-structure variations; a quantitative treatment was described on the basis of the Debye-Hückel[22-24] theory. With a tricyclic host bearing four positively charged nitrogen atoms, Schmidtchen has observed an increased binding of halide anions in 95% methanol compared to water, which was explained by the stronger anion solvation in water.[25] In a detailed study on the complexation of aromatic hydrocarbons in tricyclic azacyclophanes containing also oxygen atoms, Diederich et al.[26] recently came to the conclusion that, in protic and very likely also in aprotic dipolar solvents, solvation–desolvation processes are dominating, whereas in weakly polar solvents such as chloroform or benzene, in which the association constants decrease drastically, competitive binding of such solvents in the host cavity takes place. Jarvi and Whitlock[27] found NMR evidence for complexation of benzene as solvent inside a naphthalenophane cavity.

Medium effects on complexes of protein ligands with organic substrates are gaining practical importance, e.g., for the use of enzymes with organic solvents.[28] Maurel[29] has demonstrated how particular solvent effects on enzymatic K_M values reflect hydrophobic bonding contributions.[30] The study of salt effects on enzymes also gives insight in pertinent electrostatic interactions in the corresponding complexes.[31]

The present study contains results with macrocyclic hosts representing different binding principles in host–guest equilibria: the positively charged azoniacyclophane **1**, which resembles similar systems first investigated by Koga et al.,[33,2h] encapsulates lipophilic naphthalene derivatives with and without negative charges in the guest; α-cyclodextrin (**2**) features binding of a geometrically suited substrate by exclusive or predominating hydrophobic[34] interactions. The tetraphenolate **3** finally provides a ligand that shows strong complexation almost exclusively by electrostatic attraction.[35]

Determination of Equilibrium Constants. All measurements of equilibria[36] between a receptor R, a substrate S, and the complex RS are based on the observation of an apparent spectroscopic property x, which here refers either to a time averaged NMR shift

(4) Abraham, M. H.; de Namor, A. F. D.; Lee, W. H. *J. Chem. Soc., Chem. Commun.* **1977**, 893. See also: Abraham, M. H.; Viguria, E. C.; de Namor, A. F. D. *Ibid.* **1979**, 374.

(5) Frensdorf, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600.

(6) Lehn, J.-M.; Sauvage, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6700.

(7) Spiess, B.; Martin-Faber, D.; Arnaud-Neu, F.; Schwing-Weill, M. J. *Inorg. Chim. Acta* **1981**, *54*, L91.

(8) Cox, B. G.; Truong, N. van; Schneider, H. *J. Am. Chem. Soc.* **1984**, *106*, 1273.

(9) Izatt, R. M.; Terry, R. E.; Nelsen, D. P.; Chan, Y.; Eatough, D. J.; Bradshow, J. S.; Hansen, L. D.; Christensen, J. J. *J. Am. Chem. Soc.* **1976**, *98*, 7626.

(10) Kauffmann, E.; Lehn, J.-M.; Sauvage, J.-P. *Helv. Chim. Acta* **1976**, *59*, 1099.

(11) (a) Shamispur, M.; Rounaghi, G.; Popov, A. I. *J. Solution Chem.* **1980**, *9*, 701. (b) For a study on solvent effects on crown ether complexation kinetics, see: Strasser, B. O.; Popov, A. I. *J. Am. Chem. Soc.* **1985**, *107*, 7921.

(12) Abraham, M. H.; Ling, H. C. *Tetrahedron Lett.* **1982**, *23*, 469.

(13) Gelb, R. I.; Lee, B. T.; Zompa, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 909 and references cited therein.

(14) (a) Sigel, H.; Malini-Balakrishnan, R.; Häring, U. K. *J. Am. Chem. Soc.* **1985**, *107*, 5137. (b) Sigel, H. *Angew. Chem.* **1982**, *94*, 421; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 421 (review).

(15) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978. (b) Szejtli, J. *Cyclodextrins and Their Inclusion Complexes*; Akademiai: Kiado, Budapest, 1982. (c) Saenger, W. *Angew. Chem.* **1980**, *92*, 343; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (d) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66; *Tetrahedron* **1984**, *40*, 269.

(16) Siegel, B.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 6869.

(17) Gerasimowicz, W. V.; Wojcik, J. F. *Bioorg. Chem.* **1982**, *11*, 420.

(18) (a) Harada, A.; Takahashi, S. *J. Inclusion Phenom.* **1984**, *2*, 791. (b) See also: Tabushi, I.; Kuroda, J.; Mizutani, T. *J. Am. Chem. Soc.* **1986**, *108*, 4514. (c) Wojcik, J. F. *Bioorg. Chem.* **1984**, *12*, 130 for leading references on cyclodextrin complexation mechanisms.

(19) Schlenk, H.; Sand, D. M. *J. Am. Chem. Soc.* **1961**, *83*, 2312.

(20) Cramer, F.; Saenger, W.; Spatz, H.-C. *J. Am. Chem. Soc.* **1967**, *89*, 14.

(21) Mochida, K.; Kagita, A.; Matsui, Y.; Date, Y. *Bull. Soc. Chem. Jpn.* **1973**, *46*, 3703.

(22) (a) Debye, P.; Hückel, E. *Phys. Z.* **1923**, *24*, 185. (b) Bockris, J. O'M.; Reddy, A. K. N. *Modern Electrochemistry*; Plenum: New York, 1970; Vol. 1, p 155 ff. (c) Robinson, R. A.; Stokes, R. H. *Elektrolyte Solutions*; Butterworth: London, 1970; p 229. (d) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.

(23) Gordon, J. E. *The Organic Chemistry of Electrolyte Solutions*; Wiley: New York, 1975. (b) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; p 196.

(24) (a) For a recent review on ion solvation in aqueous solution including macroions, see: Ise, N. *Angew. Chem.* **1986**, *98*, 323; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 323. (b) For leading references on ion-pair solvation in water based on molecular dynamics simulations, see, e.g.: Beloh, A. C.; Berkowitz, M.; McCammon, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 1755.

(25) Schmidtchen, F. P. *Chem. Ber.* **1981**, *114*, 597.

(26) Diederich, F.; Dick, K.; Griebel, D. *J. Am. Chem. Soc.* **1986**, *108*, 2273.

(27) Jarvi, E. T.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 7196.

(28) For recent reviews, see: (a) Luisi, P. L. *Angew. Chem.* **1985**, *97*, 446; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 439. (b) Kazandjian, R. Z.; Dordick, J. S.; Klibanov, A. M. *Biotechnol. Bioeng.* **1986**, *28*, 417.

(29) Maurel, P. *J. Biol. Chem.* **1978**, *253*, 1677.

(30) For leading references on other solvent effects on proteins, see, e.g.: Cordone, L.; Cupane, A.; Fornili, S. L. *Biopolymers* **1983**, *22*, 1677. For ion effects: (b) Von Hippel, P. H.; Schleich, Th. *Acc. Chem. Res.* **1969**, *2*, 257.

(31) See, e.g.: Smith, H. T.; Ahmed, A. J.; Millett, F. *J. Biol. Chem.* **1981**, *256*, 4984.

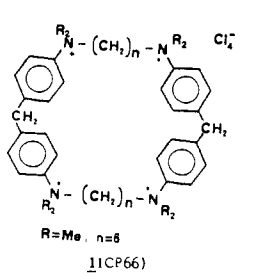
(32) (a) Schneider, H.-J.; Philippi, K. *Chem. Ber.* **1984**, *117*, 3056. (b) Schneider, H.-J., Philippi, K.; Pöhlmann, J. *Angew. Chem.* **1984**, *96*, 907; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 908. (c) Schneider, H.-J.; Pöhlmann, J. *Bioorg. Chem.* **1987**, *15*, 183.

(33) Azoniacyclophane complexes, however only with protonated azamacrocycles, have been described before: Odashima, K.; Soga, T.; Koga, K. *Tetrahedron Lett.* **1981**, *22*, 5311 and references cited therein.

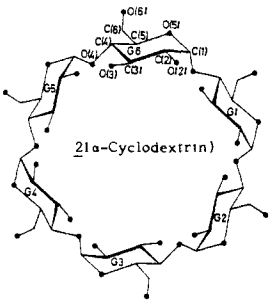
(34) Ben-Naim, A. *Hydrophobic Interactions*, 2nd ed.; Plenum: New York, 1983. Tanford, C. *The Hydrophobic Effect*, 2nd ed.; Wiley: New York, 1980.

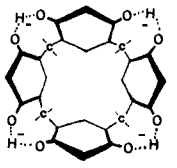
(35) Schneider, H.-J.; Güttes, D.; Schneider, U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 647. (b) Schneider, H.-J.; Güttes, D.; Schneider, U. *J. Am. Chem. Soc.*, following paper in this issue.

(36) See, e.g.: (a) Havel, J.; Meloun, M. in *Computational Methods for the Determination of Formation Constants*; Plenum: New York, 1985. (b) Hartley, R.; Burgess, C.; Alcock, R. M. *Solution Equilibria*; Ellis Horwood: Chichester, 1980. (c) Rametle, R. W. *Chemical Equilibrium and Analysis*; Addison-Wesley: New York, 1981. (d) Dahlquist, F. W. In *Methods in Enzymology*; Hirs, C. H. W., Timasheff, S. N., Eds.; Academic: New York, 1978; Part F, Vol. XLVIII, p 270 ff. (e) Cantor, C. R.; Schimmel, P. R. *Biophysical Chemistry*; W. H. Freeman: San Francisco, 1980; Part III, p 849 ff.



1ICP66)





3ITPB)

ϑ_{obsd}, to an apparent UV–vis extinction coefficient ϵ_{app}, or to an apparent fluorescence intensity I_{app}. For 1:1 complexes with an association constant K_A, one obtains[36]

$$K_A = [RS]([R][S])^{-1} = [RS](([R]_0 - [RS])([S]_0 - [RS]))^{-1} \quad (1)$$

and

$$[RS] = [S_0](x - x_f)(x_b - x_f)^{-1} \quad (2)$$

where $[R]_0$ and $[S]_0$ refer to known total concentrations and x_f and x_b refer to the property of the free and bound R or S, respectively. Identification of the unknown parameters K and x_b is achieved by measurements with different $[R]_0$ and $[S]_0$ and a suitable nonlinear curve fitting procedure. The traditional linearization methods such as the Benesi–Hildebrand treatment[37] require either $[R]_0 \gg [S]_0$ or $[S]_0 \gg [R]_0$, depending whether the property x of R or S is measured, as well as observance of only *one* species (RS) at, e.g., a given wavelength. These conditions are often difficult to maintain, particularly for weaker complexes. The curve-fitting methods used in the present work require no such approximations and furthermore allow for an improved distribution and weighing of the experimental points as compared to classical linearizations. Optimal conditions for the evaluation of complex equilibria have been discussed by several authors,[38b-f] in particular, it has been demonstrated that measurements below ~20% and above ~80% complexation yield very uncertain values.[38b,e] Most of the studies in the present work (Tables I and III) were carried out with a procedure similar to earlier work,[38e] but allowed for a variation of the optimal complexation limits (α and β, corresponding to ~20% and ~80%) as well as for simultaneous change of $[R]_0$ and $[S]_0$ (see Experimental and Computational Details). The procedure starts with a proper choice for α, β, R_0, and S_0 from an expected K value with $[S]_0 \cong 0.5K_D$ (or $[R]_0 \cong 0.5K_D$), provides the necessary increments of R_i (or S_i) to be added, and evaluates K and x_b from usually eight measurements by a Simplex optimization[39] based on eq 1 and 2 (see Experimental and Computational Details).

The choice of the spectroscopic method was largely dictated by the required sensitivity; therefore, ^{1}H NMR spectroscopy was used for $K < 10^4$, UV–vis spectroscopy for $10^2 < K < 10^5$, and fluorescence spectroscopy for $10^5 < K < 10^7$. NMR has the unsurpassed advantage to provide information on the complex geometry, whereas the optical methods can hardly differentiate between surface association and intracavity inclusion. NMR spectroscopy also furnishes *several* signals for independent K evaluations. The equilibrium constants thus obtained usually agreed within 10%, if the complexation-induced shift (CIS = x_b) was not too small (<~0.1 ppm) for a given signal; a small K (<10) also seems to affect the agreement.

Systematic and statistic deviations between simulated curves and experimental points were usually so small (see Experimental and Computational Details and Table I) that application of calculational non-1:1 models for the assumed equilibria was not warranted. The errors in K (Tables I and III) were evaluated numerically either by standard deviations of single K values obtained for the usually eight measurements compared to the regression values for K or/and, in the case of NMR titrations, by comparing the results from different signals.

UV titrations were restricted to few chromophoric compounds (Tables I and III); the complexation-induced changes used here instead of NMR shifts as x_b were $\Delta\epsilon$ = 2000–3000. Fluorescence dyes showed a substantial intensity I increase (ΔI_b) upon complexation,[32c] which was again used as x_b, allowing also for fluorescence contributions of the uncomplexed substrate.

Approximate Methods. If the spectroscopic parameter x_b is known from measurements under conditions where one *knows* the presence of, e.g., >99% complexation, single K values can be obtained from single measurements by substituting eq 2 into eq 1. This method has been extensively used by Diederich et al.,[26]

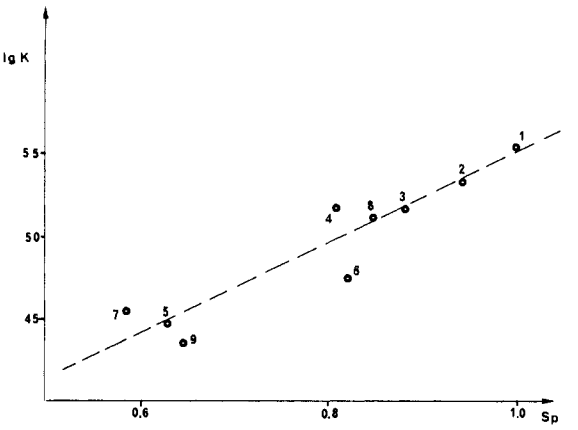


Figure 1. log K_A (association constants) vs solvophobicity values (S_p) for **1** with ANS in aqueous mixtures with methanol (1, 2, 3, 4, 5: 0, 10, 20, 30, 50%); ethanol (6, 7: 20, 40%); dioxane (8, 9: 20, 40%).

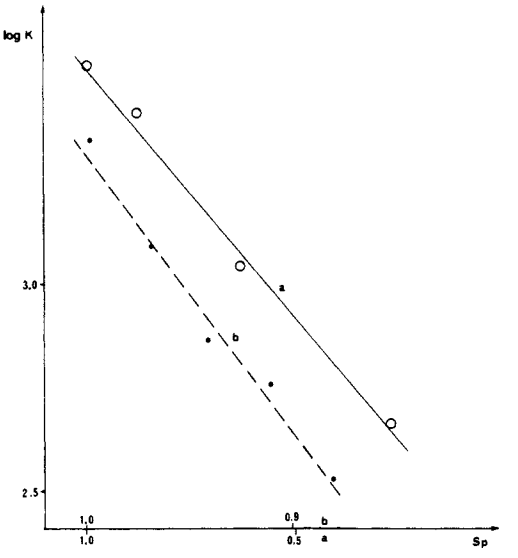


Figure 2. log K_A (association constants) vs solvophobicity S_p: (a) for **3** with Et_4NBr (open circles), (b) for **2** with $PNPO^-$ (filled circles).

(37) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
(38) (a) Person, W. B. *J. Am. Chem. Soc.* **1965**, *87*, 167. (b) Deranleau, D. A. *Ibid.* **1969**, *91*, 4044 and 4051. (c) Carta, G.; Crisponi, G. *J. Chem. Soc., Perkin Trans. II* **1982**, 53. (d) Carta, G.; Crisponi, G.; Lai, A. *J. Magn. Reson.* **1982**, *48*, 341. (e) Granot, J. *Ibid.* **1983**, *55*, 216 and references cited therein.
(39) (a) Bevington, P. R. *Data Reduction and Error Analysis*; McGraw-Hill: New York, 1969. Bayne, C. K.; Rubin, I. B. *Practical Experimental Design and Optimization Methods for Chemists*; VCH Publishers: Deerfield Beach, 1986. (b) Morgan, S. L.; Deming, S. N. *Anal. Chem.* **1974**, *46*, 1170. Nelder, J. A.; Mead, R. *Comput. J.* **1965**, *7*, 308.

Table I. Association Constants in Different Solvents[a]

no.	solvent	%	E_T	Y	S_p	K	ΔK, %	$\Delta G°_{25}$	method
				ANS + CP66 (**1**)[b]					
1	H_2O	100	63.1	3.49	1.000	3.54×10^5	10	7.6	F
2	MeOH	10	62.2	3.28	0.942	2.20×10^5	8	7.3	F
3	MeOH	20	61.0	3.02	0.881	1.53×10^5	6	7.1	F
4	MeOH	30	60.0	2.75	0.808	1.50×10^5	8	7.0	NMR
5	MeOH	50	58.3	1.97	0.631	0.31×10^5	39	6.1	NMR
6	MeOH	80	56.6	0.38	0.354	0.017×10^5	20	4.4	NMR
7	EtOH	20	60.0	3.05	0.820	0.55×10^5	5	6.5	F
8	EtOH	40	56.6	2.20	0.585	0.35×10^5	5	6.2	F
9	EtOH	60	55.0	1.12	0.345	0.19×10^5	7	5.8	F
10	dioxane	20	58.6	2.88	0.846	1.30×10^5	10	7.0	F
11	dioxane	40	55.6	1.94	0.646	0.23×10^5	5	5.9	F
				DNSA + CP66 (**1**)[b]					
12	H_2O	100	63.1	3.49	1.000	4.8×10^3	5	5.0	F
13	MeOH	10	62.2	3.28	0.942	2.8×10^3	10	4.7	F
14	MeOH	20	61.0	3.02	0.881	0.94×10^3	5	4.1	F
15	MeOH	50	58.3	1.97	0.631	0.13×10^3	5	2.9	NMR
				Naphthalene + CP66 (**1**)[b]					
16	MeOH	20	61.0	3.02	0.881	9.2×10^2	5	4.0	NMR
17	MeOH	50	58.3	1.97	0.631	0.76×10^2	5	2.6	NMR
18	MeOH	80	56.6	0.38	0.354	0.08×10^2	10	1.3	NMR
				$DNNO^-$ + CP66 (**1**)[c]					
19	H_2O	100	63.1	3.49	1.000	21.1×10^3	10	5.9	UV
20	MeOH	50	58.3	1.97	0.631	1.52×10^3	9	4.3	NMR
21	MeOH	80	56.6	0.38	0.354	0.26×10^3	9	3.3	NMR
				PNPA + CP66 (**1**)[b]					
22	MeOH	10	62.2	3.28	0.942	1.13×10^2	10	2.8	NMR
23	MeOH	20	61.0	3.02	0.881	0.64×10^2	10	2.5	NMR
24	MeOH	30	60.0	2.75	0.808	0.38×10^2	10	2.15	NMR
				$^+NEt_4Br^-$ + TPB (**3**)[d]					
25	H_2O	100	63.1	3.49	1.000	3.4×10^3	15	4.8	NMR
26	MeOH	20	61.0	3.02	0.881	2.6×10^3	8	4.6	NMR
27	MeOH	50	58.3	1.97	0.631	1.1×10^3	9	4.1	NMR
28	MeOH	90	56.1	−0.30	0.273	0.45×10^3	9	3.6	NMR
				$PNPO^-$ + α-CYD (**2**)[e]					
29	H_2O	100	63.1	3.49	1.000	2.25×10^3	3	4.56	UV
30	MeOH	5	62.4	3.37[f]	0.970[f]	1.25×10^3	3	4.21	UV
31	MeOH	10	62.2	3.28	0.942	0.73×10^3	5	4.04	UV
32	MeOH	15	61.4	3.13[f]	0.912[f]	0.56×10^3	4	4.025	UV
33	MeOH	20	61.0	3.02	0.881	0.33×10^3	15	4.005	UV

[a] At 25 ± 2 °C; solvent composition by (vol + vol); deuteriated solvents and salts in the case of NMR measurements; E_T, Y, S_p values from the literature; NMR (^1H) and F = fluorescence methods; K from curve fitting of usually eight points between 20–80% complexation; error in K (ΔK, %) from deviations between single K and average K values (see text), or/and—for NMR—from deviations between different signal evaluations; UV method (29–33), K and ΔK from two to three independent titrations for each solvent composition. [b] Under neutral conditions (pH ~7), without additional salts. [c] At pH 10.0 ($DNNO^-$ >99% dissociated), [NaOH] + [H_3BO_4] = 0.05 M. [d] At pH 12.5, [NaOD] = 0.5 M. [e] At pH 11.0 ($PNPO^-$ >99%, CYD 10–20% dissociated); [NaOH] + [H_3PO_4] + [NaCl] = 0.1 M. [f] From linear interpolations between neighbor Y and S_p values.

Table II. Correlations of Association Constants (log K_A) with Solvophobicity (S_p) and Selected Polarity (E_T) Parameters[a]

					with S_p		with E_T	
no.		a	log K^0	n	r	ψ, %	r	ψ, %
1	**2** + $PNPO^-$	7.0	−3.9	5	0.992	3	0.973	9
2	**1** + DNSA	5.9	−2.2	4	0.984	6	0.997	1
3	**1** + naphthalene	4.0	−0.5	3	0.998	1	0.995	3
4	**1** + PNPA	3.5	−1.3	3	0.997	2	0.992	5
5	**1** + $DNNO^-$	2.95	1.35	3	0.999	0.3	0.988	7
6	**1** + ANS	2.72	2.78	9	0.935	16	0.898	25
7	**3** + Et_4NBr	1.25	2.3	4	0.997	1	0.981	7

[a] Conditions, see Table I. a: slope, log K^0 abscissa from correlations of log K_A vs S_p (values from Table I). r: linear correlation coefficient. ψ: reliability parameter.

who could show that in their cases most CIS values seem to be largely solvent-independent. Such an approximation has been found to be less valid for several of our complexes;[32c] a typical error in K resulting from a CIS error of, e.g., +0.02 ppm at CIS = 0.2 ppm amounts for $K \cong 600$ to ±80%. We therefore have used the method only for the strong complexes with the cyclophane **3** after securing experimentally CIS values at >99% complexation. The justification of the method and the applied CIS values here was furthermore checked by several measurements at, e.g., ~35% and ~65% complexation, yielding K differences below 10%.

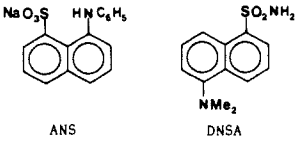
Solvent Effects on Complexations with 1–3. A quantitative correlation of complexation equilibrium constants K_A to solvent properties was until now hampered by the absence of suitable general parameters describing solvophobicity, in spite of the extensive studies available on medium effects, and in particular on the influence of water.[40] We have shown in a preliminary com-

Table III. Salt Effects on Association Constants[a]

no.	concn, N	salt	K, M^{-1}	ΔK, %	m	K_0, M^{-1}
			$DNNO^-$ + CP66 (1)			
1	0.020	NaCl	2.11×10^4		−0.98	2.46×10^4
2	0.050	NaCl	1.68×10^4		(r = 0.9987, ψ = 0.5%)	
3	0.100	NaCl	1.21×10^4			
4	0.500	NaCl	0.48×10^4			
			$^+NEt_4Br^-$ + TPB (3)			
5	0.0030	NaOD	4.8×10^4	11	−3.33	7.1×10^4
6	0.0070	NaOD	3.8×10^4	9	(r = 0.996, ψ = 1%)	
7	0.0100	NaOD	3.1×10^4	11		
8	0.100	NaOD	1.35×10^4	15		
9	0.500	NaOD	0.34×10^4	15		
10	0.100	NaCl	1.1×10^4	8		
11	0.100	NaBr	1.05×10^4	11		
12	0.100	KCl	1.15×10^4	8		
13	0.100	KBr	1.10×10^4	9		
			DNSA + CP66 (1)			
14	<0.001	MX[b]	4.8×10^3	5		
15	0.100	NaCl	4.9×10^3	6		
			ANS + CP66 (1)			
16	<0.001	MX[b]	5.5×10^5	5		
17a–g	0.010	MX	1.3×10^5	10	(MX = NaOH, NaF, NaCl, NaBr, NaI, KI, LiI)	
18	0.100	NaCl	0.52×10^5	8		
19	0.100	NaOH–glycine	0.082×10^5	11	(pH 12.0)	
			PNPO + α-CYD (2)			
20	0.100	$NaOH + H_3PO_4$	2.25×10^3	3	(pH 11.0)[c]	
21	0.100	$NaCl + NaH_2PO_4$	2.49×10^3	3	(pH 9.0)[d]	
22	1.10	$NaCl + NaH_2PO_4$	2.85×10^3	5	(pH 9.0)[d]	

[a] See footnote *a* to Table I; salt effects measured in water. m: slope from plots of log K vs νI ($PNPO^-$ + CP66) or log K vs $\sqrt{I}(1 + \sqrt{I})^{-1}$ ($^+NEt_4Br^-$ + TPB). I: ionic strength [N]. K_0: constant in salt-free water, from plot for I = 0. Methods for 1–4 and 20–22, UV–vis titration; for 8 and 9, NMR titration; for 5–7 and 10–13, NMR evaluation based on one to two single measurements with known CIS values (see text); for 14–19, fluorescence titration. [b] MX = CP66, Cl_4 (maximum concentration during titration, 0.001 M). [c] CYD 10–20% ionized. [d] CYD < 1% ionized.

munication[32b] that for aqueous binary mixtures the decrease of fluorescence intensity of suitable dyes such as ANS with increasing



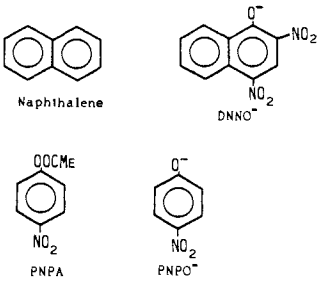
ANS DNSA

water content, or equally well the decrease of free enthalpies of transfer (ΔG_t^0) of tetramethyltin from gas into a given solvent mixture, described by Abraham,[41] shows linear correlations with log K involving complexes of **1**. After it became clear that experimental ΔG_t^0 values of many hydrocarbons in a broad range of solvents are almost linearly interrelated,[41c] we decided to use corresponding solvophobicity parameters S_p, which are defined as S_p = 1.00 in water and S_p = 0.0 in *n*-hexane.[41c,42]

Figures 1 and 2 illustrate that on this basis the change of association constants K_A not only within one binary water mixture[32b] but within a whole range of solvents can indeed be described by a general equation:

$$\log K_A = aS_p + \log K_A^0$$

The sensitivity parameter a obtained from linear regression (Tables I and II) describes the enormous differences of the measured complexations against solvophobicity changes. Thus, admixture of 30% dioxan to water ($\rightarrow \Delta S_p = 0.3$) would decrease association constants for the complex **3** + Et_4NBr by a factor of ~2, for **1** + ANS by ~3.3, for **1** + naphthalene by ~10, and for **2** + $PNPO^-$ by ~55. Obviously, this sequence indicates the increasing importance of hydrophobic contributions to the complex formation.



Naphthalene DNNO⁻ PNPA PNPO⁻

Since the S_p values are found to be almost linear in volume percent of organic solvent in aqueous binary mixtures,[41c] one can also use the equation

$$\log K_A = a'(\text{vol }\%) + \log K_A'$$

in such cases; this also allows applications to solvents for which S_p values are known only for the neat solvent but not for mixtures with water.

The observed correlations between log K and S_p are throughout good to excellent (Table II), even in cases where the sensitivity against S_p changes is smaller. Correlations with solvent *polarity* parameters such as with E_T[40a] are significantly less linear (Table II) as also found with analogous rate/S_p correlations.[42] Winstein–Grunwald Y "ionizing powers"[40a] correlate better than E_T parameters with the observed log K values; the underlying reactivity differences in the solvolysis of *tert*-butyl chloride are, however, not only a function of the solvent polarity.[41c] Polar contributions of solvent effects could have the adverse effect on all complexes comprising host–guest combinations of opposite charges, since electrostatic attractions generally could *de*crease

(40) See, e.g.: (a) Reichardt, C. *Solvent Effects in Organic Chemistry*; Verlag Chemie: Weinheim, 1979. Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* **1968**, *11*, 1. (b) Abraham, M. C. *Pure Appl. Chem.* **1985**, *57*, 1055. (c) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1965. (d) Engberts, J. B. F. N. In *Water: A Comprehensive Treatise*; Franks, F., Ed.; Plenum: New York, 1979; Vol. 6, Chapter 4.

(41) (a) Abraham, M. H. *J. Am. Chem. Soc.* **1982**, *104*, 2085. (b) Abraham, M. H.; Grellier, P. L.; McGill, R. A. *J. Chem. Soc., Perkin Trans. II* **1988**, in press, and references cited therein. (c) Private communications.

(42) S_p values have already been used to describe solvophobic effects on Diels–Alder reaction rates: Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Chem. Commun.* **1986**, 1787.

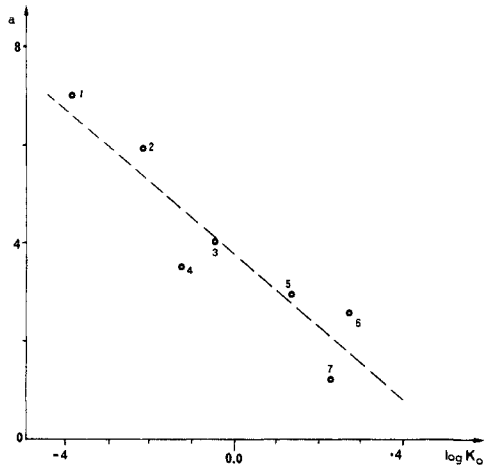


Figure 3. Correlation of log $K_A - S_p$ solvent effect correlations: sensitivity (slope a) vs log K_{AO} (ordinate for $S_p = 0.0$); 1–7 refer to the numbers in Table II.

with increasing water content. That not only with the system **1** + ANS, but even with **3** + Et_4NBr the opposite—although expectedly weaker—water effect is observed (Figures 1 and 2, Table II) indicates that, even in the presence of dominating electrostatic interactions, van der Waals forces play an important role. Complexations with the tetraphenolate **3** have been proven to be almost entirely due to electrostatic attraction, both by the extremely weak binding of electroneutral guests as well as by a quantitative Coulomb-potential dependence on the charge-separating distances.[35] Two factors are believed to be responsible for the observed K decrease with increasing S_p: in the association of the ammonium ion with the macrocyclic anion less desolvation is needed as compared to the bromide anion, and the macrocyclic anion in the complexed state is also expected to gain more by solvation in the more lipophilic solvent as compared to the halide, which exists as a solvent-separated ion pair in all the aqueous mixtures.

Inspection of the slopes a and ordinates log K_0 obtained from measurements with seven different host–guest systems (Table II) suggests that both are interrelated. A corresponding correlation of the solvent effect correlations indeed shows a significant interdependence (Figure 3), which is surprisingly linear in view of the very different interaction types and cavities involved. The results suggest that not only the sensitivity parameter (slope) a is a measure of the hydrophobic contribution to the complexation free energy but also the log K_0 value, which represents the equilibrium constant in a hydrocarbon solvent ($S_p \equiv 0$). The latter will assume values of $K < 1$ to the degree that association of both lipophilic parts is endothermic in the increasing absence of hydrophobic desolvation effects.

If we now compare the results with one host (H = **1**) with different guest compounds it seems that the slope a decreases and concomitantly log K_0 increases with increasing hydrophilicity of the substrate (Table II), although it is surprising that the interaction, e.g., with DNSA, shows more hydrophobic character than with naphthalene. Noticeably, PNPA fits into the correlation (Figure 3), although this phenyl derivative cannot fill the cavity of **1**, and in consequence also shows smaller binding constants than the naphthalene derivatives. That the large and very unpolar inside of cyclodextrins provides for an optimal hydrophobic binding contribution is nicely supported by the observed extreme values for both a and log K_0 here. The only available earlier measurements by Wojcik et al.[17] with α-cyclodextrin in DMSO mixtures are found to be only in rough agreement with our a/log K_0 correlation; this is understandable in view of the limited solvent range and the uncertain S_p values[41c] for DMSO–H_2O mixtures. Similarly, an analysis of the solvent effects reported by Diederich et al.[26] is limited by lack of several S_p values; in particular, the K_A value reported in DMSO seem to be much smaller than predicted by the corresponding S_p value, which suggests specific solvation effects[26] by such a solvent.

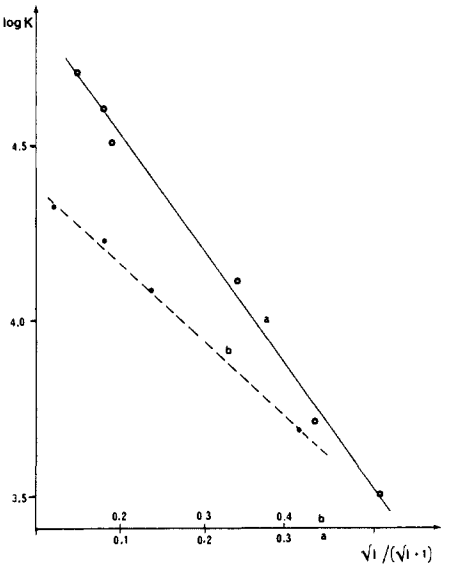


Figure 4. Salt effects: association constants (log K_A) vs Debye–Hückel ionic strength function $\sqrt{I}/(\sqrt{I} + 1)$; (a) for **3** with Et_4NBr; (b) for **1** with $DNNO^-$.

Salt Effects on Complexations with 1–3. If either the host R or the guest S, or both, are electroneutral species, addition of electrolytes even at higher concentrations will only produce small alterations of the association constants by salting-in or -out effects.[22b,c,23] This is visible in the small K_A increase observed with cyclodextrin at ~1 M sodium chloride (Table III), resulting from the increased water structuring by these relatively small and hard ions (salting-out effect[22b,c,23]). With ion–ion combinations of R and S, however, drastic K changes are found that reach, e.g., with 0.5 M alkali halide, a factor of ~10 (Table III).

The generally observed K_A decrease and its independence is the nature of the ions with the charge $z = 1$ (Table III, 10–13, 17a–g) suggested a treatment of these effects by the Debye–Hückel[22,23] description of changing activity coefficients f_i as a function of the ionic strength I. With

$$\log f_i = -0.5091 z_i^2 \sqrt{I} \qquad \text{(I)}$$

one obtains

$$\log K = \log K^0 - \log (f_{RS}/[f_R f_S]) \qquad \text{(II)}$$

For the system R + S = tetraphenolate **3** + Et_4NBr, we obtain with $z_{RS} = -3$, $z_R = -4$, and $z_S = +1$:

$$\log K = \log K^0 - 4.072\sqrt{I} \qquad \text{(IIa)}$$

It is remarkable that a plot of log K vs $\sqrt{I}$ yields a linear correlation ($r = 0.991$) with a slope $m = -4.13$, very near to the theoretical value, if one stays below the limit $I < 10^{-2}$ M for which eq II holds. Even at higher salt concentrations we see a linear dependence according to the modified equation

$$\log f_i = -0.5091 z_i^2 \sqrt{I}/(1 + \sqrt{I}) \qquad \text{(III)}$$

The corresponding plot (Figure 4) again shows linearity up to 0.5 M salt concentration ($r = 0.996$) and a sensitivity of $m = -3.33$, not too far from the expected slope. As an electrostatic counterpart with a positively charged receptor R and a negatively charged substrate S, we studied the dependence of K_A for the system **1** + $DNNO^-$ from the NaCl concentration. The Debye–Hückel plot (Figure 4) again showed linearity ($r = 0.9987$, $\psi = 0.5\%$); even the slope ($m = 0.98$) is not too far away from the Debye–Hückel prediction ($m = 4.072$ for the $z_R = +4$, $z_{RS} = +3$, $z_S = -1$) in view of the particularly large deviation of macrocycle **1** from the underlying spherical cavity model and the expected local accumulation of anions around the positively charged nitrogen atoms in **1**. In view of the very different ion diameters and anisotropic cavities involved, it is surprising that the Debye–Hückel

correlations seem to hold, which, however, is at least useful for practical applications.

Addition of glycine in 0.1 M concentrations, which is often used as buffer, leads to ~70-fold decrease of the CP66/ANS association constant (Table III). This decrease is at least 10 times higher than expected on the basis of the calculated ionic strength, which indicates that special precautions are necessary in cases where added organic ions can compete with the ionic substrate for intracavity binding.

Conclusions

The strong influence of both solvents as well as—in the case of ionic host–guest combinations—salts on association constants has important consequences for quantitative work on corresponding equilibria and kinetics. The correlations from the present work will allow predictions and interpolations with respect to equilibrium constants. The solvent studies also provide parameters measuring the hydrophobic contribution to binding in a given complex; the salt effect analysis shows that the corresponding behavior of macrocyclic ionic structures **1** and **3** in protic solvents can be largely described and predicted in the framework of the Debye–Hückel theory, with noticeable exceptions if organic salts compete with ionic substrates. Since the generalized solvent correlation seems to apply to complexes of very different types, it is hoped that protein and other bioreceptor complexes can partially also be analyzed within this quantitative framework. One attractive feature of such studies is the possibility to extrapolate eventually binding constants with biologically important host compounds to a hydrocarbon-like or even gaslike environment.

Experimental and Computational Details

Determination of Equilibrium Constants by Spectrometric Titrations. Other than in the theoretical work of Granot[38e] our procedure does not require to keep concentrations $[R]_0$ or $[S]_0$ of the stock solutions, or the volume of the whole solution, constant during the titration. If $[R]_0^i$ and $[S]_0^i$ denote the total concentrations of R and S at the titration step i, V_0 the initial volume and V^i the volume added at step i, and cd^i the corresponding complexation degree, we obtain with

$$V^i_{total} = \sum_{k=1}^{i} V^k \text{ (the volume after completion of } i \text{ steps)}$$

$$e^i = [R]_0^i/[S]_0^i = \alpha(\beta/\alpha)^{(i-1)/(n-1)} \quad (3)$$

$$\alpha = [R]_0^1/[S]_0^1;\ \beta = [R]_0^n/[S]_0^n \quad (4a,b)$$

Then

$$e^i = ([R]_0 V^i_{total})/([S]_0 V_0) \quad (5)$$

$$V^i_{total} = e^i[S]_0 V_0/[R]_0 \quad (6)$$

$$V^i = e^i[S]_0 V_0/[R]_0 - \sum_{k=1}^{i-1} V^k \quad (7)$$

$$[S]_0^i = [S]_0 V_0/(V_0 + V^i_{total}) = [S]_0/(1 + e^i[S]_0/[R]_0) \quad (8)$$

$$[R]_0^i = e^i[S]_0^i \quad (9)$$

The corresponding program then proceeds with the evaluation of the α and β values:

$$[R]_0^i = (cd^i/100)[S]_0^i + K_D/[(100/cd^i) - 1] \quad (10)$$

For cd = 80% and $i = n$, e.g.:

$$[R]_0^n = 0.8[S]_0^n + 4.0K_D \quad (10a)$$

with

$$[S]_0^n = [S]_0 V_0/V_{end} \quad (11)$$

with correction for the added volume:

$$[R]_0 = [R]_0^n V_{end}/(V_{end} - V_0) \quad (12)$$

$[R]_0^1$ is obtained for cd = 20% and $[S]_0^1 = [S]_0$, neglecting the small volume increase after the first addition

$$[R]_0^1 = 0.2[S]_0 + 0.25K_D \quad (13)$$

$$\alpha = [R]_0^1/[S]_0 \quad (14)$$

$$\beta = [R]_0^n/[S]_0^n \quad (15)$$

The program requires as input estimated values for K_A, V_0, V_{end}, and n and then calculates the necessary $[R]_0$, $[S]_0$, and V_i. These can then be modified according to technical requirements such as spectroscopically desired concentrations, solubilities, after which the program furnishes the resulting values for α and β.

The above deduction is given for the case of added R to a fixed amount of S and for the observation of a change of the spectroscopic x parameter of S; a similar treatment holds for the vice versa case. The calculations were carried out with suitable PASCAL programs on different microcomputers, which also allow for a visual inspection of the simulated regression curve with the experimental points.

Fluorescence titrations (Table I, 1–12) were carried out as described earlier.[32c] For NMR titrations based on earlier, less-optimized numerical evaluations of x and K,[32b] the following concentration ranges were used (in 10^3 M units, the values given refer always to lower/upper concentration, first for the receptor [R], then for the substrate [S]): **naphthalene**, 13 (20% MeOH) 1.52/8.33, 0.39/0.71; 14 (50% MeOH) 0.39/8.83, 1.08/1.90; 14 (80% MeOH) 36.4/189, 1.02/1.76. For all other NMR and UV titrations (Table I) the concentrations used were those evaluated by the calculational procedure described above with $\alpha \cong 20\%$ and $\beta \cong 80\%$ complexation based on K values close to the finally obtained constant; typical concentrations are described elsewhere.[32c,35b] NMR signals were used with $0.1 < CIS < 1.6$ ppm; they have been reported partially[32b,c,35] or will be described in the context of conformational studies on these complexes. Typical changes (Δx) of apparent extinction coefficients obtained in the UV titrations were for $DNNO^-$ (Table I, 16, at λ = 438 nm) $\Delta\epsilon$ = 2070; for $PNPO^-$ (Table I, 26–30 at λ = 400 nm) $\Delta\epsilon$ = 2680.

The approximate method (see p 5) was used only for the evaluation of some salt effects (5–7, 10–13 in Table III), as here the ionic strength would change too much during the NMR titration, and the CIS values could be determined directly in view of the strong complexes.

Isotope effects, possibly originating from the use of deuteriated solvents for the NMR measurements, were in one experiment shown to be below the error in K,[32c] in agreement with the literature.[26,43] The instruments used were as follows: Bruker AM 400 for 400-MHz ^1H NMR analysis; Perkin-Elmer MPF-44A for fluorescence analysis; and Kontron Uvikon 860 for UV analysis.

Compounds were either commercially available or prepared as described in the literature (**1**,[32a] **3**[35]).

Acknowledgment. This work was financially supported by the Deutsche Forschungsgemeinschaft, Bonn, West Germany, and the Fonds der Chemischen Industrie, Frankfurt, West Germany. We sincerely thank Dr. M. H. Abraham for a fruitful exchange of ideas on a general hydrophobicity scale and for making corresponding data available to us prior to publication.

Registry No. 1, 92901-70-7; **2**, 10016-20-3; **3**, 102682-60-0; ANS, 76402-43-2; DNSA, 1431-39-6; $DNNO^-$, 55154-12-6; PNPA, 830-03-5; $PNPO^-$, 14609-74-6; $^+NEt_4Br^-$, 71-91-0; naphthalene, 91-20-3.

(43) Cf. Wilhelm, E.; Battino, R.; Wilcock, R. J. *Chem. Rev.* **1977**, *77*, 219.