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Self-Association of Water and Water−Solute Associations in Chloroform Studied by NMR Shift Titrations[†]

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Association constants and the corresponding free energies Δ*G* were obtained by nonlinear least-square fitting of the water ^{1}H NMR shift changes observed at different concentrations. The only until now available earlier value (Shaw, J.-H. L.; Wang, S. M.; Li, N. C. *J. Phys. Chem.* **1973**, *77*, 236) is shown to be based on erraneous evaluations and on inaccurate data. Analysis for the self-association of water in chloroform based on a 1:1 dimer model yields $\Delta G = -3.5$ kJ/mol; based on a trimer model one obtains an almost equally good fit with $\Delta G = -15.4$ kJ/mol. The Δ*G* value in acetonitrile as solvent is with +9 kJ/mol positive (vide infra) as are all Δ*G* values observed for water−solute associations in chloroform with DMF, DMSO, diphenyl sulfoxide, and benzene, with the exception of HMPT (hexamethylphosphotriamide) and a special diamide designed to take up water by 2 hydrogen bonds. The complexation induced shifts, determined simultaneously from the NMR titrations, are between 3 and 4.5 ppm. They are similar to those observed with hydroxy compounds and show that the simulations are based on realistic models. No correlation is found between the CIS and the corresponding Δ*G* values. The only upfield shift with −4.4 ppm is found for the benzene−water complex, in agreement with theoretically derived structures.

Introduction

Self-association of water in lipophilic solvents has received until now little attention, although it can play an often decisive role for hydrogen-bonded supramolecular complexes. The same holds for corresponding interactions of water with solutes; the few available investigations[2] already show that water can interfer substantially with host−guest complex formation. Even the presence of only 3% methanol in CCl_4 lowers association constants of diamide-type structures[3] from $K = 10^4$ to below 10.

NMR titrations, based on established techniques,[4] offer a convenient way to obtain new and practically useful numbers on association constants or free energies Δ*G* . We found them to lead to results which are partially in significant contrast to published data or predictions. An advantage of the NMR method using instruments with higher sensitivity is that one can measure association constants as low as 10^{-4} M^{-1} or as high as 10^4 M^{-1}, limited only by solubilities and the necessary NMR spectrum accumulation time. The measurements were essentially restricted to chloroform as solvent in view of the necessary minimum concentrations of water for the observation of its NMR signals. This prohibited measurements in more inert solvent such as carbon tetrachloride, in which the majority of many earlier, mostly IR-based investigations were performed.[5,6] Even the large compilations of Abraham[5] and Raevsky[6] et al. contain relatively few data on associations with water. The present study was initiated also with the intend to improve the experimental basis for the prediction of corresponding equilibrium constants.

Results

Self-Association of Water. The self-association of water in $CDCl_3$ has been investigated by NMR already over 30 years ago.[7] A major purpose of the present paper is to correct the results of this early investigation, which suffers not only from necessarily larger technical problems but also, in our view, from misinterpretation of the reported shielding variations. If we evaluate these (given in Table 1 of ref 7a) with the usual nonlinear least-square fit procedures (see experimental and computational details) we obtain for the assumed[7] 1:1 association an equilibrium constant of, e.g., $K = 8.6$ M^{-1} (at 306 K), which is about 20 times higher than that reported.[7a] Noticeably, the fit for these data is at least as good with our reevaluation (Figure 1a) as in the original paper.

The underlying assumption of dominating water dimers might not be correct, even though the data fit perfectly to the model. Various structures have been proposed for water associations in lipophilic solvents. Earlier workers believed that water dissolves in aliphatic and aromatic hydrocarbons and CCl_4 primarily as monomer,[8] whereas in slightly polar solvents such as partially chlorinated hydrocarbons water was described as somewhat polymerized (reported formation constant of the trimer in tetrachloroethane:[9] 2−5 L^2 mol^{-2}). On the other hand, dimerization constants[7a,10] were reported to be around 0.5 mol/L. In contrast, a multitude of theoretical and spectroscopic investigations for which we cite only leading references[11] are predicting cyclic trimers to be particularly stable in the gas state. These studies allowed detailed insight into the structures not only of associations between water[11] but also of water with several simple acceptor molecules.[12] On the other hand, there is a scarcity on thermodynamic data for these equilibria from many of these spectroscopic studies. NMR measurements should allow convenient access to such missing affinity data. In contrast to complexes with organic molecules, NMR studies give in the present case little insight into the structure or even stochiometry of these simple but in comparison to larger organic or biological rather featureless complexes.

For the water dimer association in $CDCl_3$, we obtain on the basis of a simple 1:1 model an equilibrium constant of 4.1 L/mol corresponding to $\Delta G = -3.5$ kJ/mol (Table 1), with a fit without systematical deviations (Figure 1b). Care was taken that any phosgene content in the chloroform solutions will not by

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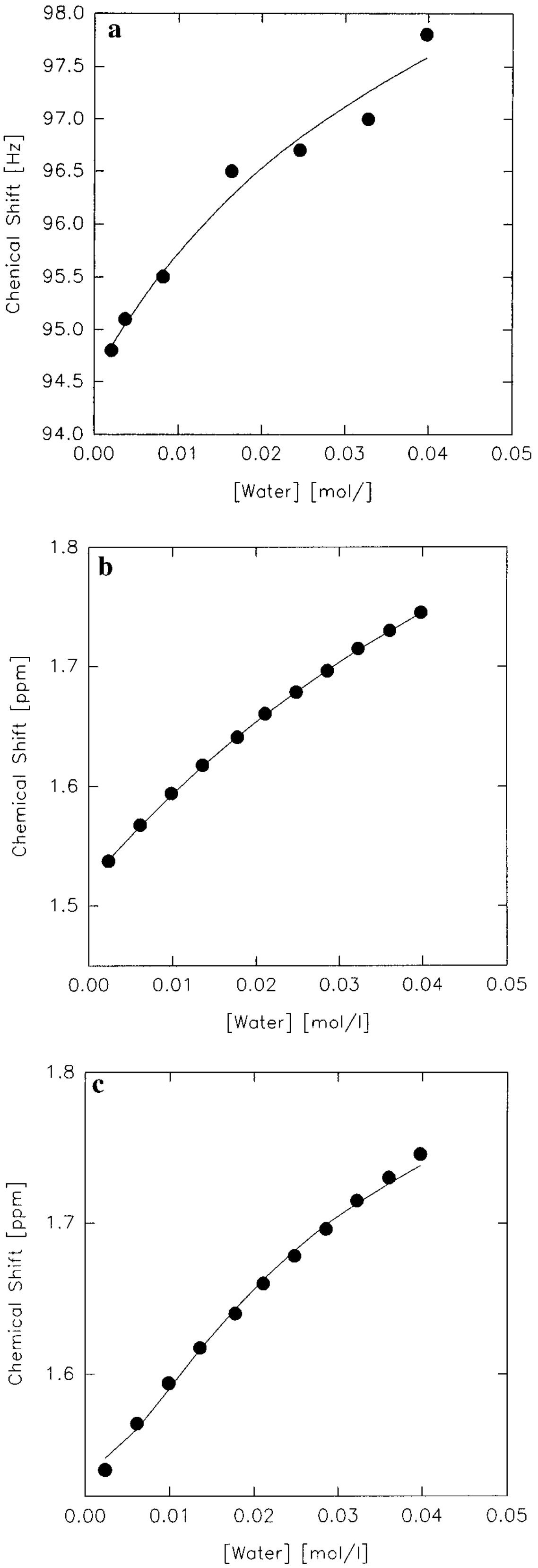

Figure 1. Experimental H NMR shifts of water protons and nonlinear least-square fit for self-association of water: (**1a**) reevaluation of literature data;[7a] (**1b**) with new data, fit based on dimer model; (**1c**) with new data, fit based on trimer model.

liberation of free HCl interfere with the measurements (see Experimental Section).

For the theoretically preferred[11] trimer we obtain an association free energy Δ*G* = −15.4 kJ/mol (Table 1). That the simulations on the basis of both the dimer and the trimer model

TABLE 1: Self-Association of Water in Chloroform: Free Energies of Association Δ*G* and Association-Induced NMR Shifts CIS (from NMR Titrations at 298 K; for Structures See Scheme 1)

	ΔG [kJ/mol]	CIS [ppm]	ΔG [kJ/mol]
1. in CD_3CN[a]	+9.14	+3.8	
2. in $CDCl_3$[a]	−3.53	+3.9	
3. in $CDCl_3$[b]	−15.4	+4.4	
3. in CCl_4[c]			+0.66 calc[c]
4. in CCl_4[c]			+0.66 calc[d]
5. in CCl_4[e]			+0.62 calc[e]
7. in CCl_4[h]			−1.95 exp[h]
8. in gas phase[i]			+6.58 exp[i]

[a] Fitted to a dimer model. [b] Fitted to a trimer model. [c] From factor values: see ref 5. [d] From factor values: see ref 6. [e] From factor values: private communicaton from C. Laurence. [f] From LFER: Coetze, J. F. *J. Solut. Chem.* **1982**, *11*, 395. [g] IR results: private communication from C. Laurence. [h] IR result: Magnusson, L. B. *J. Phys. Chem.* **1970**, *74*, 4221. [i] Gas-phase result: Curtiss, L. A.; Blander, M. *Chem. Rev.* **1988**, *88*, 827.

are realistic is also visible in the complexation-induced NMR shifts (CIS values for 100% complexation); the observed deshielding as consequence of the hydrogen-bond formation is close to CIS values observed with other hydroxylic functions.[15] As pointed out by a referee, the CIS values are in fact unexpectedly large in view their being the average of bound and "free" water protons. However, if one proton is involved in a hydrogen bond, the other one is likely deshielded also as consequence of the charge depletion at the oxygen brought about by the primary hydrogen-bond interaction. In addition we note that the CIS values are susceptible to larger errors than the equilibrium constants *K*, not only due to their sensitivity against acid traces[15] but also due to the fact that solubility problems limit the titrations to points far from saturation (see figures).

The free energies of complexation Δ*G* for the dimer and the trimer model are not as far apart as it might seem: if the dimer contains one hydrogen bond and the trimer three, as suggested by theoretical studies,[11] one would arrive at a value of approximately 4 kJ/mol for one hydrogen bond for both structures. The higher value for the trimer model, which would oppose larger entropy disadvantages, can be due to a higher acidity and basicity of water molecules already involved in hydrogen bonding.

The Δ*G* for self-association drops drastically from $CDCl_3$ to acetonitrile as solvent (Table 1), which is in accord with the known hydrogen-bond acceptor factor values for this solvent . A value of Δ*G* = 12.9 kJ/mol can be calculated for the free energy of the water/acetonitrile association from published factor values in CCl_4;[5] in comparison one calculates from factor values for water/$CHCl_3$ 6.3 kJ/mol. The available factor values allow for water/water interactions only the prediction with CCl_4 as solvent, which for solubility reasons is not accessible to NMR titrations. The resulting Δ*G* values are partially at substantial variance with the numbers derived from NMR titrations (Table 1).

Association of Water with Simple Solutes. The observed affinities of water (presumably in the form of a trimer, see above) to simple hydrogen-bond acceptor molecules (Scheme 1) show little agreement with published data for CCl_4 as solvent (Table 2) . For all solutes a satisfactory fit was obtained for a simple water/solute (1:1) model (Figure 2), which led us to refrain from simulations based on other, more extended models. Again, the CIS values obtained from the 1:1 simulations support that the model was not unrealistic. The deshielding is in a similar range as that observed with water self-association (Table 1) and with complexes involving hydroxy compounds and other,

SCHEME 1: Water Dimer (1) and Trimer (2) Models from Literature,[17] Water−Benzene Complex (3)[17] and (4−9) Structures of Other Acceptors

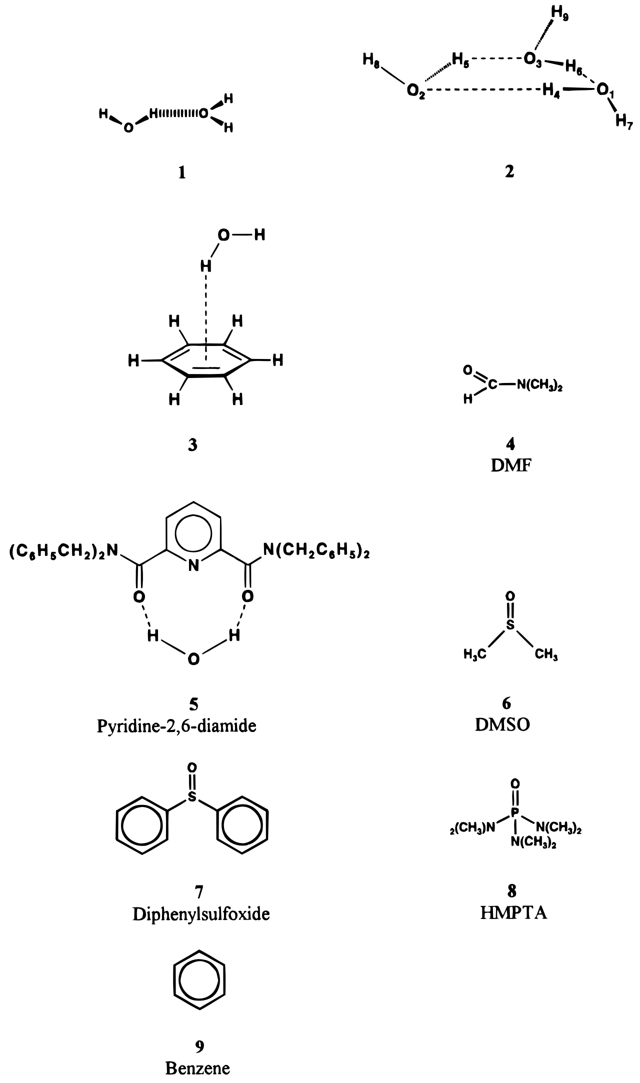

TABLE 2: Associations[a] with Water as Donor[j] with several Solutes (from NMR Titrations at 298 K; for Structures See Scheme 1)

	in $CDCl_3$		in CCl_4		
	ΔG [kJ/mol]	CIS[ppm]	ΔG [kJ/mol]		
$(Me_2N)_3PO$	−2.06	+3.9	-8.3^c	-8.4^d	-9.4^g
pyr−diamide	−0.27	+3.1			
DMF	+0.55	+3.9	-3.8^c	-3.5^d	-3.2^g
DMSO	+0.71	+3.7	-5.2^c	-5.2^d	-5.2^g
Ph_2SO	+1.1	+3.7	-3.53^c		
C_6H_6	+10.4	−5.8	$+4.05^c$	$+5.19^d$	

[a] Footnotes *a*−*g* as in Table 1. [j] With $[H_2O]$, $(3-6) \times 10^{-3}$ M.

partially ionic receptors.[13c] As observed earlier[13c] there is again no correlation between the CIS values and the strength of a hydrogen bond as far the latter is depicted by the corresponding ΔG values. Noticeably, only hexamethylphosphortriamide (HMPT, Scheme 1), which is known to be an excellent hydrogen bond acceptor, gives a negative ΔG value (corresponding to >50% complexation under standard condition in 1 M solution) except the special pyridinediamide **5** (see Scheme 1), which was designed to complex a single water molecule by strainfree 2-fold hydrogen bonding.

Benzene is the only solute producing with CIS = −4.4 ppm a substantial *shielding* on the water proton which is only slightly lower than the largest values (around 5 ppm) observed and calculated for a single proton being as close as possible above the center of aryl groups in cyclophanes.[16] This suggests that water protons are located in tight contact to the π-moiety without significant contributions of conformers in which water oxygen atoms would serve as acceptor for the slightly polarized benzene protons. Such a structure (see Scheme 1) is is in good agreement with theoretical[17] and experimental[18] results. The CIS value, which is unusually high also in view of the fact that it reflects the time averaged shift of all water protons, suggests that in addition to the ring current anisotropy effect there is disruption of water hydrogen bonds in dimers or trimers, or to the solvent, by the benzene acceptor, which enhances the total CIS value significantly.

Experimental and Computational Details

The solutes and solvents were commercially available except the diamide **5** (see below); they were purified and dried according to literature procedures.[17] Water and solute concentrations were measured/checked by NMR integration, using internal reference compounds (1,1,1-trichloroethane and 1,4-dioxane) of known concentrations.

That phosgene in chloroform, which was used as purchased from Aldrich without stabilizer, did not interfer in the titrations was secured by measuring acidity from chloroform after extraction with water: mixtures of chloroform and water (5:1 v/v) were for removal of CO_2 degassed by bubbling through nitrogen and during 10 h deliberately exposed to daylight which is known to lead to phosgene traces. The pH of the water solution then was 5.0 (corresponding to 1.0×10^{-5} M H^+); in comparison, water treated the same way but not with chloroform showed a pH of 6.2 (6.7×10^{-7} M H^+). Thus, the *maximum* proton concentration in the solutions, which contained on the average 1 mM water, was well below 1% of the proton concentration stemming from water.

Pyridine-2,6-bis(*N*,*N*-dibenzyl)diamide (5): 2 g (9.8mmol) of pyridine 2,6-dicarboxylic acid and 2.2 g (10.8 mmol) of PCl_5 were refluxed for 12 h with 100 mL of freshly distilled thionyl chloride. The excess thionyl chloride was evaporated, and the remaining oil was flushed twice with 50 mL of dry toluene in order to remove unreacted thionyl chloride. At 0 °C the acid chloride was added dropwise to a mixture of 3.87 g (19.6 mmol) of dibenzylamine and 4.5 mL of triethylamine in 100 mL of dry methylene chloride. After 5 h of stirring at room temperature, the organic phase was washed three times with 100 mL of water. The methylene chloride solution was dried over K_2CO_3 and evaporated. The resulting brown oil was purified by column chromatography (SiO_2/ethyl acetate). The diamide cristallized on addition of dry ether. The R_f value on silica gel TLC with EtOAc is 0.64; white powder; mp 182−184 °C.

^1H NMR ($CDCl_3$) δ (ppm) 7.88 (1H, t, $^3J = 7.72$ Hz, Pyr-4-H); 7.76 (2H, d, $^3J = 7.79$, Pyr-h-3,5); 7.31−7.08 (m, 20H, Ar-H); 4.63, 4.45 (2s, 2 × 4H, benzyl−CH_2 cis + trans isomer around amide bond). ^{13}C NMR ($CDCl_3$) δ (ppm) 168.6 (C=O); 153.0 (Pyr C2, C6); 138.2 (Pyr C4); 136.59, 136.40 (Phenyl-C1, cis + trans); 124.8 (Pyr-C3, C5); 128.6§ (phenyl-C2); 128.3§ (phenyl-C3); 127.4 (phenyl-C4); 51.1, 47.65 (benzyl-CH_2, cis + trans) [§: assignments interchangeable].

Anal. Calcd for $C_{35}H_{31}N_3O_2$: C, 79.97; H, 5.94; N, 7.99. Found: C, 79.30; H, 5.75; N, 7.97.

NMR measurements were carried out with Bruker AM400 and DRX 500 systems at 298 K.

NMR Shift Titrations. (a) For the dimer model: Calculation by nonliner least-squares fit using the program Sigmaplot from

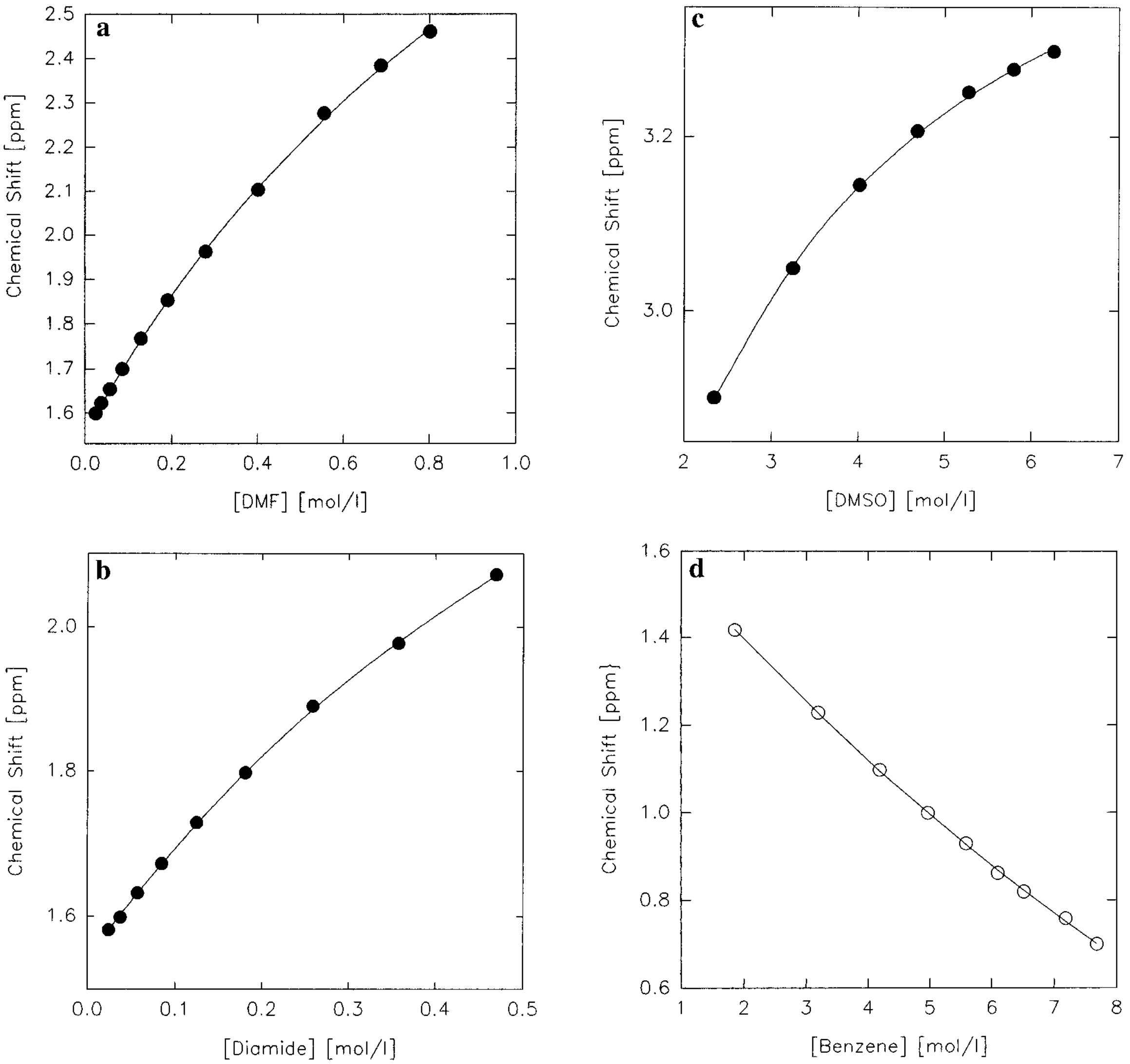

Figure 2. Experimental H NMR shifts of water protons and nonlinear least-squares fit for associations of water with several solutes: (**2b**) with DMF **4**; (**2b**) with pyridinediamide **5**; (**2c**) with DMSO **6**; (**2d**) with benzene **9A** (for structures see Scheme 1).

Jandel (Marquardt–Levenberg algorithm), based on equations for self-association:

$$C_d = (1 + 4C_0K_a)/8K_a - b$$

$$b = (((1 + 4C_0K_a)/8K_a)^2 - C_0^2/4)^{1/2}$$

$$d = (C_0 - 2C_d)d_m/C_0 + C_dd_d/C_0$$

where C_d = equilibrium concentration of dimer; d_m = shift of monomer; d_d = shift of dimer; K_a = association constant; C_0 = analytical concentration; d = observed shift.

(b) For Water–Solute Interactions:[3]

$$d = d_S + Dd/2S_0[K_d + R_0 + S_0 - \{(K_d + R_0 + S_0)^2 - 4R_0S_0\}^{1/2}]$$

where d = observed shift; d_S = shift of observed compound before complexation; S_0 = concentration of observed compound; R_0 = concentration of added compound; Dd = complexation induced shift (CIS); K_d = dissociation constant = $1/K_a$.

(c) For the Trimer Model: The formation constant for the water trimer was fitted by Monte Carlo optimization using the program Chem Equi from Dr. Vitaly P. Solo'vev, IPAC, Chernogolovka, Russia.

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