Solvent and Structural Effects on Hydrogen Bonds in Some Amides and Barbiturates. An Additive Scheme for the Stability of Corresponding Host-Guest Complexes[1)]

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Received January 23, 1989

Key Words: Amides / Barbiturates / Hydrogen bonds / Linear free-energy relations / Solvent effects

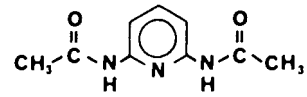
NMR shift titrations with 2,6-diacyldiaminopyridines as well as with the parent benzene derivative and barbiturates indicate strong hydrogen bond attenuation by steric hindrance, by flexible side chains, and by chloroform as solvent. Analysis of unhindered associations and of corresponding host-guest complexes reported in the literature shows a linear correlation of complexation free energy ΔG^0 with the number n of hydrogen bonds for $n > 1$, which amounts to $\Delta G^0 = (5 \pm 1)$ kJ/(mol · n) in $CDCl_3$; this value is expected to increase in carbon tetrachloride to $\Delta G^0 \approx 10$ kJ/(mol · n) as judged by extrapolation from 2 measurements.

Intermolecular hydrogen bonds are of paramount importance not only for biopolymers and their function, but also for the construction of organic host compounds which are capable to bind suitable guest molecules in organic solvents. The elegant systems designed by e.g. Hamilton[2)], Rebek[3)], Still[4)], and their collaborators have already led to strong and selective complex formation by the implementation of several hydrogen donor and acceptor functions in complementary positions.

In line with our efforts to understand and to predict noncovalent interactions in supramolecular systems on a quantitative and general basis, we recently have found a simple additive scheme for electrostatic interactions, essentially based on the number of ion pairs in different host-guest complexes in aqueous solution[5)]. We wanted to see whether a similar approach would be possible for complexes involving intermolecular hydrogen bonds of amides, imides, or barbiturates. At the same time it was felt to be necessary to take into account self-association of substrates, which hitherto has been analyzed only occassionally[6)], as well as the solvent dependence of the association constants. Most of the recently reported measurements[2-4)] were performed in chloroform ($CDCl_3$) which is known[7)] to complex amides with association constants of $K \approx 1$; as a result the substrates used in earlier studies[2-4)] will be present largely as chloroform complexes and not in free form.

The substrates for our measurements were chosen to enable the simultaneous formation of up to 2 hydrogen bonds of the amide type (Scheme 1). Complex titrations were carried out similar to procedures described earlier, as far as possible in a range of 20–80% complexation[8)], by following N–H proton NMR shifts, in some cases also C–H proton shifts. Calculations were performed as outlined earlier[8)], or – for weaker complexes – using a program CHEMSIM[9)], which carries out a nonlinear least-square curve fit with consideration of the independently determined self-association (Table 1). The complexation-induced NMR shifts (CIS, intrinsic values for 100% complexation) obtained simultaneously with the equilibrium constants K from the computer simulations were 1.7–4.6 ppm for N–H, and only up to 0.15 ppm for C–H protons; the latter nevertheless rendered similar constants K as the N–H protons.

Scheme 1



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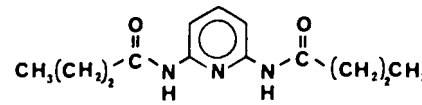

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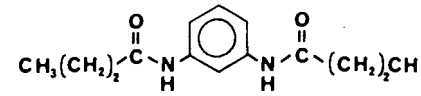

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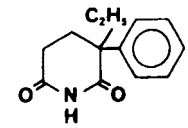

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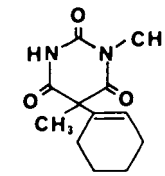

5

Table 1. Complexation constants K [M^{-1}] for compounds **1**–**5**[a)]

	In $CDCl_3$	In CCl_4
1 + **4**	200	[b)]
1 + **5**	200	[b)]
2 + **4**	155	3000
2 + **5**	120	1900
3 + **4**	5.8	[b)]
3 + **5**	4.4	[b)]
4 + **4**	0.8	4.1
5 + **5**	4.0	25

[a)] At 295 ± 5 K. – [b)] Not measurable due to limited solubility.

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Literature values for the free energy ΔG^0 observed for *one* single amide hydrogen bond formation vary substantially[10], depending on the environment, and possibly also on the methods used. ΔG^0 values reported for the *N*-methyl acetamide association in carbon tetrachloride are e.g. 4[10b], or 7 kJ/mol[10c]. The association constants for complexes discussed in this work which contain *several* hydrogen bonds are considerably higher as expected on the basis of the older value for a single interaction[10]. Thus, the constants observed for the complexes of the diacetyl diaminopyridine[11] **1** with the barbiturates **4** and **5** correspond to $\Delta G^0 = 13$ kJ/mol in chloroform, completely in line with earlier measurements[2,3] with host compounds which also can materialize 2 hydrogen bonds simultaneously. In the inert solvent carbon tetrachloride the equilibrium constants increase by a factor of 10 to 20, as seen by measurements with **2** and **4** or **5** (Table 1). (Due to insufficient solubility such a comparison was not possible with **1**.) This would correspond to $\Delta G^0 \approx 10$ kJ/mol for *one* hydrogen bond in an inert solvent such as carbon tetrachloride. The decreasing association observed with the butyramide **2** compared to the acetamide **1** can be ascribed to the larger entropy disadvantage involved in the complex formation for the longer alkyl chains in **2**.

Diaminobenzenes **3** – in contrast to the corresponding pyridines **1**, **2** – could also in principle materialize 2 amide-type hydrogen bonds. The observed constants, however, are much lower (Table 1) than expected on this basis. Inspection of molecular models reveals, that this is obviously a consequence of the central C2–H bond in **3**, which pushes the acceptor molecules **4** and **5** in the complexes so far away, that either only 1 hydrogen bond of normal length or 2 weak bonds of extended length are possible.

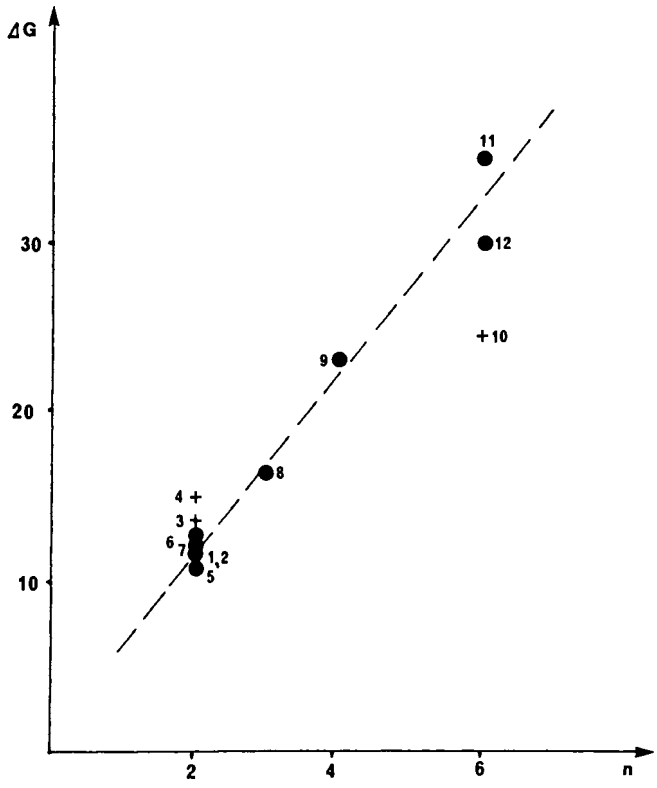

Figure 1. Complexation free energies ΔG^0 [kJ/mol] as a function of the number *n* of hydrogen bonds. Data for points 1–5, 9: from ref.[3]; for 6, 7: from Table 1; for 8, 10–12: from ref.[2]; + + +: points deviating by additional stacking[3] (3, 4) or by entropy disadvantages in open-chain compounds (10)[2]. Slope of the least-squares regression line 5.2 kJ/mol · *n*; $r = 0.9877$; reliability $\Psi = 3\%$

In conclusion, one can expect an additive scheme in which complex stabilities are essentially a function of the number of hydrogen bonds only under the condition, that (a) solvent effects are similar, (b) differential steric or entropy effects can be neglected, and (c) an optimal approach of donor and acceptor is possible. If we examine the amide complexes reported in the literature[2,3] together with corresponding values from Table 1 by comparing the complexation free enthalpy ΔG^0 obtained in chloroform solutions with the number *n* of possible hydrogen bonds, we find a quite linear correlation (Figure 1) yielding an average apparent value in chloroform solution of 5 ± 0.5 kJ/mol per hydrogen bond. Deviations from the regression line, although being usually quite small, indicate additional binding effects, e.g. by stacking[3], or destabilization, e.g. in cases where flexible open chains[2] are involved. It should be kept in mind that the increment of $\Delta G^0 = 5$ kJ/mol contains the competition to chloroform as solvent and can increase to ca. 10 kJ/mol in inert solvents such as carbon tetrachloride, although for the barbiturate self-association a smaller enhancement is observed (Table 1).

The additivity of interaction energies in systems with multiple hydrogen bonds holds promise for the predictability of corresponding complexes, particularly in view of the recent success in the correlation of hydrogen bond energies between different donor and acceptor functions[12]. The application of regular increments for amide hydrogen bonds is furthermore essential for computer-aided structure and binding analysis of proteins as well as for their modification by genetic engineering[13]. The strong hydrogen binding decrease even with a weak donor as chloroform is in line with earlier conclusions[14], that in the presence of water such associations in proteins are only entropy-driven. In contrast, *negative* entropy contributions of quite varying degree have been found in many studies of amides or related complexes in nonprotic solvents[10,15], which in the presented ΔG^0 correlation for amides in chloroform obviously remain either constant, or cancel enthalpy variations.

CAS Registry Numbers

1: 5441-02-1 / **2**: 101630-92-6 / **3**: 25227-76-3 / **4**: 77-21-4 / **5**: 56-29-1

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