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Stabilities of Hydrogen-Bonded Supramolecular Complexes with Various Numbers of Single Bonds: Attempts To Quantify a Dogma in Host–Guest Chemistry**

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It is generally accepted that optimal preorganization for molecular recognition requires an optimal geometric fit between convergent binding sites A(H), A′(G), B(G), B′(G), etc. of host and guest molecules H and G.[1] If binding sites within host and/or guest are connected by single bonds, this can give rise to enthalpy or strain penalties if a transoid fragment must convert into a *gauche* conformation for an optimal orientation of binding sites. At the same time the presence of freely rotatable single bonds can lead to a loss of rotational freedom on complexation, which is generally regarded as a major drawback of, for instance, open-chain versus macrocyclic receptors. However, systematic analyses of complexes with crown and open-chain poly(ethylene glycol) ethers show that the formation of macrocyclic hosts is based to a large degree on enthalpy advantages (macrocyclic effect).[2]

Entropic contributions to the formation of noncovalent bonds are one of the most often invoked problems in molecular recognition, and until now they were among the least predictable factors. Systematic analyses of free energies of association ΔG_{cplx} of many supramolecular associations show little dependence of ΔG_{cplx} on the presence of single bonds in either host or guest molecule, and $\Delta\Delta G_{\mathrm{cplx}}$ contributions from the different binding sites are generally additive.[3] However, most of the investigated complexes were constructed so as to avoid the presence of many freely rotatable bonds. This also holds for the few studies of noncovalent intramolecular interactions, which also show little strengthening upon rigidification of the underlying frameworks.[4] In the gas phase one expects rotational entropy contributions ΔS_{rot} of 13–21 J mol^{-1} K^{-1} per single bond.[5, 6] If the rotations were completely frozen upon complex formation, which is expected only if rigid covalent bonds are formed,[6] the corresponding loss of free energy $\Delta\Delta G_{\mathrm{rot}}$ would be 3.9–6.4 kJ mol^{-1} at room temperature. For noncovalent interactions Williams et al. assume a value between 2 and 6 kJ mol^{-1} per restricted bond.[7]

Unfortunately these numbers translate into a large uncertainty of prediction. The presence of only two nonrestricted bonds[8] in host and guest would correspond to differences in the association constant K of between 2 and 11 M^{-1}. Therefore, it seems to be essential to obtain experimental values for the change of free energy ΔG_{cplx} associated with the presence of single bonds in host–guest complexes. Surprisingly, there were no studies till now in which the number of single bonds in supramolecular complexes was systematically varied. We chose a series of α,ω-diamides as hydrogen-bond donors[9] and α,ω-dicarboxylates as acceptors.[10] The tetrabutylammonium salts of the latter are soluble in chloroform. The functional groups were connected by spacers of different length and flexibility (Scheme 1). The advantage of these chloroform-soluble compounds is that interactions other than hydrogen bonds are suppressed, and problems in the measurements, such as self-association and salt effects, are minimized.

The initially prepared amides of long-chain fatty acids were only sparingly soluble in chloroform, probably owing to strong dispersive interactions between the alkyl chains in the solid state. Therefore, derivatives with the bulky and more spherical adamantyl group were prepared from the corresponding adamantyl acid chloride and, as expected, were sufficiently soluble in chloroform. Dilution experiments with these amides in $CDCl_3$ in which the chemical shift of the NH protons was monitored gave dimerization constants $K < 30$ M^{-1}, so that at least 85 % of the monomer was present in the observed concentration range ($\leq 5 \times 10^{-3}$ M). Equilibrium constants were determined according to ref. [11] and gave a satisfactory fit to a 1:1 model for the association between host and guest monomers (e.g., Figure 1). The spacers were chosen to allow contact between the corresponding binding sites without buildup of substantial strain; this was checked by computer-aided molecular modeling (Figure 2). All amide groups and the alkyl chains can retain their transoid

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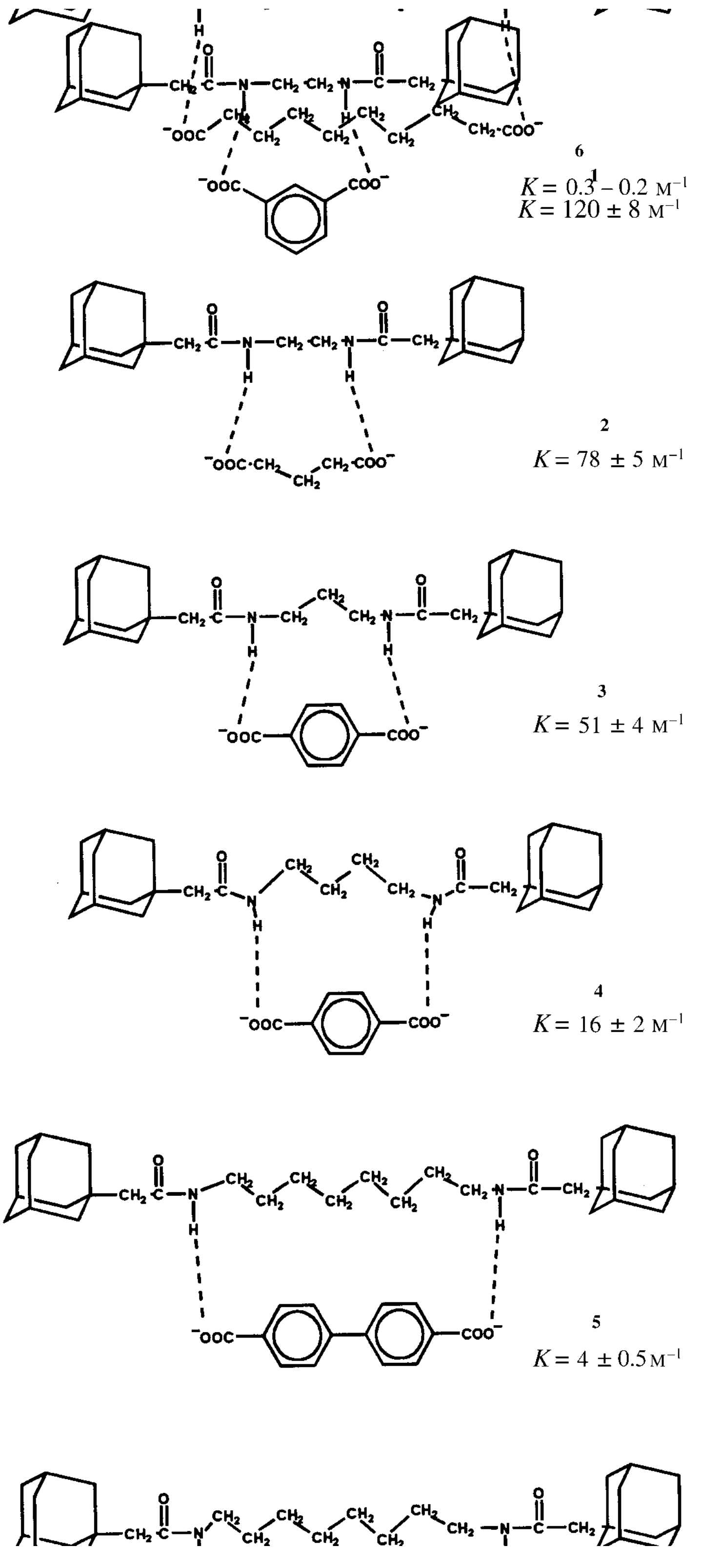

Scheme 1. Structures and association constants of complexes **1**–**6** in $CDCl_3$ at 298 K.

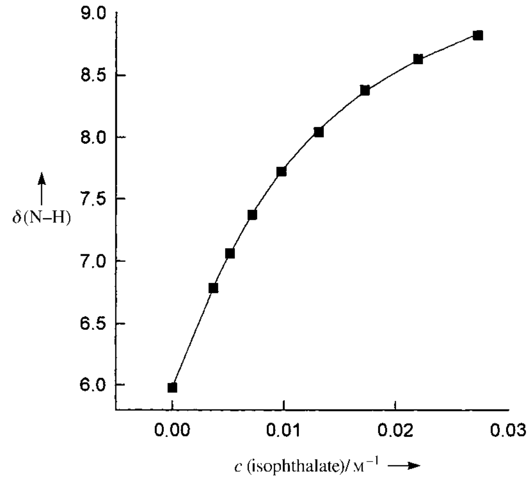

Figure 1. Experimental (dots) and calculated (line) chemical shifts of the NH protons in the titration of **1** in $CDCl_3$.

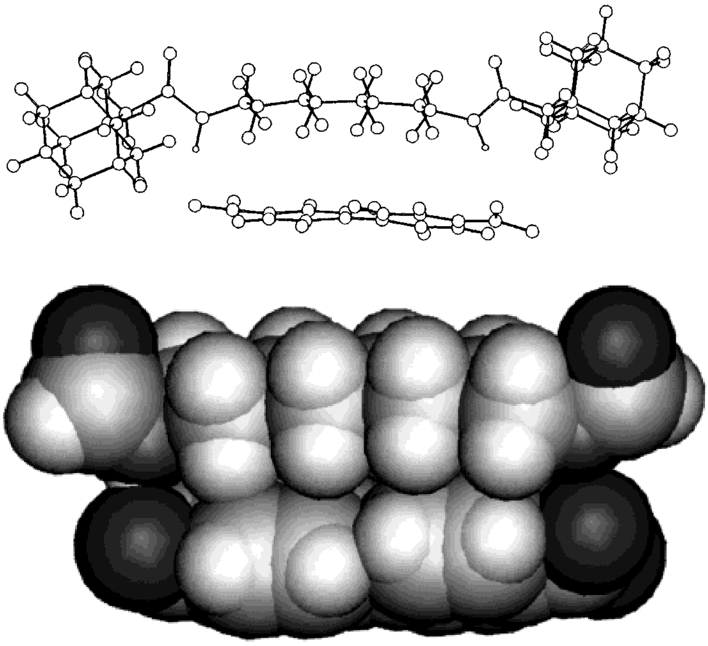

Figure 2. Quanta/CHARMm Structure of **5**. For the sake of clarity, the adamantyl groups are omitted from the space-filling model.

conformations on complexation. The chemical shifts of the NH protons at 100% complexation (complexation-induced shift, CIS), obtained by nonlinear least-squares fitting, were consistent and agreed with published CIS values for the deshielding of these protons in other amide associates.[10a, c, e, 12]

The measured ΔG_{cplx} values (Table 1) show a remarkably small decrease with increasing flexibility of the spacer between the binding sites. Thus, **1** and **2** (Scheme 1) differ only by 10% in complexation free energy, although **2** has two more rotatable bonds than **1**. Similarly small differences are found for the other complexes. Only if the number of single bonds n in both host and guest is increased to nine, that is, a total of 18 (**6**), does the association constant become too small to be obtained from a titration curve. It was therefore estimated by comparison of the observed NH chemical shifts with other CIS values.

Table 1. Experimental and calculated data for complexes **1**–**6**.

Complex	ΔG_{exp} [kJ mol^{-1}] (±5%)	n	ΔG_{calcd}[a] [kJ mol^{-1}]	pK_a[d]	ΔG_{calcd}[b] [kJ mol^{-1}]	CIS (±3%)
1	−11.9	3	−11.1	4.62	−11.9	3.9
2	−10.8	7	−7.1	5.41	−10.4	3.2
3	−9.7	4	−10.1	4.34	−9.3	3.1
4	−6.7	5	−9.1	4.34	−8.0	4.0
5	−3.4	9	−5.1	4.31	−2.6	3.9
6	+2.8–3.9[c]	18	+3.7	5.54	+3.4	3.1–4.0[c]

[a] $\Delta G_{calcd} = n \cdot 0.99 - 14.1$; $r = 0.941$. [b] $\Delta G_{calcd} = 6.14 + 1.31 \cdot n - 4.78 \cdot$ pK_a. Plot: $\Delta G_{calcd} + 4.78 \cdot$ p$K_a = 6.14 + 1.31 \cdot n$; $r = 0.995$. [c] Calculated from the NH shift at the highest possible concentration and from the highest or lowest CIS values of the other complexes. [d] From the Stability Constant Database, IUPAC and Academic Software, **1993**, Version 1.16.

The steadily decreasing ΔG_{cplx} values from **1** to **6** allow for the first time the derivation of at least an upper limit for the binding loss ΔG_{cplx} involved with the presence of single bonds. An almost linear correlation (correlation coefficient $r = 0.941$; slope $m = 0.99$) between ΔG_{cplx} and the number of freely rotatable bonds n indicates a constant additive contribution of a freely rotatable bond. If one also takes into account the CO–NH, Ph–Ph and Ph–CO bonds the correlation changes only slightly ($r = 0.973$, $m = 1.15$). Taking into account the differences in dicarboxylate basicity leads to an extended correlation of the form $\Delta G_{cplx} = s + m \cdot n + p \cdot$ pK_a. Multilinear fitting then yields $s = 6.14$, $m = 1.31$, and $p = -4.78$. Although the correlation between ΔG_{cplx} and n is improved significantly ($r = 0.995$, Figure 3), the value of $m = 1.3$ kJ mol^{-1} per single bond is close to that found without taking into account the different pK_a values and shows its relatively small influence. The intercept $s = 6.14$ leads through $\Delta\Delta G_{cplx} = 6.14 - 4.78 \cdot$ pK_a with corresponding pK_a values to association energies between −14.5 and −20.3 kJ mol^{-1}. These values are close to the typical values for interactions between two carboxylates and amides or amide-like groups in chloroform.[10a, c, d] These findings also confirm the reliability of the present analysis. The value of 1.3 kJ mol^{-1} for the loss of ΔG due to the presence of a single bond, which has been experimentally determined for the first time, is considerably lower than the previously proposed minimum values.[7]

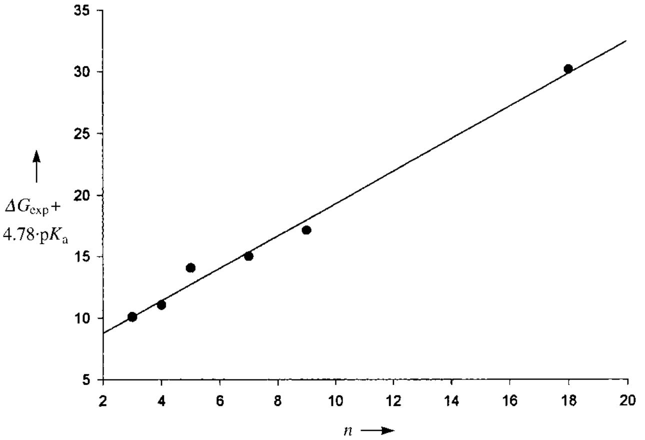

Figure 3. Plot of ($\Delta G_{exp} + 4.78 \cdot$ pK_a) versus the number of freely rotatable single bonds n. Regression: y axis intercept 6.14, slope $m = 1.31$, correlation coefficient $r = 0.995$, standard deviation 0.8.

One might expect that the entropic disadvantage will drastically increase with increasing binding strength.[6, 7] Indeed the dissociation rate constants in our relatively weak complexes approach $k = 10^6$ s^{-1} if diffusion-controlled association rates are assumed. Since rotational barriers[14] also lie in the range of $k = 10^6$ s^{-1}, dissociation of the complex would allow rotation to occur, especially as this would require only one of the two hydrogen bonds to be opened.[6, 7] However, even in much more stable complexes, such as those between transition metal ions and substituted ethylenediamines with association constants up to 10^8 times stronger than those with **1**–**6**, the presence of a rotatable bond does not substantially change ΔG_{cplx}, as exemplified by literature data[15] for complexes of **7** and **8** (Scheme 2). The relatively small sensitivity of ΔG to the presence of single bonds may partially be the result of enthalpy–entropy compensation, which seems to be typical for many noncovalent interactions.[16]

7		**8**	
ΔG [kJ M^{-1}]		ΔG [kJ M^{-1}]	
Ni^{2+}	43.6	Ni^{2+}	45.0
Cu^{2+}	64.3	Cu^{2+}	63.5

Scheme 2. Free energies of association of complexes **7** and **8** with Ni^{2+} and Cu^{2+}.[15]

That the efficiency of molecular recognition processes obviously suffers less than generally assumed from the presence of rotatable bonds is of importance for the rational design of artificial receptors and effectors. The need to reduce the number of single bonds in a host compound has become an almost unquestioned dogma in synthetic host–guest chemistry. Since single bonds can better accommodate strain arising from the induced fit between ligand and receptor, better results will generally be achieved with more flexible host compounds. The acceptable number of rotatable bonds will depend on the strength of interaction between the complementary binding sites, which in many cases will compensate any disadvantages introduced by flexible bonds. It is noteworthy that that nature has developed nearly perfect systems for molecular recognition on the basis of linear peptides containing many single bonds.

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A Gas-Phase Model for the Pt$^+$-Catalyzed Coupling of Methane and Ammonia[**]

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Dedicated to Professor Heribert Offermanns on the occasion of his 60th birthday

The activation of methane has been referred to as one of the central challenges in contemporary chemical research.[1] In addition to various academic aspects, methane activation is of eminent industrial importance. One economically attractive process is the coupling of ammonia and methane according to reaction (1) to afford hydrogen cyanide, a valuable feedstock for chemical synthesis. Reaction (1) is, however, endothermic[2] by 61 kcal mol^{-1} and the thermochemical equilibrium must be shifted to the right by appropriate means. Two concepts have been pursued in the chemical industry,[3] both of which rely on platinum catalysts.[4] In the Degussa process, reaction (1) is performed at elevated temperatures (ca. 1500 K), while in the Andrussow synthesis of HCN, molecular oxygen is added to shift the energy balance by formation of water rather than molecular hydrogen.

$$\mathrm{CH_4 + NH_3 \rightarrow HCN + 3\,H_2} \tag{1}$$

Details of the reaction mechanism of the Pt-catalyzed coupling of methane and ammonia remain uncertain.[3] Gas-phase studies can complement catalyst research by providing information about the elementary steps of bond activation and formation as well as the characterization of possible reaction intermediates. Here, we describe the reactions of atomic platinum cations with methane and ammonia examined using Fourier transform ion cyclotron resonance (FTICR) mass spectrometry.[5–7]

As has been described previously,[8, 9] bare platinum cations dehydrogenate methane to afford the platinum carbene cation $[\mathrm{PtCH_2}]^+$ with an apparent rate constant of $k = 8.2 \times 10^{-10}$ cm^3 molecule^{-1} s^{-1}.[9a] Subsequently, $[\mathrm{PtCH_2}]^+$ reacts with an excess of methane to form $[\mathrm{PtC_2H_4}]^+$ and higher $[\mathrm{PtC}_n\mathrm{H}_m]^+$ ions, but the associated rate constants are small as compared to that of reaction (2).[9a]

$$\mathrm{Pt^+ + CH_4 \rightarrow [PtCH_2]^+ + H_2} \tag{2}$$

$$\mathrm{Pt^+ + NH_3 \rightarrow [Pt(NH_3)]^+} \tag{3}$$

$$\mathrm{Pt^+ + NH_3 \not\rightarrow [PtNH]^+ + H_2} \tag{4}$$

When Pt$^+$ is allowed to interact with ammonia under FTICR conditions ($p \approx 10^{-8}$ mbar) only adducts such as $[\mathrm{Pt(NH_3)}]^+$ and subsequently $[\mathrm{Pt(NH_3)_2}]^+$ form. The association reaction (3) proceeds quite slowly ($k \approx 5 \times 10^{-13}$ cm^3 molecule^{-1} s^{-1}), even though B3LYP calculations predict an appreciable $\mathrm{Pt^+{-}NH_3}$ binding energy of 74 kcal mol^{-1}.[10, 11] Further, although dehydrogenation of ammonia to yield the NH fragment is less endothermic (101 kcal mol^{-1}) than that of methane to afford methylene (111 kcal mol^{-1}),[2] formation of $[\mathrm{PtNH}]^+$ by means of reaction (4) is not observed. While this result may be attributed to kinetic barriers, the B3LYP calculations suggest that reaction (4) is endothermic by 17 kcal mol^{-1}, and thus its nonoccurrence is a consequence of a thermodynamic restriction.

Mass-selected $[\mathrm{PtCH_2}]^+$ reacts rapidly with ammonia ($k = 6.2 \times 10^{-10}$ cm^3 molecule^{-1} s^{-1}) to form three different product ions according to reactions (5a–c) in a ratio of 70:25:5.

$$\mathrm{[PtCH_2]^+ + NH_3 \rightarrow CH_2NH_2^+ + [PtH]} \tag{5a}$$

$$\mathrm{[PtCH_2]^+ + NH_3 \rightarrow [Pt,C,N,H_3]^+ + H_2} \tag{5b}$$

$$\mathrm{[PtCH_2]^+ + NH_3 \rightarrow NH_4^+ + [PtCH]} \tag{5c}$$

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