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Molecular tweezers as synthetic receptors: the effect of pressure and temperature on the formation of host–guest complexes

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ABSTRACT: For the formation of the supramolecular complexes between the molecular tweezers **1** and **2** and the aromatic guests **3**–**5** the volumes of reaction ΔV were determined from the pressure dependence of the association constants K by the use of high-pressure ^{1}H NMR spectroscopy and the enthalpy ΔH and entropy ΔS of reaction from the temperature dependence of K. The small pressure dependence of K and, hence, the small variation of the reaction volumes around the zero value ($\Delta V \approx 0$ cm^3 mol^{-1}) clearly indicate that the contraction in volume resulting from the host–guest association is compensated for by the expansion in volume resulting from the desolvation of the free host and guest which has to proceed during the complexation. The association and desolvation are expected to have similar effects on ΔS compensating each other. The significant deviations of ΔS from the zero value are, however, good evidence that the size of ΔS not only depends on the processes mentioned above but moreover is influenced by other factors such as the conformational mobility of the guest molecule inside the receptor cavity. Copyright © 2002 John Wiley & Sons, Ltd.

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KEYWORDS: high-pressure ^{1}H NMR spectroscopy; molecular recognition; non-covalent interactions; molecular tweezers; supramolecular chemistry

INTRODUCTION

Attempts have been made to model protein folding, molecular recognition of substrates by enzymes or membrane formation in biological systems, for example, by simple synthetic receptors with molecular pockets or cavities.[1] The investigation of the structural and thermodynamic parameters of receptor–substrate (host–guest) complexes reveals the role of non-covalent interactions such as hydrogen bonding,[2] ion pairing,[3] arene–arene interactions (π–π, CH–π, cation–π)[4,5] and hydrophobic interactions in aqueous media[6] that are responsible for the formation and structure of supramolecules. In many cases the complex stability results from a favorable enthalpy of reaction ($\Delta H < 0$) whereas the entropy of reaction can be either negative ($\Delta S < 0$), as expected for an association, or positive ($\Delta S > 0$), which may be explained by the desolvation of receptor and substrate (release of solvent molecules) during the complex formation.[7] A study of reaction volumes ΔV should provide further insight into the mechanism of complex formation. A volume contraction ($\Delta V < 0$) is expected for the association, but in the case when desolvation is important in the process of complexation, the release of solvent molecules should lead to a volume expansion ($\Delta V > 0$) compensating or even overcompensating for the effect of contraction caused by the association. From these considerations, a correlation between entropy and volume of reaction can be expected. An almost linear correlation of ΔV with ΔS has been found for the dissociation of ~30 carboxylic and other acids which was related to the solvation change brought by ionization.[8]

Although the effect of pressure on the structures and reactions of biomolecules such as proteins and enzyme reactions can be very large, e.g. $\Delta V = +41.4 \pm 2.0$ cm^3 mol^{-1} for the small all-β protein tendamistat on going from the unfolded to the native state,[9] only a few studies of the pressure effect on the formation of simpler host–guest complexes have been reported hitherto. Large effects of pressure have been observed for reactions in

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which atoms or molecules are compressed into the empty cavities of container molecules so that the volume of reaction is highly negative. Examples of this are the incorporation of helium atoms into the cavity of buckminsterfullerene (C_{60}) at 2.5 kbar and 600 °C[10] and of three acetonitrile molecules into the cavity of one of Cram's hemicarcerands at 11.5 kbar and 110 °C.[11] (G. Vayner, J. Chen, K. Nakamura, K. N. Houk, A. E. Wigger and F. G. Klärner, unpublished results). Volume data were reported for the formation of host–guest complexes between crown ethers and cryptands as hosts and alkali metal ions or the *tert*-butylammonium ion as guests.[12,13] Most of the reaction volumes found for the complexation of alkali metal ions (in MeOH, MeCN or DMSO), however, are positive, which was explained by the desolvation of the cations before binding of the host can take place.[12] On the other hand, the complexation of the *tert*-butylammonium ion shows a negative volume of reaction, indicating that this lipophilic cation is not solvated in the uncomplexed state as much as the alkali metal cations. In the complex the primary ammonium cation is certainly strongly hydrogen bonded to three oxygen atoms of the crown ether, leading to a substantial volume contraction. The inclusion of C_{60} in the cavity of *p*-benzylcalix[5]arene in toluene solution reported by Isaacs *et al.*[14] is associated with a dramatic partial molar volume change of $\Delta V = +195\,\mathrm{cm^3\,mol^{-1}}$, which is consistent with the displacement of two toluene molecules from the cavity of the calixarene. Reaction volumes between -20 and $+20\,\mathrm{cm^3\,mol^{-1}}$ have been reported for the inclusion of short guest molecules into the cavity of cyclodextrins and the sequential threading of cyclodextrins on to long guests.[15,16]

We have recently reported syntheses and some supramolecular properties of receptors with a ribbon-type concave topology.[17–24] These compounds, owing to their ability to bind selectively electron-deficient aromatic and aliphatic substrates, can be regarded as molecular tweezers. This paper is devoted to the temperature and pressure dependence of the host–guest complex formation of the naphthalene-spaced tweezer **1** and the diacetoxy-substituted derivative **2**, respectively, with aromatic guests (Fig. 1). In particular, we are interested in the potential correlation between volume and entropy of reaction.

RESULTS AND DISCUSSION

The dependence of the association constant K on temperature and on pressure is given in Tables 1 and 2, respectively, and the experimental results are summarized in Table 3.

The ^{1}H NMR chemical shifts of the guest protons δ_G in the presence of host **1** and **2**, respectively, show a substantial temperature dependence (Fig. 2), whereas the temperature dependence of δ_G in the absence of **1** or **2** is relatively small. From these data, the enthalpy and entropy of reaction (ΔH and ΔS) (Table 3) are calculated as described in the Experimental section.

The pressure dependence of δ_G in the presence of **1** or **2** (one example is shown in Fig. 3) and, hence, of K (Table 2) is, however, small compared with the temperature dependence of δ_G leading to a small variation of the

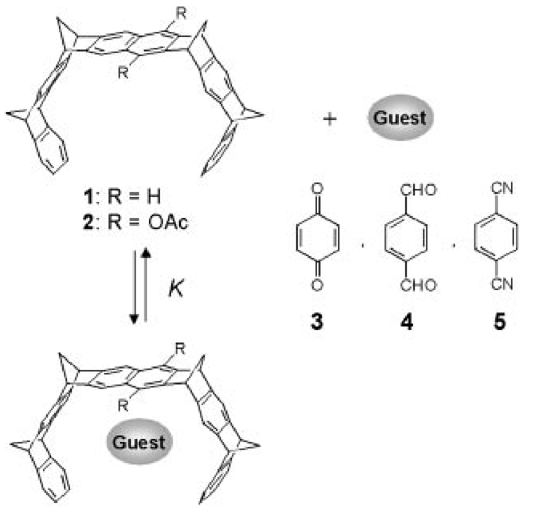

Figure 1. Molecular structure of tweezers and guests and reaction scheme for host–guest interaction of molecular tweezers

Table 1. Temperature dependence of the association constant K for host–guest complexes (guest@host) of molecular tweezers **1** and **2** with aromatic guests **3, 4** and **5**

3@1 in $CDCl_3$								
T (K)	294	268	253	238	223			
K ($\mathrm{l\,mol^{-1}}$)	21	41	67	121	260			
4@1 in $CDCl_3$								
T (K)	294	276	260	245	229			
K ($\mathrm{l\,mol^{-1}}$)	35	60	103	232	1028			
5@1 in $CDCl_3$								
T (K)	294	278	268	258	243			
K ($\mathrm{l\,mol^{-1}}$)	114	151	180	219	290			
5@1 in C_6D_6								
T (K)	282	294	310	323				
K ($\mathrm{l\,mol^{-1}}$)	187	143	97	72				
3@2 in $CDCl_3$								
T (K)	298	283	268	253	238	223		
K ($\mathrm{l\,mol^{-1}}$)	14	17	23	31	42	54		
4@2 in $CDCl_3$								
T (K)	293	283	273	263	253	243	233	223
K ($\mathrm{l\,mol^{-1}}$)	18	20	24	28	33	40	48	58
5@2 in $CDCl_3$								
T (K)	303	283	263	243				
K ($\mathrm{l\,mol^{-1}}$)	111	147	191	240				
5@2 in C_6D_6								
T (K)	328	308	298	288	280			
K ($\mathrm{l\,mol^{-1}}$)	267	453	599	789	970			

Table 2. Pressure dependence of the association constant K for host–guest complexes (guest@host) of molecular tweezers **1** and **2** with aromatic guests **3, 4** and **5**

3@1 in $CDCl_3$													
P [MPa]	0	5	27	48	74	99	129	151	176	196			
K (l mol^{-1})	20.0	20.1	20.7	21.3	22.0	22.8	23.7	24.4	25.2	25.8			
4@1 in $CDCl_3$													
P [MPa]	4	5	27	48	76	100	128	150	176	195			
K (l mol^{-1})	35.0	35.0	34.8	34.6	34.4	34.2	34.0	33.8	33.6	33.5			
5@1 in $CDCl_3$													
P [MPa]	0	9	26	51	75	106	126	151	177	194			
K (l mol^{-1})	110	109	108	107	105	103	102	101	99	98			
5@1 in C_6D_6													
P [MPa]	5.9	8.3	17.7	24.8	29.1	36.3	42.2	48.3	53.8	59.9	64.8	70.2	
K (l mol^{-1})	145	146	146	147	147	147	148	148	149	149	149	150	
5@2 in C_6D_6													
P [MPa]	1.2	4.2	11.0	17.3	23.7	28.8	37.2	42.9	48.7	53.9	59.9	65.2	71.8
K (l mol^{-1})	841	843	847	851	854	858	863	866	870	873	877	880	885

Table 3. Host–guest interaction of molecular tweezers **1** and **2** with aromatic guests **3, 4** and **5**[a]

			NMR titration		VT NMR		HP NMR	
Host	Guest	Solvent	K (l mol^{-1})	$\Delta\delta_{max}$ (ppm)	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})	ΔV (cm^3 mol^{-1})	$\Delta\delta_{max}$ (ppm)
1	**3**	$CDCl_3$	20[b]	2.8[b]	-27 ± 3	-64 ± 13	-3.0 ± 0.1	2.5
1	**4**	$CDCl_3$	35	1.6/0.6[c]	-25 ± 3	-59 ± 9	$+0.6 \pm 0.1$	1.4/0.6
1	**5**	$CDCl_3$	110[b]	4.3[b]	-11 ± 1	$+2 \pm 2$	$+1.5 \pm 0.1$	4.2
1	**5**	C_6D_6	145[b]	2.7[b]	-16 ± 1	-13 ± 2	-1.1 ± 0.2	2.7
2	**3**	$CDCl_3$	12	3.2	-11 ± 1	-16 ± 2		
2	**4**	$CDCl_3$	18	1.6/0.6[c]	-9 ± 1	-10 ± 1		
2	**5**	$CDCl_3$	110	4.1	-8 ± 1	$+32 \pm 2$		
2	**5**	C_6D_6	850	2.1	-16 ± 1	-1 ± 2	-1.1 ± 0.4	2.1

[a] Experimental results of ^{1}H NMR titration at 294 K, variable-temperature (VT) single-point NMR analysis and high-pressure (HP) NMR study at 298 K. The error values given for ΔH, ΔS and ΔV correspond to one standard deviation; the experimental errors are estimated to be three times higher. For K and $\Delta\delta_{max}$ the relative experimental error is estimated to be ±10% and ±5%, respectively.

[b] Values taken from the literature.[19]

[c] $\Delta\delta_{max}$: arene–H/CH = O

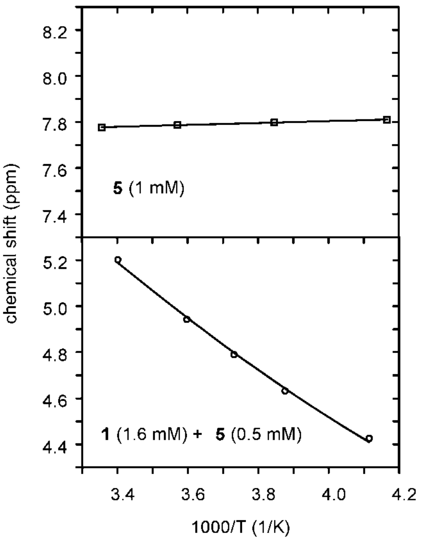

Figure 2. Temperature dependence of the chemical shift of guest **5** alone (top) and together with tweezer **1** (bottom) in $CDCl_3$ ($CHCl_3$ reference peak at $\delta = 7.25$)

reaction volumes around the zero value ($\Delta V = -3.0$ to $+1.5$ cm^3 mol^{-1}).

The thermodynamic parameters (Table 3) clearly indicate that the complex formation between the host molecules **1** or **2** and the aromatic guests **3, 4** or **5** is largely the result of an enthalpic interaction (ΔH). The comparison of the ΔH values with the corresponding entropy values (ΔS), which vary in the relatively broad range from +32 to −64 J mol^{-1} K^{-1}, provides evidence for an enthalpy–entropy compensation showing different slopes for the complexation of *p*-benzoquinone (**3**) and terephthalaldehyde (**4**) on the one hand and for that of 1,4-dicyanobenzene (**5**) on the other [Fig. 4(a)]. The enthalpy–entropy compensation generally found for association processes involving weak interactions can be explained as follows. In the association of two molecules the number of degrees of freedom is reduced from 12 to six, involving a loss of entropy ($\Delta S < 0$).[25] The stronger the enthalpic interaction between the two molecules, the more rigid is the associate and the larger is the loss of entropy. In a weakly bound associate,

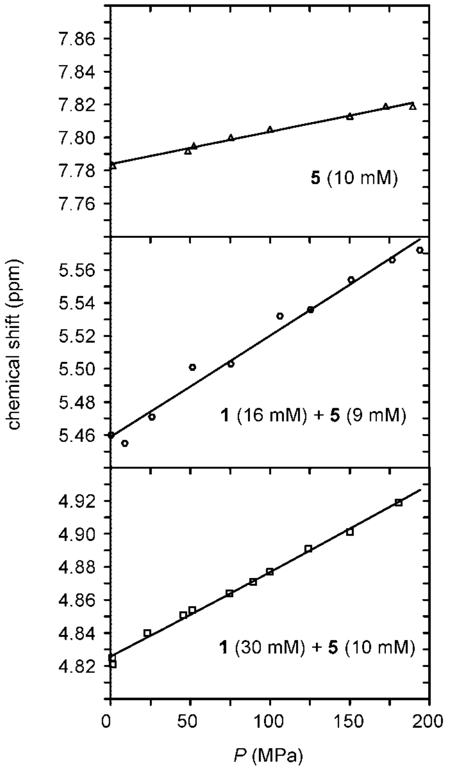

Figure 3. Pressure dependence of the chemical shift of guest **5** alone (top) and together with tweezer **1** (middle and bottom) in $CDCl_3$ at 301.5 K ($CHCl_3$ reference peak at $\delta = 7.25$)

however, the two molecules keep their flexibility to a certain extent so that the loss of entropy is smaller in this case. Thus, the enthalpy–entropy compensations observed here are already an indicator that effects different from solvation and desolvation, respectively, are important for the understanding of the thermodynamic parameters. Clear evidence for this hypothesis comes from the volume data.

The reaction volumes of all host–guest interactions investigated here show only a small variation around the zero value ($\Delta V = -3.0$ to $+1.5\,\mathrm{cm^3\,mol^{-1}}$). Consequently, the decrease in volume resulting from the complexation of the guest in the cavity of the tweezer is more or less compensated by the increase in volume caused by the desolvation of host and guest (release of solvent molecules) during the complexation. *There is no correlation between the volumes and entropies of reaction* [Fig. 4(b)]. This means that the large differences observed for the reaction entropies cannot be the result only of the desolvation effect. The entropy values are surprisingly positive in the case of the complexation of *p*-dicyanobenzene (**5**) with both tweezers **1** and **2** in $CDCl_3$ (+2 and +32 J mol^{-1} K^{-1}, respectively), whereas strongly negative values were obtained for the complexation of *p*-benzoquinone (**3**) and terephthalaldehyde (**4**) with **1** and **2** in $CDCl_3$ (−64, −59, −16 and −10 J mol^{-1} K^{-1}, respectively), as expected for bimolecular associations. However, the effect of bimolecular association does not show up in the corresponding reaction volumes ($\Delta V = -3.0$ and $+0.6\,\mathrm{cm^3\,mol^{-1}}$ for the reaction of **1** with **3** or **4**) which should be more negative provided that they result only from association. In order to explain this contradiction, we assume that the mobility of the guest molecule inside the tweezer cavity is important for the magnitude of the entropy but has only a small influence on the volume of the complex. According to single-crystal structure analyses and ^{1}H NMR investigations, the complexes **5@1** and **5@2** exhibit structures comparable to that of **5@1**,[19,23] as shown in Fig. 5. From the chemically induced shifts of the guest protons in the complexes and the temperature dependence of their ^{1}H NMR spectra in solution, it was concluded that two processes a, '60° jump' and a '180° rotation', rapid on the NMR time-scale, are responsible for the equilibration of the two non-equivalent guest protons H^a and H^b. In the crystalline state these conformational interconversions are sterically hindered by the lattice, so that separated signals for H^a and H^b are observed in the solid-state ^{1}H NMR spectrum. From the broadening and coalescence of the two signals at higher temperature (410 K), the Gibbs activation enthalpy was estimated as $\Delta G^{\neq} = 72\,\mathrm{kJ\,mol^{-1}}$ for the exchange of H^a

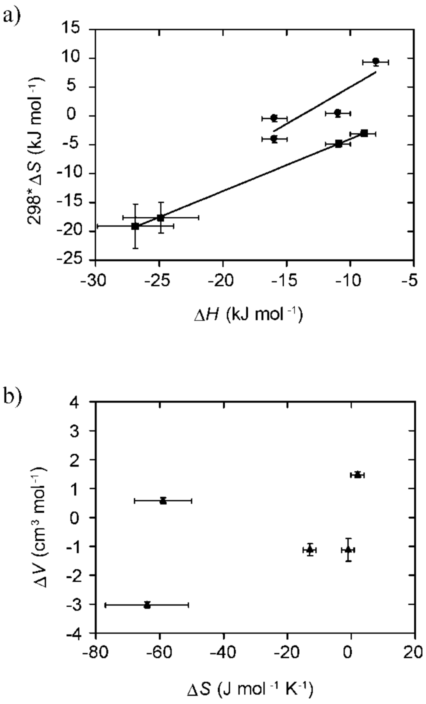

Figure 4. (a) Enthalpy–entropy compensation for the complex formation of hosts **1** and **2**, respectively, with guests **3** and **4** (■), respectively and with guest **5** [● (here two different solvents)]. (b) Correlation between volumes and entropies of reaction. All values are taken from Table 3. The error bars correspond to one standard deviation

and $\mathrm{H^b}$ in the crystal.[24] In the ^{1}H NMR spectrum of a mixture of **1** ($c = 0.05$ M) and **5** ($c = 0.02$ M) in $\mathrm{CDCl_3}$ a specific broadening, resharpening and shift of the signal at $\delta = 4.9$ (21 °C) assigned to the protons $\mathrm{H^a}$ and $\mathrm{H^b}$ of **5** is observed on cooling the NMR sample from +21 to −70 °C ($\delta = 3.8$ at −70 °C). The broadening of this signal is certainly due to the exchange between free and complexed guest **5**,[26] but there is no experimental indication that the exchange between $\mathrm{H^a}$ and $\mathrm{H^b}$ is 'frozen' on the NMR time-scale. According to quantum chemical calculations, (C. Ochsenfeld, unpublished results) the activation enthalpy of the '60° jump' and the 180° rotation in the gas phase is calculated to be lower than 16 kJ mol^{-1} and 40 kJ mol^{-1}, respectively, so that the activation barriers of the two conformational interconversions in solution are certainly similar to those calculated for the gas, here. These rotations give a positive contribution to the entropy and together with the effect of desolvation obviously overcompensate the negative contribution to ΔS resulting from the association. For the complexes **3@1** and **4@1**, a more symmetric orientation of the guests inside the tweezer cavity has been concluded leading to a negative contribution to ΔS.[23] The differences between the entropies found for the formation of the complexes **3@1, 4@1** and **3@2**, **4@2** may be explained by the asymmetry introduced by the

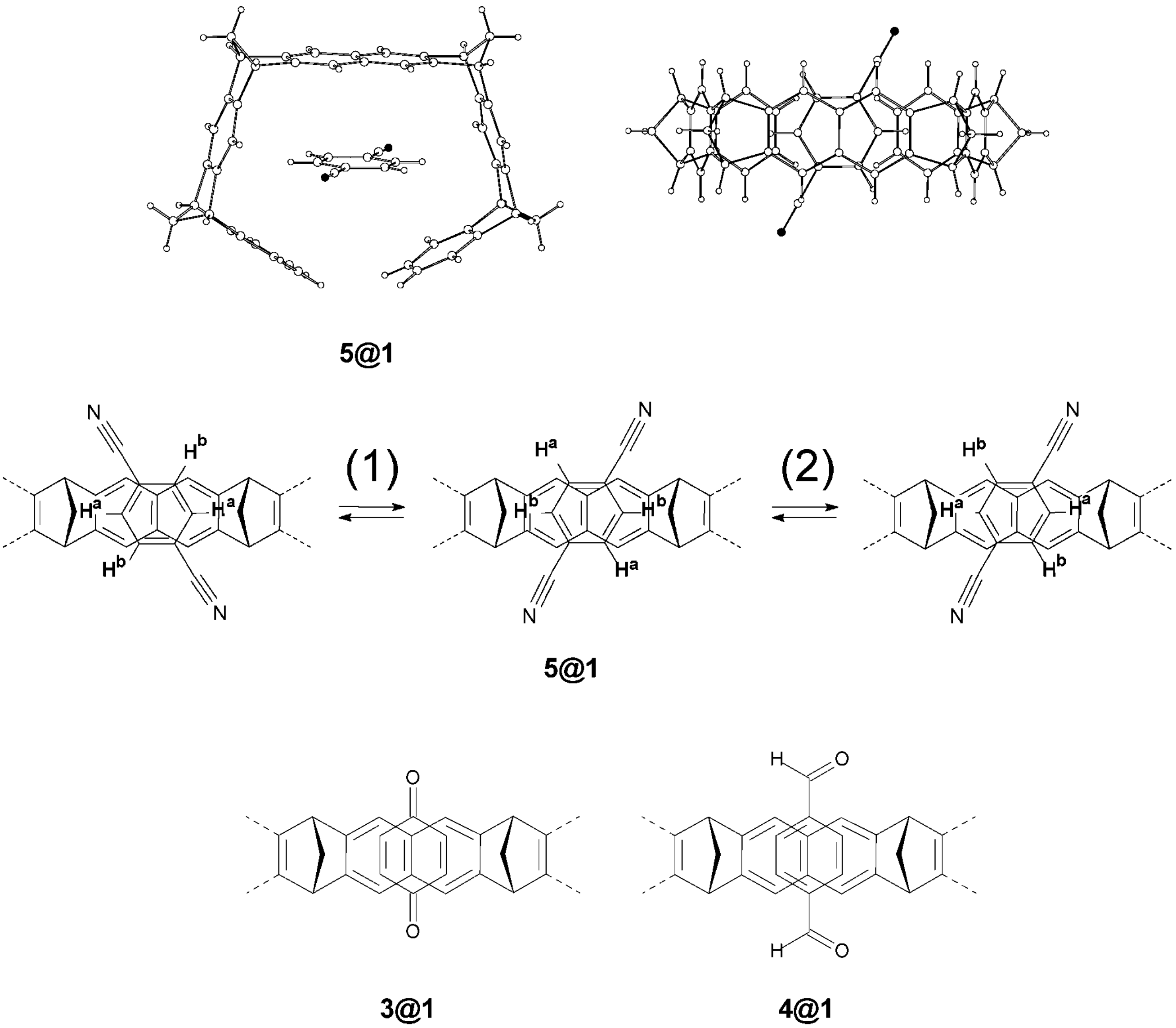

Figure 5. Top: crystal structure of the complex **5@1**. Front view into the tweezer's cavity (left) and view from the top (right). Middle: possible conformational interconversions inside the complex **5@1** as found by 2D ^{1}H double quantum magic angle spinning NMR. (1) '60° flip' of the guest; (2) '180° rotation' of the benzene moiety around the NC—C···C—CN axis. Bottom: view through the naphthalene moiety of tweezer **1** on to the guest for complex **3@1** (left) and **4@1** (right)

acetoxy substituents in the latter complexes. The question of why the ΔS values found for the formation of **5@1** and **5@2** in C_6D_6 are negative without showing a similar tendency in ΔV values remains open.

CONCLUSION

From this study, it can be concluded that the volume of reaction provides important information on the desolvation (the release of solvent molecules) during the formation of supramolecular complexes. In the complexes investigated here the nearly pressure-independent association constants and the small variation of the reaction volumes around the zero value clearly indicate that the decrease in volume caused by the association is compensated for by the increase in volume resulting from the release of solvent molecules during the complexation. Here, the desolvation of the receptor cavity should have the largest effect on the volume. From this we can predict that the use of bulky solvents, which do not fit into the receptor cavity, should lead to highly negative volumes of complexation.

The effect of the entropy on these association is more complex. In addition to the negative and positive contributions to ΔS resulting from the association and desolvation, respectively, the conformational freedom of the guest molecules inside the receptor cavities evidently provide a significant contribution to ΔS so that the interpretation of ΔS is certainly more complicated than that of ΔV.

EXPERIMENTAL

Materials and NMR equipment. The tweezer compounds **1** and **2** were synthesized and purified as described previously.[19,23] ^{1}H NMR titration experiments were performed on a Varian Gemini XL spectrometer (200 MHz) at 21 °C. Variable-temperature single-point analyses were carried out on an Avance DRX 500 spectrometer from Bruker (500 MHz). High-pressure liquid NMR spectra were recorded on a Bruker ARX 400 spectrometer (400 MHz) equipped with a laboratory-built, narrow-bore, high-resolution probehead.[27,28] The latter was thermostated by a circulating fluid and the temperature was measured by a built-in thermocouple. In all cases, the undeuterated amount of solvent was used as internal standard.

^{1}H NMR titrations. These experiments were performed to determine the association constant K [Eqn. (1)] for the reaction of host (H) **1** and **2** with the three guests (G) **3, 4** and **5** and also the maximum chemically induced shift $\Delta\delta_{max}$ for G in the corresponding complex (GH), given in Eqn. (2), where δ_G refers to the chemical shift of the free guest and δ_{GH} to the chemical shift of the guest bound in the complex. The data treatment was executed according to the literature.[19]

$$K = \frac{[\mathrm{GH}]}{[\mathrm{G}][\mathrm{H}]} \tag{1}$$

$$\Delta\delta_{\max} = \delta_{\mathrm{G}} - \delta_{\mathrm{GH}} \tag{2}$$

Data fitting base. In order to treat the temperature- and pressure-dependent data, Eqn. (3) was used to describe the observed chemical shift δ_{obs} based on the host–guest interaction with an exchange between free guest and guest bound in the complex fast on the NMR time-scale. The concentration of the host–guest complex [GH] is expressed by Eqn. (4), where $[G]_0$ and $[H]_0$ are the initial concentrations of the guest and of the host, respectively. For a detailed deduction of the equations we refer to the supporting information. The analysis of the data was accomplished with the non-linear least-squares fitting program Scientist.[29] The reported errors correspond to one standard deviation.

$$\delta_{\mathrm{obs}} = \delta_{\mathrm{G}} \frac{[\mathrm{G}]_0 - [\mathrm{GH}]}{[\mathrm{G}]_0} + \delta_{\mathrm{GH}} \frac{[\mathrm{GH}]}{[\mathrm{G}]_0} \tag{3}$$

$$[\mathrm{GH}] = \tfrac{1}{2}([\mathrm{G}]_0 + [\mathrm{H}]_0 + K^{-1}) - \sqrt{[\tfrac{1}{2}([\mathrm{G}]_0 + [\mathrm{H}]_0 + K^{-1})]^2 - [\mathrm{G}]_0[\mathrm{H}]_0} \tag{4}$$

Variable-temperature single-point analyses. Since the chemical shifts of the protons of the complexed guests δ_{GH} did not significantly vary with temperature, the enthalpy ΔH and entropy ΔS of association could be easily determined by single-point analyses of the temperature dependence of δ_{obs}.[19] Therefore, Eqns (3) and (4) and the van't Hoff equation, Eqn. (5), were used in the fitting procedure with consideration of the separately analyzed temperature dependence of δ_G as given by Eqn. (6), where δ_G^{298} is the chemical shift of the guest at 298 K and a is the corresponding temperature coefficient. An example of the dependence of δ_{obs} on temperature is shown in Fig. 2.

$$K = \exp\left(-\frac{\Delta H}{RT} + \frac{\Delta S}{R}\right) \tag{5}$$

$$\delta_{\mathrm{G}} = \delta_{\mathrm{G}}^{298} - \frac{a}{298} + \frac{a}{T} \tag{6}$$

To test the influence of a theoretically possible dependence of δ_{GH} on temperature, a further data treatment was performed, where a similar equation to that for δ_G was applied for the complex [Eqn. (7)]. The resulting enthalpy and entropy values did not differ significantly within the estimated experimental error and, since the fitted values of the corresponding temperature coefficient b turned out to have no physical sense, it was decided not to include Eqn. (7) in the fitting procedure of the final results. This is in agreement with the above-mentioned justification of the single-point analyses.

$$\delta_{\mathrm{GH}} = \delta_{\mathrm{GH}}^{298} - \frac{b}{298} + \frac{b}{T} \tag{7}$$

Variable-pressure study. Five different host–guest–solvent combinations were chosen for a variable-pressure ^{1}H NMR study in order to obtain the reaction volume ΔV of the association process. As an example, the pressure dependence of the chemical shift of guest **5** alone and together with the tweezer **1** in two different concentration ratios measured in $CDCl_3$ is shown in Fig. 3. The calculation of ΔV and $\Delta\delta_{\max}$ based on pressure-dependent NMR data takes into account the K values from NMR titration and variable-temperature experiments, respectively. The pressure dependence of K in the pressure range used here can be assumed to be monoexponential as given in Eqn. (8), where K^0 is the association constant at zero pressure ($P = 0$) and ΔV is the reaction volume.

$$K = K^0 \exp\left(-\frac{\Delta V}{RT} P\right) \tag{8}$$

In Eqns (9) and (10) the pressure dependence of δ_{G} and δ_{GH}, respectively, is considered; δ_{G}^0 and δ_{GH}^0 are the corresponding chemical shifts at zero pressure and a' and b' are the pressure coefficients.

$$\delta_{\mathrm{G}} = \delta_{\mathrm{G}}^0 + a'P \tag{9}$$

$$\delta_{\mathrm{GH}} = \delta_{\mathrm{GH}}^0 + b'P \tag{10}$$

For all calculations, Eqns (3), (4) and (8) and the pressure dependence of δ_{G} [Eqn. (9)] were included. It has been shown that the pressure dependence of δ_{GH} has no significant influence on the results within the experimental error. Therefore, b' was set to zero to fit the final parameters.

Details of the temperature and pressure dependence of δ_{G} and δ_{GH} and their influence on the final results are given in the supporting information available at the epoc website at http://www.wiley.com/epoc.

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