Energy landscape of a hydrogen-bonded non-degenerate molecular shuttle[†]

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In rotaxane 1, two co-conformations are populated in $CDCl_3$ at temperatures between 250 and 330 K. The thermodynamic parameters show strong enthalpy–entropy compensation, and a non-negligible heat capacity difference between the two forms.

The understanding of the fundamental forces involved in the non-covalent interactions that govern molecular recognition in biological and other (macro)molecules is of paramount importance in contemporary chemistry.¹ Molecular architectures in which components are mechanically bonded are an attractive research tool for the study of such relatively weak interactions, because the interlocking allows their study under a wide range of conditions, including those under which similar noninterlocked complexes would dissociate.² In rotaxane molecular shuttles a macrocyclic ring trapped on a dumbbell-shaped axle or thread can move between different distinct binding sites ("stations"), giving rise to different co-conformations.³⁻⁵ In order to design systems with a predictable distribution of co-conformers, accurate knowledge of the relative binding free energies is needed.^{5,6} In the present work we have studied rotaxane 1 (Scheme 1) in which hydrogen bonding forms the main interaction between the ring and the two stations. Using ¹H NMR spectroscopy, the populations of the two co-conformers are obtained, and from the temperature dependence of the equilibrium constant, the differences in free energy, enthalpy



Scheme 1 Co-conformational equilibria in rotaxanes **1** and **2** (CDCl₃, 298 K).

‡ Present address: Reckitt Benckiser Produktions GmbH, Ludwig-Bertram-Str. 8-10, 67059 Ludwigshafen, Germany. and entropy of the two forms are derived. Interestingly, the van't Hoff plot is distinctly non-linear, indicating that a non-negligible heat capacity change is involved. Such detailed thermodynamic studies of hydrogen bonded molecular shuttles have hitherto not been reported.

In the previously studied naphthalimide/succinamide rotaxane $2^{,7-9}$ the succ co-conformation predominates very strongly in the neutral state. Translocation of the macrocycle from the succ station to the ni-station occurs upon oneelectron reduction of the naphthalimide unit using electrochemical or photochemical methods.⁷⁻⁹ In rotaxane 1 we have inserted an amide unit (glycine) in the thread, in order to facilitate binding of the ring near the ni-station.

Comparison of the ¹H-NMR spectra of **1** and the corresponding thread¹⁰ **3** in CDCl₃ (Fig. 1) shows that the methylene protons H_p and H_r are shielded due to the aromatic ring current effect of the *p*-xylylene rings. However, the extent of shielding is less (1.1 ppm) than what was observed in the previously studied rotaxane **2** (1.45 ppm).^{7,8} Moreover, also the H_d protons are markedly shielded in rotaxane **1** compared to thread **3**, which shows that a significant fraction of rotaxane **1** exists as the ni-co-conformer.

Upon lowering the temperature, the resonances associated with the H_d protons are less shielded, which indicates that the population of the ni-co-conformer decreases when the temperature is decreased. Over the whole temperature range studied the shuttling remains fast on the NMR time scale, and the chemical shifts are population weighted averages,¹¹ in agreement with published results for related systems.¹²

In order to obtain a measure of the shielding of the H_d protons in a pure ni-co-conformer, a symmetrical model



Fig. 1 1 H-NMR spectra (400 MHz) of rotaxane 1 and thread 3 in CDCl₃ at 298 K.

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Scheme 2 Structure of model rotaxane 4.

rotaxane **4** was used. This consists of two ni-gly units, linked with a saturated C_{12} chain (Scheme 2). In this rotaxane the macrocycle can only hydrogen bond to one of the ni-gly units, so that an intrinsic shielding of the CH₂ group (1.178 ppm at 298 K) could be derived by comparison with the corresponding thread **5**.¹⁰

The population (α) of the ni-co-conformer in **1** was calculated from eqn (1). The δ 's refer to the chemical shifts of H_d in **1**, **3**, **4** and **5**. Knowing α , the population of the succ-co-conformer is simply given by $1 - \alpha$, and the equilibrium constant K can be obtained as $K = (1 - \alpha)/\alpha$.

$$\alpha = \frac{\delta_1 - \delta_3}{2(\delta_4 - \delta_5)} \tag{1}$$

A van't Hoff plot of ln *K vs.* T^{-1} is shown in Fig. 2. The non-linearity of this plot (see also ESI,[†] Fig. S13) points to a non-negligible heat capacity difference $\Delta C_p^{0.13}$ Inclusion of this in the thermodynamic model leads to eqn (2), which allows an excellent fit to the data, giving the parameters $\Delta H_0 = -18 \pm 1 \text{ kcal mol}^{-1}$, $\Delta S_0 = -300 \pm 30 \text{ cal mol}^{-1} \text{ K}^{-1}$ and $\Delta C_p^{0} = 52 \pm 4 \text{ cal mol}^{-1} \text{ K}^{-1}$.

$$R\ln K = -\frac{\Delta H_0}{T} + \Delta C_p^0 \ln T + \Delta S_0 - \Delta C_p^0 \qquad (2)$$

From these parameters, the reaction enthalpy ΔH^0 , entropy ΔS^0 and Gibbs free energy ΔG^0 at any temperature can be calculated, as shown in Fig. 3. The Gibbs free energy for the equilibrium is only slightly temperature dependent, increasing from -1.1 kcal mol⁻¹ at 268 K to -0.7 kcal mol⁻¹ at 328 K, but the contributions from enthalpy and entropy $(-T\Delta S^0)$ are of opposite sign and change strongly with temperature.

Another possible cause of the non-linearity of the van't Hoff plot could be that more than two species are present in the conformational equilibrium. At 298 K, the shielding of the



Fig. 2 Plot of ln $K vs. T^{-1}$ for the equilibrium succ–ni in 1 in CDCl₃. Fit of the data according to eqn (2). The error bars were derived assuming errors in the chemical shifts (eqn (1)) of 0.003 ppm.



Fig. 3 ΔG^0 , ΔH^0 and $-T\Delta S^0$ vs. temperature for the co-conformational equilibrium of rotaxane 1.

succinamide protons indicates a population of *ca*. 76% of the succ-co-conformer. From the shielding of H_d a population of 20% of the ni-co-conformer is derived. Thus, if a third co-conformer exists, it is minor (<5%), and its presence cannot account for the non-linearity of the van't Hoff plot (see ESI† for more detailed discussion).

The interaction between the macrocycle and the stations primarily involves hydrogen bonding. Because of its enormous importance in the chemistry of biological molecules as well as synthetic materials, simple predictive models for the strengths of hydrogen bonds are very useful.¹⁴ Although such models provide useful guidelines, accurate a priori prediction of hydrogen bond strengths remains difficult. Ab initio calculations can in principle give very accurate interaction enthalpies for model systems,¹⁵ but, as the present results underscore, entropy factors can also be very important, and these are difficult to calculate. Moreover, even in a relatively simple system as 1, the conformational space is quite large. The two translational co-conformers really correspond to low-energy valleys in the free energy landscape in which several local minima are populated. In Schemes 1 and 2, the hydrocarbon chains are drawn in the most favorable extended conformation, but at room temperature several gauche kinks will be present. The macrocyclic rings were drawn in Scheme 1 in patterns that are frequently encountered in molecular dynamics simulations,¹⁶ but the rings can adopt several other conformations as well. Interactions between the two stations may occur in the threads, and secondary interactions may exist between the macrocyclic ring and the station which it does not encircle. Such folded conformers have been detected in IR studies of 2 and its radical anion, but they were of relatively minor importance.⁹ Moreover, the NMR shielding parameters are sensitive primarily to the position of the *p*-xylylene rings with respect to the thread protons. Therefore they report on the position of the macrocycle on the thread, and are not very sensitive to the other aspects of the three-dimensional molecular structure. We believe that the co-conformational equilibrium in 1 will be an attractive target for the development of force fields and advanced simulation techniques that aim at free energies with chemical accuracy.¹⁷

Entropy-enthalpy compensation is typically associated with weak interactions, because optimization of the stabilizing enthalpic contribution requires some extent of freezing of the conformational freedom.^{18,19} In the succ-co-conformer of 1, the macrocyclic ring must adopt a chair conformation and the succinamide unit must be in a (planar) trans form for hydrogen bonding to be optimal. In the ni-co-conformer any of the C=O groups may point to the inside of the macrocyclic ring, to make a hydrogen bond with the glycine N–H. One amide group is free, allowing low-frequency movements.

Large ΔC_p effects have been observed in supramolecular complexation based on hydrophobic interactions.^{13,19,20} The characteristic changes in the enthalpy, entropy, and heat capacity that accompany protein (un)folding have been attributed to hydrophobic effects as well, although hydrogen bonding may also be important.²¹ Also for the folding of nucleic acids, heat capacity effects are substantial.²² The role of heat capacity in the conformational equilibrium of synthetic molecular shuttles has never been investigated, as far as we know. Our data analysis leads to a value of $\Delta C_p^{0} \approx$ 50 cal mol⁻¹ K⁻¹. This is a relatively small magnitude compared to the effects seen in protein chemistry,²³ but of similar magnitude as the effects in host–guest binding.¹³

Although in terms of free energy the binding of the macrocyclic ring to the ni-gly station is only slightly less favorable than the binding to the succ station, the latter is a much better template for the synthesis of the macrocyclic ring in the 5-component clipping method.²⁴ The synthetic yield of rotaxane **4** with only the ni-gly template was only 8%, much smaller than that of **1** (30%). On the other hand, weaker binding of the macrocycle to a ni-gly motif should allow faster switching of molecular shuttles, on a sub-microsecond timescale,^{3,8} and work along these lines is now in progress.

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