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Judging on Host–Guest Binding Mode Uniqueness: Association Entropy as an Indicator in Enantioselection

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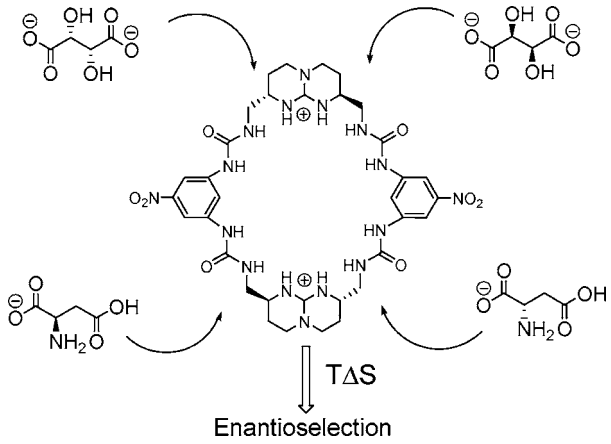
ABSTRACT



Supramolecular enantiodifferentiation was studied by isothermal titration calorimetry in an effort to address the order–disorder distinction in the diastereomeric complexes formed from a chiral macrocyclic host and enantiomeric carboxylates. As a result, the association entropy component *TΔS* emerged as an indicator in the enantioselection of tartrate 14 and aspartate 15 by the macrocycle 13 containing two guanidinium anchor groups connected to each other by four urea units. The parent monotopic guanidinium compounds 1 or 2 did not show any enantioselection for chiral carboxylates.

Structural definition in host−guest binding is a decisive determinant of function as has been amply demonstrated in biological systems. Correspondingly, the design of abiotic systems targeting molecular recognition a priori presumes the formation of a unique complex structure on host−guest association, in general without proving the validity of this assumption. The requisite order−disorder distinction cannot be assessed easily by the ordinary tools of structure elucidation due to rapid structural averaging in a solution phase. In some cases, however, the cautious interpretation of thermodynamic state functions, in particular of the entropy and heat capacity of association promises a remedy.[1,2]

One of the most prominent applications is the supramolecular enantiodiscrimination, which is well recognized to vitally depend on differential structuring of the host−guest aggregates.[3] Particularly relevant examples address the enantiorecognition of chiral carboxylate anions.[4−6] The most successful cases exploit the coordination of α-functionalized carboxylates such as mandelate or α-amino acid anions at transition metal cationic sites supporting the suspicion that the structure generating influence of partly covalent metal

(1) (a) Schmidtchen, F. P. *Top. Curr. Chem.* **2005**, *252*, 1−29. (b) Schmidtchen, F. P. *Coord. Chem. Rev.* Submitted for publication.

(2) (a) Jadhav, V. D.; Schmidtchen, F. P. *Org. Lett.* **2005**, *7*, 3311−3314. (b) Haj-Zaroubi, M.; Schmidtchen, F. P. *ChemPhysChem* **2005**, *6*, 1181−1186.

(3) Davis, A. P. Chiral Guest Recognition. In *Encyclopedia of Supramolecular Chemistry*; Steed, J., Atwood, J.,Eds.; Dekker: New York, 2004; Vol. 1, pp 236−244.

(4) Stibor, I.; Holakovsky, R.; Mustafina, A. S. R.; Lhotak, P. *Collect. Czech. Chem. Commun.* **2004**, *69*, 365−383.

(5) Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc.* **2005**, *127*, 7996−7997.

(6) Alfonso, I.; Dietrich, B.; Rebolledo, F.; Gotos, V.; Lehn, J.-M. *Helv. Chim. Acta* **2001**, *84*, 280−295.

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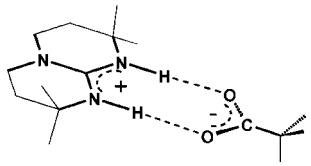


Figure 1. Idealized recognition motif of carboxylates to bicyclic guanidinium anchor groups.

ion coordination is a decisive factor.[7] Truly noncovalent binding has been achieved, e.g., with appropriately substituted chiral guanidines,[8−11] but the enantiorecognition retained a somewhat adventitious character and did not reach preparatively useful levels. In no case was the energetics explored to evaluate the origin of the confusing results. To understand the principles governing enantiodifferentiation of carboxylates by chiral guanidines and delineate guidelines for their further development we determined the thermodynamic state functions in associations with the well-established bicyclic guanidinium anchor group (Figure 1) in acetonitrile solution.[12]

The observation of two diastereomeric complexes by ^{1}H NMR in the interaction of the chiral guanidinium silyl ether **1** with *N*-acetyl-D,L-alanine **3a**/**3b**[12] fostered the hope to find different energetic signatures in the host−guest binding of **1** or **2** with the enantiomeric mandelates **4a**, **4b**. The individual calorimetric determinations, however, revealed no differential effect (Table 1). The affinities (ΔG) as well as

Table 1. Energetics of Host−Guest Binding of **1** I^- and **2** ClO_4^- with D- and L-Mandelate **4a**/**4b** (Tetraethylammonium Salts) in Acetonitrile at 298 K

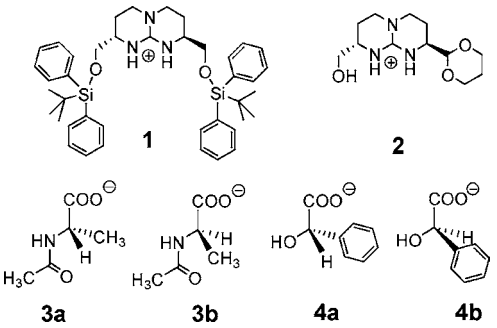
	guest	K_{assoc} (M^{-1})	$\Delta G^{o\,a}$	$\Delta H^{o\,a}$	$T\Delta S^{o\,a}$
1	**4a**	2.8 x 10^4	−25.4	−16.5	+9.0
	4b	2.2 x 10^4	−24.8	−16.3	+8.6
2	**4a**	7.2 x 10^4	−27.7	−20.5	+7.2
	4b	7.0 x 10^4	−27.6	−20.3	+7.4

[a] kJ mol^{-1}.

the component enthalpies and entropies seen in clean 1:1 stoichiometric complex formations are the same within experimental error. Clearly, the lack of enantiodiscrimination in these cases does not arise from enthalpy−entropy compensation that is frequently observed in supramolecular interactions.[16] The chiral centers appear too remote in the complexes to influence each other. A similar conclusion was reached on interaction of a set of tetra-substituted bicyclic guanidinium hosts with benzoate.[13]

Both guanidinium compounds exhibit clean 1:1 stoichiometric binding which is driven by negative enthalpies and positive entropies the latter contributing the respectable share of about 30% to the free energy of binding. The enhanced affinity by a factor of 3 shown by **2** may be attributable to an additional hydrogen bond formed between the hydroxymethylene substituent of this host and the carboxylate anion.

The supplementary attraction surfaces as a substantially more negative enthalpy that is partially balanced by a decrease in the entropy term suggesting marginally more restricted association modes.



The results indicated that recognition of the spatial layout of α-chiral carboxylates required complexation in a more confined binding pocket. As a straightforward consequence, we envisaged the construction of the macrocycle **13** containing two chiral guanidinium anchor groups connected to each other by 4 urea units that were supposed to assist in the complexation of carboxylate anions.[14] Molecular modeling using the Hyperchem 7.0 package (Amber force field) revealed the risk that the individual urea groups might engage in intramolecular hydrogen bonding and thus diminish the affinity for a guest anion (cf. Figure 2). In addition, the macrocycle turned out to be rather flexible despite the presence of many rotationally restricted bonds. However, with respect to the nominal dimensions macrocycle **13** was judged suitable to bind C_4-carboxylic acid anions which constitute a prominent subset of the natural chiral pool. The building blocks necessary for macrocyclization by amine-to-isocyanate addition were prepared from **1** and from commercial nitroisophthalic acid as depicted in Scheme 1. The final one-step-cyclization furnished the target compound in 10% yield as the iodide salt after chromatographic isolation and purification.

Taking isothermal titration calorimetry as a sensitive analytical tool the complexation characteristics of the bis-guanidinium macrocycle **13** with a series of simple oxo-

(7) (a) Folmer-Andersen, J. F.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 7986−7987. (b) Zhu, L.; Zhong, Z., Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 4260−4269.

(8) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994−4995.

(9) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160.

(10) (a) Kumamoto, T.; Ebine, K.; Endo, M.; Araki, Y.; Fushimi, Y.; Miyamoto, I.; Ishikawa, T.; Isobe, T.; Fukuda, K.. *Heterocycles* **2005**, *66*, 347−359. (b) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243−244.

(11) Chincilla, R.; Nájera, C.; Sánchez-Agulló, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393−1402.

(12) Gleich, A.; Schmidtchen, F. P.; Mikulcik, P.; Müller, G. *J. Chem. Soc., Chem. Commun.* **1990**, 55−57.

(13) Haj-Zaroubi, M.; Mitzel, N.; Schmidtchen, F. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 104−107.

(14) (a) Brooks, S. J.; Edwards, P. R.; Gale, P. A.; Light, M. E. *New J. Chem.* **2006**, *30*, 65−70. (b) Chmielewski, M.; Jurczak, J. *Chem. Eur. J.* **2005**, *11*, 6080−6094.

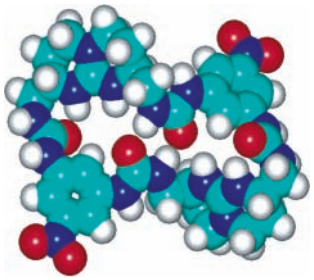


Figure 2. Energy-minimized structure of the macrocycle **13** using the Amber force field in vacuo. Two urea subunits pair by hydrogen bonding leading to a collapse of the macrocyclic cavity.

dianions of varying dimensions was undertaken (cf. Table 2). Compared to similar studies of host−guest binding of

Table 2. Energetics of Dianion Binding (Tetraethylammonium Salts) to Macrocycle **13** in Acetonitrile at 298 K (Stoichiometry *n* Refers to the Number of Stepwise Association Constants)

guest	model[a]	K_{assoc} (M^{-1})	ΔG^o (kJ mol^{-1})	ΔH^o (kJ mol^{-1})	$T\Delta S^o$ (kJ mol^{-1})
1 squarate^{2-}	A, $n = 2$	6.5×10^6	−38.9	−14.2	+24.6
2 oxalate^{2-}	A, $n = 2$	6.4×10^5	−33.1	−21.4	+11.9
3 malonate^{2-}	no sufficient heat effect				
4 succinate^{2-}	B, $n = 1$	1.8×10^6	−35.8	−7.0	+28.8
5 fumarate^{2-}	C, $n = 1$	1.7×10^7	−41.2	−52.8	−11.5
6	C, $n = 2$	8.7×10^4	−28.1	−8.3	+19.8
7 glutaconate^{2-}	C, $n = 1$	5.0×10^5	−32.5	−5.2	+27.3
8	C, $n = 2$	2.9×10^4	−25.4	−50.9	−25.4
9 t,t-muconate^{2-}	A, $n = 2$	3.8×10^5	−31.8	−26.7	+5.2

[a] A = titration mode: host into guest solution; one-site-model; ligand-in-cell; guest/host stoichiometry = *n*, B = titration mode: guest into host solution; one-site-model; guest/host stoichiometry = *n*, C = titration mode: host into guest solution; two sequential site model; ligand-in-cell.

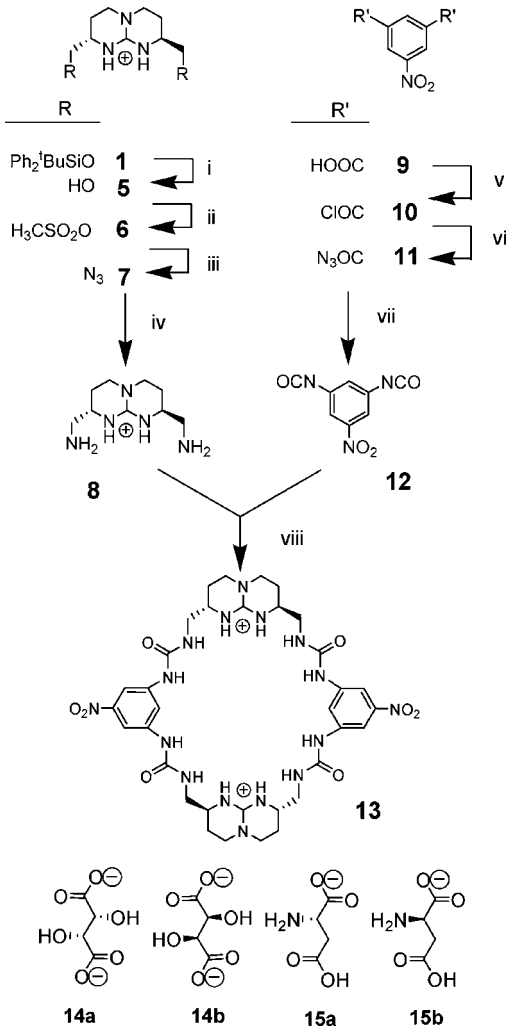
dianions to hydrogen bond donor macrocycles[14b,15] which generally show a clean correlation with guest dimensions, the binding patterns in the present case were considerably more subtle and contained some unexpected clues. Titrating the macrocyclic host **13** into a solution of the guest dianions (as tetraethylammonium salts) at submillimolar concentrations to promote complete dissociation of the salts the formation of higher order complexes in addition to regular 1:1 binding was invariably observed.

Depending on the absolute difference in the free energies of the individual steps the titration curve displayed an ordinary sigmoidal shape, however, possessing the inflection point at a 1:2 host−guest molar ratio when the affinities were rather similar. Differences in binding constants of more than a factor of 10 resulted in distorted shapes that were fitted conveniently to a two-site sequential-binding model.

Except for malonate, which eluded the analysis due to insufficient heat evolution, three distinct energetic patterns could be distinguished within the guest series. In the first

(15) Hosseini, Mir W.; Lehn, J.-M. *Helv. Chim. Acta* **1986**, *69*, 587−603.

Scheme 1[a]



[a] Key: (i−iii) fluoride/polymer, THF, rt, 12 h; CH_3SO_2Cl/Et_3N, CH_2Cl_2, 0 °C, 30 min; NaN_3, DMF, 90 °C, 12 h, overall 60%; (iv) Pd−C/H_2, CH_3OH, rt, 3 h, 95%; (v) $(COCl)_2$, CH_2Cl_2, rt, 22 h, 51%; (vi) $(CH_3)_3SiN_3$, CH_2Cl_2, rt, 16 h, 92%; (vii) toluene, 110 °C, 1 h, 70%; (viii) EDIPA, CH_3CN, −10 °C, 10%.

example comprising squarate, succinate, and one binding step each of fumarate and glutaconate a small exothermicity (−Δ*H*) is fortified by a large and positive entropic contribution to yield quite high affinities (−Δ*G*). In essence, such a signature resembles unspecific ion-pairing which typically emerges from minute structuring in the associated molecular species. Somewhat lower association entropies accompanied by substantially more negative enthalpies are exhibited by oxalate (entry 2) and *trans*,*trans*-muconate (entry 9), suggesting more intimate structuring but, however, a definite global misfit of host and guest as clean 1:2 host−guest stoichiometries are maintained. The energetic scenario is dramatically changed in the case of the rigid olefinic dicarboxylates fumarate (entry 5) and glutaconate (entry 8), both featuring a massive exothermic binding step that is counteracted to some extent by a strongly negative entropy component. The free energy outcome as a merger of both contributions leaves fumarate as the example of highest

Table 3. Energetics of Enantioselective Binding of Tartrates and Aspartates (as Tetraethylammonium Salts) to Macrocycle **13** in Acetonitrile at 298 K

entry	guest	model[a]	K_{assoc} (M^{-1})	ΔG^o (kJ mol^{-1})	ΔH^o (kJ mol^{-1})	$T\Delta S^o$ (kJ mol^{-1})
1	L-tartrate^{2-} **14a**	A, $n = 1.0$	3.1×10^6	−37.0	−40.5	−3.4
2	D-tartrate^{2-} **14b**	A, $n = 1.0$	8.8×10^5	−33.9	−45.0	−11.0
3	L-aspartate^{1-} **15a**	A, $n = 2.8$	4.1×10^5	−32.0	−34.5	−2.5
4	D-aspartate^{1-} **15b**	A, $n = 3.0$	3.9×10^5	−31.9	−30.1	+1.8

[a] A = titration mode: host into guest solution; one-site-model; ligand-in-cell; guest/host stoichiometry = *n*.

affinity in this series while glutaconate having just one methylene group more than the former shows much diminished affinity. Comparing the energetics of both dianions to succinate as the closest congener leads to the conclusion that plain solvation effects cannot account for the differences found. Apparently, there is an interaction mode common to all three species (entries 4, 6, and 7) featuring moderately negative enthalpies and large positive entropies indicative of extensive desolvation of host and guest on unspecific complex formation. Additionally, the olefinic substrates fumarate and glutaconate appear to conquer the sticky hydrogen-bonding sites of the host in a fashion that freezes internal motility in the complexes leading to very restricted structural variability concomitant with strongly negative entropies. The occurrence of this mode does not correlate with affinity and cannot be read from the magnitude of the binding constant. Hence, in the case of fumarate strong structural dedication of both host−guest partners as indicated by a negative association entropy (entry 5) apparently enables a large binding enthalpy resulting in the highest association constant found in this series. To reach a similar extent of dedicated host−guest attraction the {glutaconate ⊂ **13**} complex must lose even more degrees of freedom in configurational/conformational space as is read from the more negative entropy component (entry 8). The merger of both contributions ($\Delta G = \Delta H - T\Delta S$) renders a smaller affinity (ΔG) than is even seen in the ion-pairing mode (entry 7). A naive and innocent comparison of the stepwise constants not only would relate incompatible binding modes of both guests, but also is prone to misassign the structurally best defined complex as this is the one of weakest affinity (entry 8).

Yet, the uniqueness of the binding mode is considered a decisive determinant in the differentiation of geometric configurations as in enantiomeric discriminations. A corresponding analysis involving the macrocycle **13** and the enantiomeric tartrates **14** and aspartates **15**, respectively, is collected in Table 3. With respect to the assignment of a better or worse fit in the diastereomeric host−guest complexes the evaluation of chiral recognition holds the virtue of bona fide independence from solvation effects. The starting situation (before complexation) is exactly alike for both enantiomers and also the complexed states are very similar since they are identical in chemical nature and in the number of functional groups and the overall sizes must be very close. Thus, any differences in the observed entropies of association rather reflect changes in the configurational entropy in the diastereomeric complexes and address the bilateral structuredness. In this sense, tartrate exhibits a respectable effect, the $T\Delta\Delta S$ reaching 7.6 kJ mol^{-1} (Table 3) that, taken alone, would translate into a factor of 20 in enantiodifferentiation. Enthalpy−entropy compensation,[16] however, almost annihilates the entropic advantage leaving just a factor of 3.5 in the association constants at ambient temperature. If the initial premise holds that the observable entropy is dominated by the configurational component this leads to an amazing conclusion: The complex of better geometrical fit (lower entropy of association, entry 2) displays *weaker* affinity than the more disordered counterpart. Thus, if structuredness is the determining factor in enantiodifferentiation, maximizing host−guest affinity is a false trait to reach this goal.

A similar energetic result was obtained on titrating the aspartate monoanions with host **13**. Again the difference in structural order between the diastereomeric complexes surfaced as a gap in entropy ($T\Delta\Delta S$) which was readily closed by a compensating enthalpy effect that left no significant free energy difference in the final outcome. The 1:2 host−guest stoichiometry found proves that both complexes are composed as ternary species. Most likely, the chiral macrocycle **13** complexes a dimer of the aspartate formed by intermolecular multiple hydrogen bonding between the carboxylic acid and amine moieties in acetonitrile.

Calorimetric analysis of host−guest binding using sets of closely related substrates can unfold the order−disorder problem that is crucial to supramolecular design in structure-based applications such as assembly or enantiodifferentiation. In special instances the uniqueness of the host−guest binding mode may no longer remain a credulous assumption, but can be put on a well-founded experimental footing.

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Supporting Information Available: Experimental procedure, analytical data for the macrocycle **13,** and isothermal calorimetric titration experimental graphs corresponding to the entries depicted in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Dunitz, J. D. *Chem. Biol.* **1995**, *2*, 709−712. (b) Exner, O. *Chem. Commun.* **2000**, 1655−1656.