Electrostatic molecular recognition in rigid frameworks

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Complexation of six organic dianionic hosts (1cc–2tt) with methylguanidinium, tetramethylammonium and ammonium salts in various protic solvents has been studied by NMR spectroscopy. Stability of the 1:1 electrostatic complexes is shown to decrease with increasing distances between the carboxylate groups in the host compounds. Spectroscopic data and the results of molecular modelling support non-symmetrical structures of some of the complexes which contain one tight and one loose ion pair. The difference between the contributions of the tight and loose ion pair formation into the binding free energy can be predicted by the Fuoss theory of ion pairing on the basis of interionic distances calculated by molecular modelling.

Introduction

Ionic interactions in solution serve as one of the primary driving forces for molecular recognition. Development of quantitative approaches that allow one to evaluate the role of electrostatic interactions among other non-covalent binding mechanisms is essential for successful molecular design and synthesis of novel molecular structures capable of strong and selective binding to organic and biological molecules.

Despite the relative simplicity of the description of ionic interactions as compared with *e.g.* hydrophobic, van der Waals or hydrogen bonding,[1] no uniform theory is available that would be able to predict the strength of interactions between ionic compounds of complex structure with different numbers and relative positions of the charged functional groups. Most elaborate theories describing association of ions in solution developed in the works of Bjerrum[2] and Fuoss[3] are concerned with the formation of complexes between simple spherical ions in the absence of specific interactions with the solvent.[4] Owing to the inherent limitations of these theories, as well as the difficulty of their extrapolation to the interactions of more complex ionic compounds, they are rarely used for predicting binding affinities in the design of synthetic molecular recognition entities.

An alternative approach that has been used by Schneider and Theis to predict the energies of intermolecular ionic association in supramolecular complexes[5] is based on the linear free-energy relationships and yields surprisingly good correlations between the numbers of tight ion pairs (salt bridges) in well-designed supramolecular complexes and the binding free energies. Such correlations, however, are predicated upon complementarity of the interacting moieties in which every salt bridge is formed by counterions separated by distances close to the sum of their van der Waals radii.

In the ensuing paper we attempt to address the problem of non-optimal electrostatic binding in the systems where the rigid framework of a charged host molecular prevents it from forming the ideally-shaped complexes with oppositely charged guests. Apparently, this problem is relevant not only to the analysis of 'ill-designed' molecular receptors, but also to the prediction of binding affinities in numerous cases of polytopic molecular recognition. In many complexes involving natural and synthetic receptors, not every type of interaction is realised to the maximum possible extent. The polytopic binding of inhibitors to enzymes, association of intercalators and groove binders with the DNA double helices often lead to remote position of counterions in the complex, as imposed by the complex structure of the biomolecules. In order to predict the strength of electrostatic binding in these systems, one should be able to quantify the effects of ionic interactions weaker than those provided by the optimal distance salt bridges.

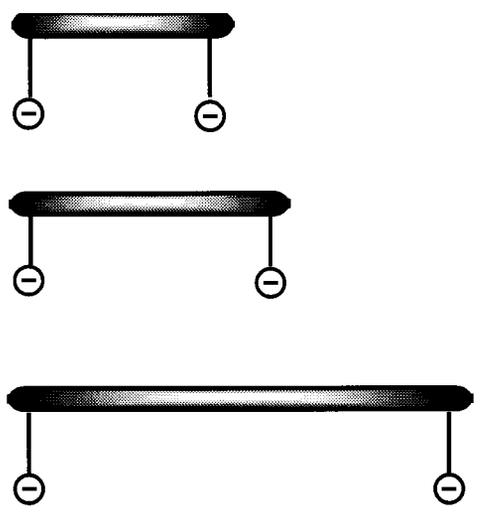


Fig. 1 Schematic representation of the rigid dianionic hosts with varying distance between the charged groups

Results and discussion

The purpose of this study was to explore and quantify the effect of relative position of the interacting charged groups in supramolecular complexes on the binding strength. The following features of the experimental design were essential. (*i*) The binding between the chosen compounds should be driven primarily by electrostatics, whereas other types of non-covalent interactions should be mostly eliminated. (*ii*) One of the interacting counterions (host compounds) should bear more than one charged group (in the simplest case two). The distances between the charged groups within the host compound should vary from one host to another, but the framework of the hosts should not allow the groups to come closer than some given distance (Fig. 1). (*iii*) The chemical nature of compounds with multiple charges should not substantially vary within the series. In this way, the differences in binding affinity between the host compounds would be primarily due to different position of the charged groups.

Based on these considerations, we chose molecular scaffolds **1** and **2** as the anionic molecular receptors capable of binding with simple cations. Each of the two compounds contains two

Table 1 Shortest distances[a] between the carboxylates in compounds **1tt–2cc**

Dianion	Distance/Å
1tt	11.6
1ct	9.3
1cc	6.0
2tt	12.3
2ct	9.0
2cc	5.2

[a] Distances were measured in molecular models between formal points corresponding to the middle position between the carboxylate oxygens.

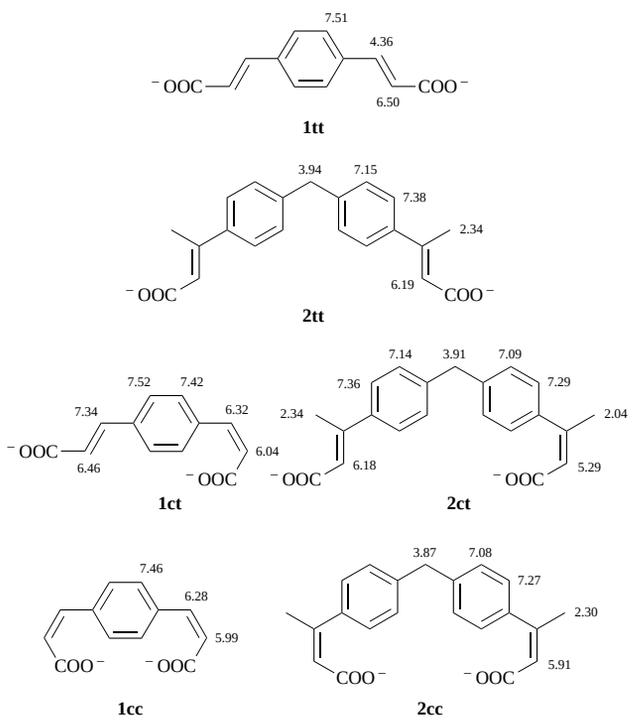


Fig. 2 Structures and ^{1}H NMR chemical shifts of the dianionic host compounds

carboxylate groups and can exist in three isomeric forms: *cis*,*cis* (**cc**), *cis*,*trans* (**ct**) and *trans*,*trans* (**tt**) (Fig. 2). The important feature of compounds **1tt–2cc** is that the distance between the carboxylates varies in different isomeric forms. In other words, the relatively rigid frameworks of **1** and **2** prevent the carboxylate groups from approaching each other closer than some minimum distance. The shortest distance the carboxylates can be brought to by conformational changes without rotation around the double bond was estimated from molecular modelling of every host compound (Table 1). One can see that the array of compounds **1tt–2cc** essentially represents a set of dianions of similar structure in which the distance between the negatively charged groups varies in the range of *ca.* 5–12 Å.

Further features of our experimental design included varying effective van der Waals radii of the guest cations and the solvent polarity. We evaluated binding affinity of the dicarboxylate receptors to methylguanidinium, tetramethylammonium and ammonium cations in protic solvents and their mixtures with the relative permittivity ranging from 17.7 to 37.2 (Table 2). Protic solvents were used in order to diminish the contribution of hydrogen bonding into the host–guest complexation.

The diacids of **1** (commercially available) and **2** (synthesised *via* the reaction sequence shown in Scheme 1) were converted to their disodium salts for the complexation studies. The dicarboxylates of **1** and **2** primarily exist in their most stable *trans*, *trans* configurations. In order to evaluate the binding affinities of the *cis*,*trans* and *cis*,*cis* isomers, the working solutions of the disodium salts of **1** and **2** were irradiated with a broad-band

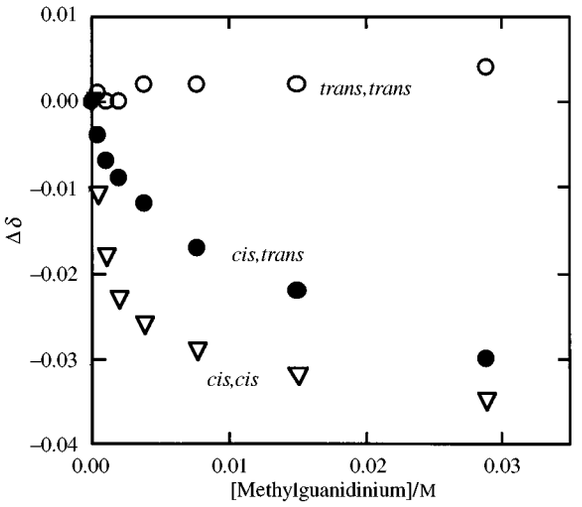
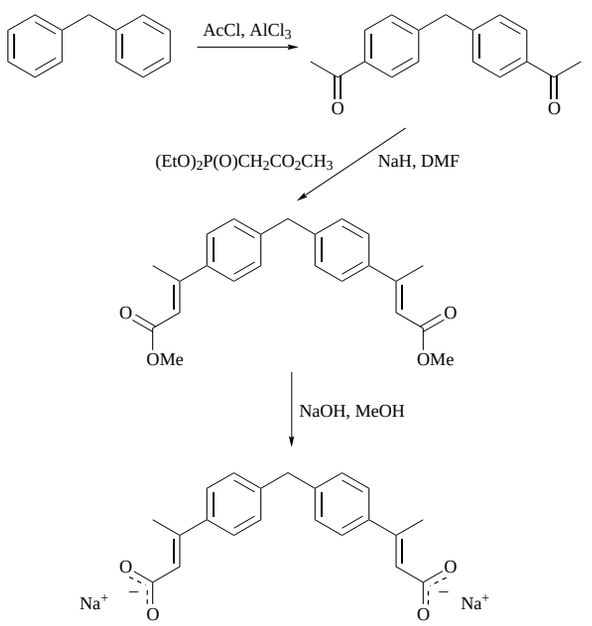


Fig. 3 ^{1}H NMR titration curves of 5×10^{-4} mol l^{-1} mixture of the isomers of **2** with methylguanidinium hydrochloride in [$^2H_6$]ethanol ($\Delta\delta$ changes are indicated for the signals of aromatic protons adjacent to the double bonds)



Scheme 1

UV–VIS light yielding a mixture of the three isomers in the ratio close to the photostationary distribution (*ca.* 45:30:25 of **1tt**:**1ct**:**1cc** and 20:30:50 of **2tt**:**2ct**:**2cc**). ^{1}H NMR spectra of the mixtures contained sufficiently resolved signals of the individual isomers (Fig. 2). The binding constants were then measured by the NMR titrations on the mixture of isomers with the chloride salts of corresponding guest cations by monitoring the changes in the chemical shifts of the host signals (see examples in Fig. 3). A non-linear regression analysis of the titration curves was done assuming the 1:1 complexation mode and in most cases provided a good fit of the experimental data.† Binding constants of the individual isomers calculated from the regression parameters are given in Table 2.

Two general qualitative conclusions can be made from the date in Table 2. (*i*) The energy of the ditopic electrostatic binding depends on the configuration of the host compounds and is

† In many cases we observed a steady linear drift in the chemical shifts of host signals upon increasing the guest concentration above 0.1 mol l^{-1}. Such drift, supposedly related to the ionic strength effect on the complexation, complicated estimations of the binding constants lower than 5–10 l mol^{-1} as well as the analysis of possible 2:1 and higher complexes.

Table 2 Association constants of the dicarboxylates of **1** and **2** with cationic ligands in protic solvents

Cation	Solvent	ε	K/l mol^{-1}					
			1tt	**1ct**	**1cc**	**2tt**	**2ct**	**2cc**
Methylguanidinium	10% D_2O in [$^2H_4$]methanol	37.2	*a*	*a*	*a*	<20	<20	86
	[$^2H_4$]Methanol	32.6	<3	72 ± 5	170 ± 12	44 ± 17	120 ± 15	213 ± 9
	[$^2H_6$]Ethanol	24.3	4 ± 3	150 ± 50	980 ± 90	*b*	*b*	*b*
	10% D_2O in [$^2H_{10}$]*tert*-butyl alcohol	17.7	40 ± 25	790 ± 110	<2500	*b*	*b*	*b*
$N(CH_3)_4^+$	[$^2H_4$]Methanol	32.6	9 ± 5	84 ± 15	99 ± 10	*a*	*a*	*a*
NH_4^+	[$^2H_4$]Methanol	32.6	308 ± 50	350 ± 70	360 ± 60	*a*	*a*	*a*

[a] *K* values were not determined in part because of the low spectral changes. [b] Receptor solubility was too low for the NMR titrations.

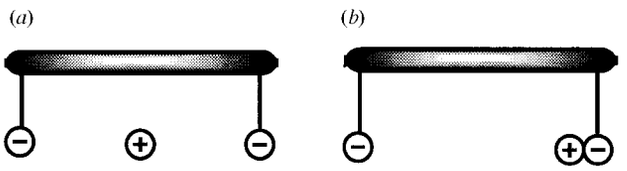


Fig. 4 Possible accommodation of the guest cation in the complex with a dianionic host

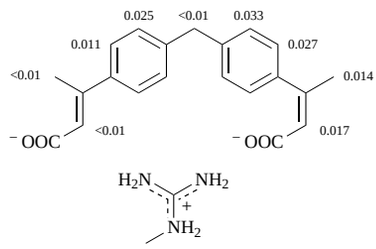


Fig. 5 Changes in the ^{1}H NMR chemical shifts of host compound **2ct** induced by complexation with methylguanidinium in methanol

most likely determined by the distance between the carboxylate groups responsible for the salt bridge formation. (*ii*) The discrimination factor between the host isomers increases with decreasing solvent polarity being mostly pronounced in the *tert*-butyl alcohol–water mixture ($\varepsilon = 17.7$, $K_{cc}/K_{tt} > 60$; $\Delta G_{cc} - \Delta G_{tt} > 11$ kJ mol^{-1}).‡

We then attempted to relate the variations in binding strength to structural differences between the electrostatic complexes. Apparently, in the ideal case when the host structure in its optimal conformation is matching the guest geometry [see, for example, Fig. 6(*a*)], the most stable complex is formed. This, for instance, is the case with the complexes of **1cc** and **2cc** with the guanidinium cation in which the salt bridges with both carboxylates are formed with closest contacts allowed by the ionic radii. However, in the complexes with less perfect guests (*cis*, *trans* and *trans*,*trans* isomers) bearing more remote carboxylates, the single guest cation should find its position somewhere between the host anionic groups to maximise the free energy of binding. The Coulomb force of the elecrostatic binding decreases with distance as $1/r^2$. For this reason, an intuitive feeling tells us that the time-averaged position of the cation in the complex must be such that a tight salt bridge is formed with one of the carboxylates leaving a weaker remote contact with the second one [Fig. 4(*b*)] as opposed to the middle position of the guest [Fig. 4(*a*)].

Spectroscopic evidence for this suggested configuration was obtained from the analysis of the complexation-induced chemical shifts in the complexes of non-symmetrical *cis*,*trans* isomers (Fig. 5). The signals of the protons in the *cis*-side of the host anion undergo stronger shifts upon complexation with guanidinium and other cations than the signals from the *trans*-side. This effect may be also contributed to by weaker cation–π interactions with the aromatic part of the host,[6] but it undoubtedly means that the position of the cation inside the complex is non-symmetrical and closer to the *cis*-side. Similar positional preferences of one of the anionic sites can be expected in the complexes with the *trans*,*trans* isomers. (Spectroscopic assignment, however, is not possible in this case, since the exchange of the guests between the equivalent binding sites is fast on the NMR timescale.)

The non-symmetrical position of the guest cation inside the complex was also supported by the results of molecular modelling. We performed docking calculations on all studied ionic complexes with the aid of the Tripos force field. In the initial complex model, the guest cation was docked at approximately equal distance between the host carboxylate groups. The subsequent minimisation of the complex structure resulted in migration of the cation to one of the carboxylates (*cis*-side in the cases of **1ct** and **2ct**) until the van der Waals contacts between the counterions had been formed. Examples of the minimised structures of guanidinium with the isomers of **2** are presented in Fig. 6. Such non-symmetrical complexation modes were consistently reproduced on modelling complexes with different guests and on applying different relative permittivity values.

Electrostatic binding free energy of a complex with a non-symmetrical structure [Fig. 4(*a*)] should therefore be a sum of two unequal contributions from the 'strong' and 'weak' salt bridges. The strong : weak contributions ratio is determined by several factors, such as ionic radius of the guest, the distance of the guest cation from the remote carboxylate and the solvent polarity. In order to evaluate quantitatively the contribution of the 'weak', non-optimal electrostatic contact, we looked at the theories that embrace both the effect of interionic distance and the relative permittivities of the medium on the ionic association constants.

The classical theory developed by Bjerrum[2] describes the association constants of spherical ions separated in the complex by their solvation shells and is generally applicable to the complexes of relatively small ions in the absence of specific interactions.[4c] Bjerrum theory is expressed by eqn. (1) where

$$K = 4000\pi N a^3 b^3 Q \qquad (1)$$

$b = (|z1 \cdot z2|e^2)/(4\pi\varepsilon_o\varepsilon akT)$, $Q = \int_2^b y^{-4}e^y \, dy$, $y(r) = (|z1 \cdot z2|e^2)/4\pi\varepsilon_o\varepsilon rkT)$, N is the Avogadro number, ε is the permittivity of vacuum, ε is the relative permittivity and a the interionic distances (all in SI units).

The elaboration proposed by Fuoss[3] extended the Bjerrum theory to the 'contact' ion pairs in which the interacting ions are held at the distance of their van der Waals radii with no solv-

‡ Surprisingly, we observed little or no discrimination of the isomers of **1** by the ammonium cation. It cannot be excluded that the apparent 1 : 1 binding constants were effected by the formation of 2 : 1 and higher complexes with the compact ammonium ions. However we failed to estimate the degree of formation of these higher complexes because of the ionic strength effects mentioned above. For this reason, the complexes with ammonium were excluded from further quantitative correlations.

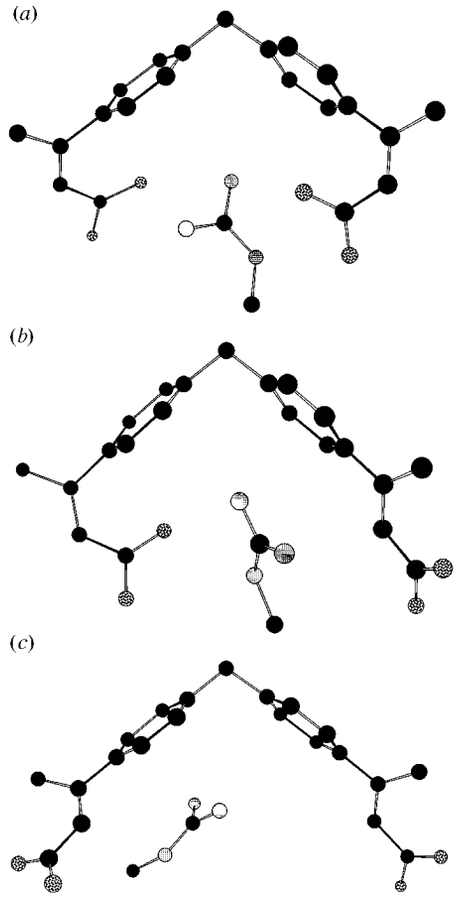


Fig. 6 Simulated structures of the host–guest complexes of (*a*) **2cc**, (*b*) **2ct** and (*c*) **2tt** with methylguanidinium

ation shells in between. Corresponding binding constants in this case can be calculated using a particular integrated form of the Bjerrum equation [eqn. (2)].

$$K = 4000\pi N a^3 \frac{b^3}{3} e^b \qquad (2)$$

Both Bjerrum and Fuoss descriptions are, strictly speaking, limited to the interactions of simple spherical ions. Their direct application to our ditopic electrostatic receptors would appear to be extremely difficult. However, it may be possible to describe the relative energies of the close and remote ion pairs in terms of one of these theories. We used the following approach to such a description.

(*i*) Force field docking calculations were performed to obtain minimised structures of the 1:1 complexes between the dianionic hosts and the guest cations listed in Table 2 (examples of the complex models are presented in Fig. 6). The minimisations were done with the corresponding values of relative permittivities given in Table 2, but the complex geometries simulated thereby appeared to be almost insensitive to the relative permittivities of the media within the given range.

(*ii*) The distances between the positive and negative ionic groups were measured in each of the simulated complex structures. The following formal points were used to locate the charges of functional groups: for the carboxylates, the middle of the line connecting two oxygen atoms; for guanidinium, the central carbon atom; for NME_4^+, the nitrogen atom.

(*iii*) Using the obtained array of interionic distances (a_i), we calculated the set of imaginary association constants from eqns. (1) (K_{iB}) and (2) (K_{iF}). Thus, each of these constants would correspond to the association of two single point-charges separated by distance a_i in the solvent with the relative permittivity ε_i. Comparing the calculated binding constants for different

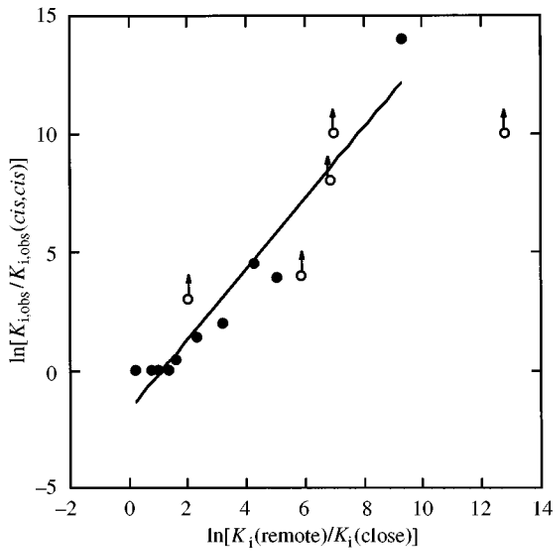


Fig. 7 Correlation between the calculated and experimental ratios of the remote/close ion pair stabilities [*cf.* eqn. (3)]; hollow symbols (◊) indicate the values for which only the lower limits could be estimated

distances one can evaluate the theoretical difference between the free energies of close and remote ion pairs [eqn. (3)].

$$\Delta G(\text{remote}) - \Delta G(\text{close}) = -RT \ln[K_i(\text{remote})/K_i(\text{close})] \qquad (3)$$

(*iv*) We then assumed that the difference in the ΔG of complexation between the 'good' hosts (**1cc** and **2cc**) and the 'bad' hosts (*cis,trans* and *trans,trans* isomers) is entirely due to the more distant position of the second, remote carboxylate from the guest cation. Then the free energy difference between the formation of one close and one remote ion pairs with a 'bad' host (ΔG_{obs}) and the formation of two close ion pairs with a 'good' host [$\Delta G_{obs}(cis,cis)$] would indicate the experimental difference between ΔG of the close and remote ion pairs [eqn. (4)].

$$\Delta G_{obs} - \Delta G_{obs}(cis,cis) = -RT \ln[K_{i,obs}/K_{i,obs}(cis,cis)] \qquad (4)$$

If this assumption is correct, the observed constants $K_{i,obs}$ should obey eqn. (5).

$$\ln[K_{i,obs}/K_{i,obs}(cis,cis)] = \ln[K_i(\text{remote})/K_i(\text{close})] \qquad (5)$$

All of the studied ionic complexes were formed in organic solvents which create relatively bulky solvation shells. Under these conditions, the complex formation is most likely to occur with the contact ion pairs and would be more properly described by eqn. (2). The plot in Fig. 7 displays the correlation between the parts of eqn. (5) in which the right side has been calculated by the Fuoss formula [eqn. (2)].

Fig. 7 represents a reasonably good correlation between the calculated and experimental data and incorporates the *K* values from different host and guest compounds in different solvents. The slope of the regression curve equals 1.5 meaning that the experimental ratios of the weak/strong energy contributions slightly exceed the calculated values. This may be due to the fact that the local relative permittivity in the space between the remote ions is somewhat lower than that of the bulk solvent.

Similar calculations performed with the aid of eqn. (1) (Bjerrum) resulted in much more scattered calculated ratios. Furthermore, a number of such calculations yielded negative *K* values for the remote ion pairs apparently indicating that the system parameters were beyond the limitations of the Bjerrum theory. The fact that the Fuoss equation provides a better description of the experimental data also supports formation of the 'contact' ion pairs.

The ability to predict the effect of complex geometry on the effectiveness of the electrostatic binding has an important implication for the selectivity of molecular recognition. According to our original design, the guanidinium ion was expected to show a high discrimination between the isomers of **2**.[7] While this expectation has been supported by our current studies, one might expect that any cation that can fit between the closely positioned carboxylates of **2cc** would be capable of providing such discrimination. However, as shown in Table 2, the tetramethylammonium cation binds equally well to **2cc** and **2ct**, and considerably worse to **2tt**. The molecular modelling shows that, due to its large size, NMe_4^+ actually forms two close ion pairs both with **2cc** and with **2ct**, whereas the second ion pair in the complex with **2tt** is looser. The resulting change in affinity–selectivity is well described by eqn. (2). This is only one example of the experimental results that can be predicted on the basis of molecular modelling combined with an estimate of the electrostatic energies of binding.

Conclusions

We have shown that the strength of electrostatic binding in molecular recognition systems with more than one binding site is largely dependent on structural complementarity of the interacting charged moieties. The stability of ion pairs in a particular receptor–ligand system can therefore be controlled by varying the relative position of the charged groups in the synthetic scaffold. Although the latter conclusion essentially supports a common sense belief of many a supramolecular chemist, the quantitative estimate resulting from our studies allows one to predict how effective the binding may be with a non-ideally shaped host. Both in the design of artificial molecular receptors and in the generation of ligands for biomolecules secondary, long-range interactions, including electrostatic forces, commonly affect binding strength and selectivity. Our analysis demonstrates that the combination of molecular modelling with a quantitative description of the subunit interactions can be used for predicting the energies of the non-optimal electrostatic binding.

Experimental

General

Phenylenediacrylic acid (the diacid of **1**), methylguanidinium hydrochloride, ammonium salts and all components for synthesis were purchased from Aldrich and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 and 300 MHz instruments in deuterated solvents with at least 99.5% deuterium enrichment; chemical shifts are given in ppm, *J* values are given in Hz. The content of the isomeric mixtures was confirmed by the reversed-phase HPLC (Beckman System Gold) equipped with the photodiode array detector.

Synthesis

Bis(4-acetylphenyl)methane. This was synthesised by the acylation of diphenylmethane[8] in a 75% yield after recrystallisation from ethanol. δ_H(300 MHz, $CDCl_3$) 7.90, 7.26 (8H, dd, *J* 8.3, Ar), 4.09 (2H, s, CH_2) and 2.58 (4H, s, Me).

Dimethyl *p,p′*-methylenebis(3-phenylbut-2-enoate). A solution of 3.64 g (17.3 mmol) of methyl diethylphosphonoacetate in 5 ml of anhydrous *N*,*N*-dimethylformamide (DMF) was added dropwise to a stirred suspension of 0.472 g (20 mmol) of NaH in 10 ml DMF at 0 °C in an argon atmosphere. The mixture was brought to room temperature and kept for 30–40 min until the solution became transparent and no further gas formation was observed. A solution of 1.98 g (7.86 mmol) of bis(4-acetylphenyl)methane in 10 ml of DMF was added dropwise for 30 min and the resulting mixture was stirred overnight at ambient temperature. Then the solvent was removed *in vacuo* and the residue was redissolved in diethyl ether, extracted twice with water and dried over Na_2SO_4. The crude product was purified by chromatography on silica gel in 5% EtOAc in $CHCl_3$ yielding 1.28 g (45%) of the analytically pure product. δ_H(300 MHz, $CDCl_3$) 7.42, 7.20 (8H, dd, *J* 8.5, Ar), 6.13 (2H, d, *J* 1.3, C=CH), 4.01 (2H, s, CH_2), 3.75 (6H, s, OCH_3) and 2.57 (6H, d, *J* 1.3, C=CCH_3).

***p,p*-Methylenebis(3-phenylbut-2-enoic acid), 2tt.** 0.90 g (2.47 mmol) of the dimethyl ester of **2tt** was dispersed in a solution of 0.237 g, (5.93 mmol) of NaOH in 10 ml of MeOH–water (3 : 1 v/v). After refluxing for 2 h the solution was acidified with HCl to pH 2.5, the resulting precipitate was filtered, washed with water and dried. Yield 0.705 g (85%). δ_H(300 MHz, [$^2H_6$]DMSO) 7.44, 7.24 (8H, dd, *J* 8.0, Ar), 6.05 (2H, s, C=CH), 3.94 (2H, s, CH_2) and 2.42 (6H, s, CH_3). **2tt·2Na** δ_C(75 MHz, D_2O) 184.1, 150.4, 148.7, 147.3, 136.1, 133.4, 130.5, 47.5 and 24.1.

Determination of binding constants by NMR titration

The diacids of **1** and **2** were converted into their disodium salts by dissolving in aqueous NaOH at pH 7.5–8. After lyophilisation of the solution, the resulting salts were redissolved in appropriate deuterated solvents and irradiated in the NMR tube with a mercury lamp in a Rayonet photochemical reactor for 20–30 min to generate the mixture of isomers. ^{1}H NMR and HPLC§ analysis of the resulting mixtures showed that the short-time irradiation led to the formation of the host isomers without any detectable side products. The resulting mixture containing a total of 0.5–4 mmol l^{-1} of all isomers was titrated with the chloride of the corresponding guest cation with increasing concentration of the latter from $[G]_t$ = 0–130 mmol l^{-1}. The individual binding constants *K* of every isomer were then determined from the changes in chemical shifts ($\Delta\delta$) of the host signals by a non-linear regression fitting to eqn. (6) for the

$$\Delta\delta = \Delta\delta_\infty K[G]_t/(1 + K[G]_t) \quad (6)$$

1 : 1 complexation mode, where $[G]_t$ is total concentration of the added cationic host.¶ With a few exceptions, the variations of the binding constants determined from the shifts of different protons did not exceed the experimental error.

Molecular modelling

Force-field minimisations and docking calculations were performed on a Silicon Graphics workstation with the aid of a Sybyl/Tripos software package. The structures of individual compounds were minimised prior to docking calculations. The structures of the guest cations were docked to the host scaffold and the energy of the resulting structure was then minimised in 1000–5000 iterations. The force-field set included the electrostatic energy component with the relative permittivity values indicated in Table 2. Several different initial positions of the cations with respect to the host structures were tested to insure reproducibility of the minimised complex structures. Variations in the initial guest positions within *ca.* 2 Å usually led to less than 0.5 Å differences in their positions in the minimum energy conformation of the complex.

Acknowledgements

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§ HPLC analysis of the irradiated **1** (50% MeCN in water, 1 ml min^{-1}, 25 cm Beckman Cyano column) showed the presence of three peaks [3.3 min, λ_{max} 319 nm (**1tt**); 4.4 min, λ_{max} 305 nm (**1ct**); 6.8 min, λ_{max} 281 nm (**1cc**)]. The analysis conditions for **2** are given in ref. 7.

¶ The fitting equation is derived in the assumption that $[G]_t \gg [HG]$. This condition was held throughout the titration range. Thus, the first point in Fig. 3 corresponds to $[G]_t$ = 0.5 mM, whereas concentration of the strongest complex is *ca.* 0.05 mM.

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