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# The Incremental Approach to Noncovalent Interactions: Coulomb and van der Waals Effects in Organic Ion Pairs[1]

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**Abstract:** The equilibria of 10 ion pairs with aromatic units in one or both ions are determined in water by UV/vis and partially by NMR and conductivity experiments, showing in most cases satisfactory agreement. UV/vis measurements at different wavelengths usually exhibit weaker 1:2, in addition to 1:1, complexes. On the basis of a generalized principle of additive binding increments, the results from about 40 ion pairs—many from the literature—show a surprisingly constant Coulomb increment of $\Delta G = 5 \pm 1$ kJ/mol per single salt bridge. The van der Waals forces in the aromatic ion pairs also lead to a linear increase of the complexation strength with the number of aryl groups in the complexes. A corresponding two-term correlation yields, in agreement with other studies, a vdW increment of 1–2 kJ/mol per aryl unit, which is shown to be due to ion-induced dipoles in the $\pi$-system. Conformations were partially modeled with force field calculations (CHARMm); they are in qualitative agreement with complexation-induced shifts obtained from NMR titrations. The CIS-NMR values explain deviations from the correlations for three ion pairs due to steric hindrance and contradict edge-to-face arrangements of benzene rings. Charge-transfer (CT) interactions, although visible in typical UV/vis absorptions, do not contribute significantly (<0.5 kJ/mol) to the associations. Selected measurements with less polar solvents added show the expected binding increase but no correlation with the bulk dielectric constant.

## I. Introduction

**The Additivity of Intermolecular Binding Increments.** The quantification of noncovalent interactions is of paramount importance for the further development of supramolecular chemistry,[2] as well as for a rational approach to biological systems[3] including protein structure and function, antibody binding, or drug design. In a most simple approach, the total free energy $\Delta G_{HG}$ holding host and guest molecules (H and G) together is described as the sum of individual attraction energies $\Delta G_i$ between interacting centers A/K, B/L, C/M, etc. (Scheme I):

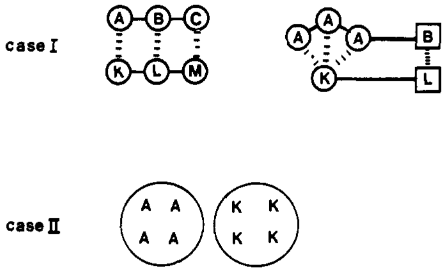
$$\Delta G_{HG} = \Delta G_{AK} + \Delta G_{BL} + \Delta G^*_{CM} \tag{1a}$$

or

$$K_{HG} = K_{AK} K_{BL} K_{CM} \tag{1b}$$

The chelate effect by simultaneous action of multiple binding sites has a number of general advantages: besides enhancing the often too low complexation strength and leading to better defined host–guest structures, it offers an opportunity to single our particular interactions either by keeping constant all but one of the binding sites or by studying complexes of different geometries with the same type, but with different numbers $n$, of interacting functionalities. In this case a plot of the observed total binding energies $\Delta G_{HG}$ vs the number of interactions $n$ will show a linear correlation, the slope of which will give the average $\Delta G$ increment per noncovalent bond. The method also allows one to minimize differential *entropy* contributions, $\Delta S$, which for bimolecular associations can lead to $T\Delta S$ = 105–150 kJ/mol;[4] these, in a first approximation, can be considered to be paid by the one strong interaction or by several weaker interactions kept constant while varying only one. Furthermore, multi-binding-site complexes can be designed in a way that solvation/desolvation terms per binding site remain approximately constant.

**Scheme I.** Additivity and Nonadditivity of Binding Increments $\Delta G$



What are the conditions then for the use of additive binding increments according to eq 1? Obviously, the complementary binding centers must match each other in "sign" (attractive) and in geometry. The geometrical conditions as well as strain variations in supramolecular complexes which usually accompany an induced fit between host and guest can be controlled by force field calculations. One single center may interact with $n$ other centers, yielding again a multiplicative chelate effect with $n$ single $\Delta G$ values; the opposite case is represented by, for example, large ions bearing several charges $z$, which cannot all be in contact simultaneously (Scheme I). Other prerequisites for the application of eq 1 are that the different binding sites have a negligible influence on each other (and also on their solvation/desolvation $\Delta G$ values) and that the shape and nature of the total binding surface remain comparable. Embedding binding centers into a cavity can enhance complexation energies by several magnitudes as a consequence of hydrophobic forces;[5] the interference of hydrophilic moieties in the vicinity of hydrogen-bond centers may lead to a strong decrease of the observed total binding. These conditions are difficult to control in biopolymers, which may be the reason for the quite different reports on, for example, the strength of a peptide hydrogen bond which vary between ~2[6,7a] and ~20[7b] kJ/mol.

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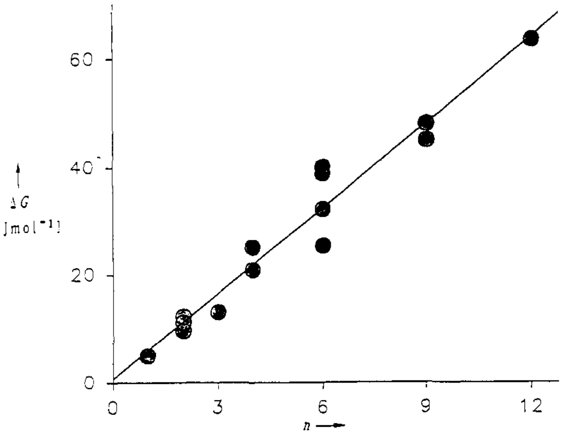

**Figure 1.** Free energies of complexation $\Delta G$ in ion pairs vs. the number of salt bridges $n$ (cf. eq 4). One point at $n = 2$ represents the average of nine ion pairs, another at $n = 4$ is from three pairs (Table I*, supplementary material).

On the basis of incremental analysis under well-defined conditions, we recently obtained from measurements with several amides a $\Delta G$ value of about 5 kJ/mol per hydrogen bond in $CDCl_3$ and of ~10 kJ/mol in $CCl_4$ solution.[8] Synthetic receptors are particularly amenable to incremental binding analysis, which was already tried with complexes of crown ethers,[9] cucubutyril derivatives,[10] as well as with ionic (Coulomb),[11] amide hydrogen bond,[8] and van der Waals[12a] binding contributions.[12b]

## II. Coulomb Interactions

Electrostatic forces play a decisive role in many synthetic host–guest complexes as well as in biological systems.[9,13] Detailed investigations, particularly of inorganic ion pairs, have shown that their formation in water is often dominated entropically by desolvation, and thus water liberation, and that van der Waals forces can contribute significantly to association.[14] The Bjerrum eq 2, which is derived from pure Coulomb point charge potentials and furthermore neglects differences between internal and solvent-separated ion pairs, describes the association constant $K$ as a function of charges $z$, the dielectric constant $\epsilon$, and a factor $Q(b)$ which contains the minimum and the effective mean distance ($d$) between the ionic centers A and B.[15] In spite of its limitations, the Bjerrum eq 2 predicts the stability of smaller and less polarizable *spherical* ion pairs fairly well with realistic distances of $5 < d < 7$ Å;[13a] larger deviations are found in cases of geometric mismatch, for example, between dicarboxylates and inorganic cations.[13a] If we now analyze, however, the $\Delta G_{HG}$ values of many organic ion pairs in water as function of the number of possible salt bridges $n$ between ions in contact, we observe a surprisingly linear correlation, giving an average increment of $\Delta G = (5 \pm 1)$ kJ/mol per salt bridge (Figure 1; eq 3). The selected ion pairs correspond largely to Scheme I, case I, implying a separation between the charges within the host H or the guest G which is at least as large as the distance $d$ between the counterion centers. The observed increment roughly corresponds to Bjerrum's Coulomb-based prediction, e.g., to $K \approx 100$ for $z_A = z_B = 2$ with $d \approx 6$ Å, but is unexpectedly uniform in spite of large differences in size and particularly in polarizability of the participating ions ($COO^-$, $SO_3^-$, $OPO(OH)O^-$, $OPOO_2^{2-}$, phenolate-$O^-$, $R_2NH_2^+$, $R_4N^+$, pyridinium $N^+$, $R_4P^+$; see Tables I* and II* of the supplementary material). The values reported by Tam and Williams[13a] for a number of organic ion pairs also *do* fall into the correlation (Figure 1); the deviations are mostly smaller than their experimental error and therefore do not—as implied by these authors—indicate significant entropy differences. We note, however, that the aromatic ion pairs generally show an increase in the binding energies with the number of aryl units (see section III).

$$K = \frac{4\pi N}{1000}\left[\frac{|z_A z_B|}{\epsilon k T}\right]^3 Q(b) \tag{2}$$

$$\Delta G_{ES} = (5 \pm 1)n \text{ kJ/mol} \tag{3}$$

That the charge distribution in the different ions has little influence on the total Coulombic energy, $E_{ES}$, is borne out by model calculations on the complex C (**1** + **8**). On the basis of rather extreme differences in point charges, e.g., varying for the $N^+$ atom in **1** from (a) 0.0 (with the point charges +1.0 placed entirely on the nitrogen atom) to (b) +0.130 (CNDO calculation) or (c) −0.151 (Gasteiger method as applied in the QUANTA/CHARMm[16] treatment[17]), we obtain by a point charge Coulomb calculation for $\Delta E_{ES}$ 160 (a), 108 (b), or 127 (c) kJ/mol, respectively (Table III* of the supplementary material). One can dismiss the less realistic model a in which the negative charge was also placed only at the three oxygen atoms in **8** and then must take into account the considerable charge delocalization by the solvent water as well as the desolvation processes of the ions. If we apply an attenuation factor of ~10, obtained by comparison of the $\Delta E_{ES}$ calculations (~50 kJ/mol) per salt bridge with the experimentally derived value of $\Delta G = 5 \pm 1$ kJ/mol (eq 4), the difference between the charge distribution models b and c becomes indeed quite small with $\Delta\Delta E_{ES} \approx 1$–2 kJ/mol (Table I* of the supplementary material). Other reasons for the surprisingly constant increment of 5 kJ/mol are (i) the relatively large distances $d$ (eq 3) in comparison to distances separating the fractional charges within the ions, cancellations between (ii) entropy terms as well as (iii) in desolvation energies and Coulombic attraction (small and hard ions require more desolvation but at the same time provide for closer Coulomb contacts), and finally (iv) the higher polarizability of larger ion shells, leading to smaller effective $d$ values in spite of larger vdW diameters. It is especially noteworthy that peralkylated and protonated ammonium ions show the same effective $\Delta G_{ES}$ increment (for examples, see Table II* in the supplementary material and related unpublished results with methylated compared to protonated azoniacyclophanes). This is in line with MO calculated charge distributions, which show most of the positive charges residing on the hydrogen atoms of $R_3N^+CH$ groups[18] (Table III*, supplementary material). Hydrogen bonds such as $N^+H\cdots{}^-OR$ play no additional role here in view of the similar $\Delta G_{ES}$ increments observed with $N^+CH_3\cdots{}^-OR$ systems; they are also incorporated in the Coulombic interactions

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**Table I.** Equilibria from Conductivity and/or NMR Measurements and NMR-CIS Values[a]

| ion pair[b] | ions[b] | $n$ | $m$ | $K$ | method[c] | $\Delta G$ | CIS, ppm ($\Delta G_s$) H-1 | H-2 | H-3 | H-4 |
|---|---|---|---|---|---|---|---|---|---|---|
| A | **1** | 2 | 4 | 480 | C | 15.3 | −0.268 | −0.393 | −0.504 | |
| | **6** | | | | | | −0.197 | +0.007 | | |
| B | **1** | 2 | 4 | 525 | C | 15.5 | −0.240 | −0.446 | −0.676 | |
| | **7** | | | | N | | −0.456 | −0.385 | −0.287 | |
| C | **1** | 2 | 4 | 715 | C | 16.3 | −0.130 | −0.271 | −0.467 | |
| | **8** | | | | | | −0.232 | −0.155 | −0.149 | |
| D | **1** | 2 | 3 | 250 | C | 13.7 | | | | |
| | **9** | | | | | | | | | |
| E | **2** | 2 | 3 | 320 | C | 14.3 | −0.224 | −0.392 | −0.566 | |
| | **8** | | | | | | −0.156 | −0.157 | −0.443 | |
| F | **3** | 2 | 2 | 150 | C | 12.4 | | | | |
| | **8** | | | | | | | | | |
| G | **4** | 2 | 2 | 190 | C | 13.0 | | | | |
| | **8** | | | | | | | | | |
| H | **5** | 3 | 7 | 4400 | N | 20.4 | −1.200 | −0.989 | −0.532 | −0.315 |
| | **10** | | | | | | (19.3) | (20.2) | (21.0) | (21.2) |
| I | **10** | 3 | 4 | 1000 | N | 17.1 | −0.121 | | | |
| | **11** | | | | | | (17.1) | | | |
| J | **10** | 3 | 6 | 7460 | N | 22.1 | −0.182 | −0.104 | −0.228 | −0.254 |
| | **5** | | | | | | (21.8) | (22.7) | (22.4) | (21.3) |

[a] Equilibrium constants $K$ (in $M^{-1}$); free energy of complexation $\Delta G$ (in kJ/mol); complexation-induced NMR shifts (in ppm). Measurements in $H_2O$ or $D_2O$ at 25 °C; $K$ and $\Delta G$ are without corrections for ionic strength differences. If several single $K_s$ or $\Delta G_s$ values are available for one complex, $\Delta G$ is the average from single $\Delta G_s$ values. Number of salt bridges in a complex, $n$; number of aromatic moieties, $m$. [b] See Scheme I. [c] $K$ was obtained from conductivity (C) and/or NMR (N) measurements.

in all point charge model calculations used.

## III. Aromatic Systems: van der Waals and Charge-Transfer Contributions

The new measurements reported in this section are based on ions containing largely rigid aromatic fragments, which should minimize entropic differences and allow us to study the special interactions between charges and aromatic moieties,[6,19] as well as those between electron-deficient and electron-rich arenes (Chart I). At the same time, we wanted to compare methods for equilibrium measurements[20] comprising NMR and UV/vis spectroscopy as well as conductivity. The conductivity measurements,[13a] which can be carried out with high accuracy, are described in detail elsewhere;[21] they are limited by partially arbitrary assumptions with respect to the interionic distances and by their theoretical basis in pure Coulombic interactions, and for reliable results they are also limited to 1:1 or 2:2 ion pairs (such as A to G in Chart I, Table I), as well as by the necessary absence of additional electrolytes. These factors can lead to larger deviations found in comparison to as well as within literature data. Nevertheless, the one complex (B from **1** + **7**) measured by *all* three methods showed $\Delta G$ = 15.5 (conductivity), 15.8 (NMR, from three independent signals), and 14.2 (UV/vis), kJ/mol, a gratifying agreement. It should be kept in mind that the optical measurements refer largely to contact ion pairs and also show the presence of non-AB (1:1) ion pairs (see below, Table II); both factors usually lead to smaller $\Delta G_{HG}$ values with this method. For complex C (**1** + **8**) acceptable agreement was again obtained between conductivity (16.3 kJ/mol) and UV/vis (13.7), whereas A (**1** + **6**) shows smaller values (9.4 for AB and 7.0 for $AB_2$ kJ/mol) by the UV/vis method.

**NMR titrations** were carried out and evaluated as described earlier[22] with the ion pairs H, I, and J featuring 3 + 3 charges, in addition to B. The aromatic ring current and the field effects of the ionic centers produce shift differences upon complexation. In contrast to a recent ion pair study in dimethyl sulfoxide,[23] the CIS values are large enough to allow accurate $\Delta G_{HG}$ determinations from up to four different signals, which usually agreed within ±5% (Table I). Complexation-induced NMR shifts (CIS), which were determined for H, I, J, and B simultaneously with the equilibrium constants by nonlinear least-squares fits of the NMR titration curves,[22] also provide the most valuable insight into the *structure* of such complexes in solution. Therefore, CIS values were also obtained in selected cases (A, C, E) without NMR titration from single NMR measurements at complexation degrees known from the independently evaluated equilibrium constants.[24]

**Table II.** UV/vis Spectroscopic Determinations[a,b]

| | $K_{AB}$ | $K_{AB_2}$ | $\Delta G_{AB}$ | $\Delta G_{AB_2}$ | extinction coefficients $\epsilon$[c] λ | AB | $AB_2$ |
|---|---|---|---|---|---|---|---|
| A (**1** + **6**) | 44 | 17 | 9.4 | 7.0 | 380 | 107 | 386 |
| | | | | | 400 | 40 | 183 |
| | | | | | 410 | 16 | 112 |
| B (**1** + **7**) | 305 | 28 | 14.2 | 8.3 | 420 | 168 | 201 |
| | | | | | 430 | 121 | 196 |
| | | | | | 440 | 81 | 173 |
| C (**1** + **8**) | 250 | 55 | 13.7 | 9.9 | 370 | 128 | 30 |
| | | | | | 390 | 62 | 55 |
| | | | | | 400 | 54 | 73 |

[a] See footnote a of Table I. [b] $K$ and $\Delta G$ are from best fit curves measured at the three wavelengths λ (nm) given. [c] Corresponding UV extinction coefficients.

The CIS values of paraquat **1** show a regular shielding increase from, for example, −0.13 ppm at the periphery (H-1) to −0.47 ppm, and more, at the center. This is in general agreement with the complex structures obtained from CHARMm simultaneous which picture the aromatic moieties sandwiched (Figure 2). This shifts clearly *contradict* edge-to-face conformation with the electropositive C–H edge of one benzene unit in contact with the electronegative π-cloud of another.[25] The protons of the ionic counterparts **7** in B and **8** or **2** in C and E again show the shielding variations expected for face-to-face structures (Figure 2); the different CIS values observed on **6** in A may be the consequence

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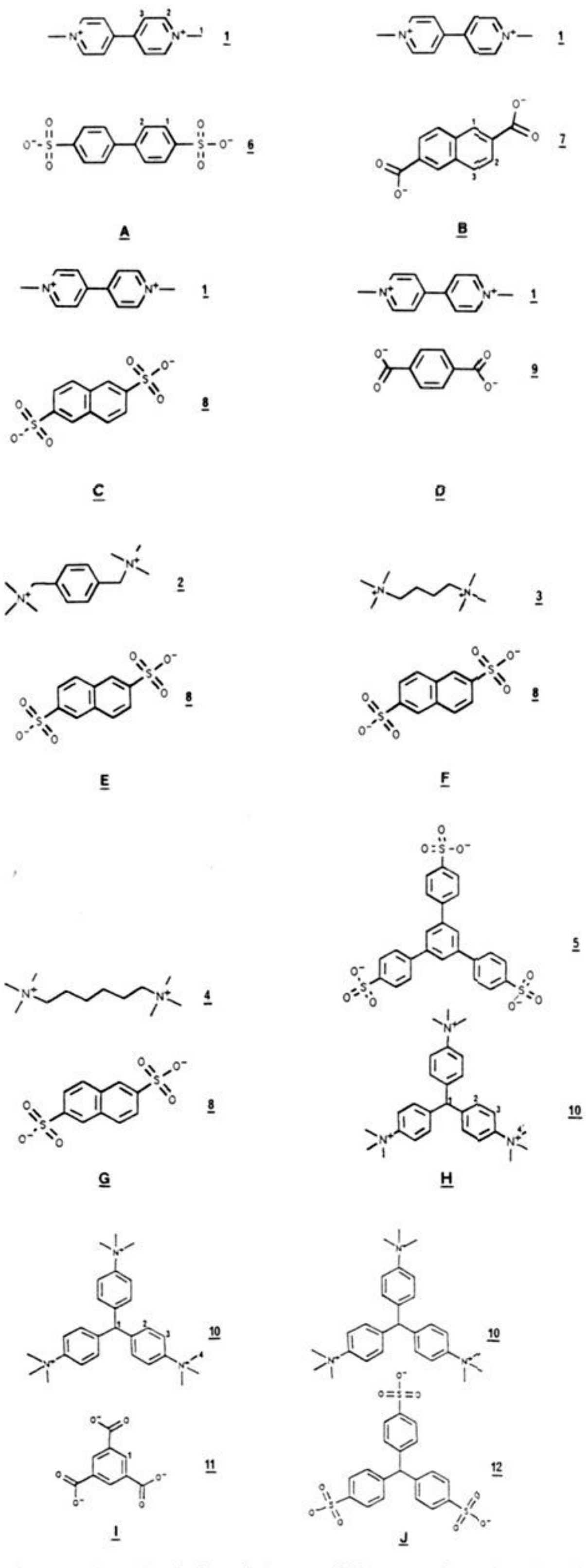
**Chart I.** Overview of Structures



of a complexation-induced change of the central torsional angle in the biphenyl unit. In contrast to ion pairs A–G, the 3 + 3 counterions H, I, and J allow *no* face-to-face sandwiching of all aryl units nor full contact between all ionic centers of opposite charge. This is visible in model observations by selected molecular mechanics (CHARMm) simulations (Figure 3); the CIS values, furthermore, are large only in the ion pair H (on **10**) due to the additional aryl unit present in **5**.

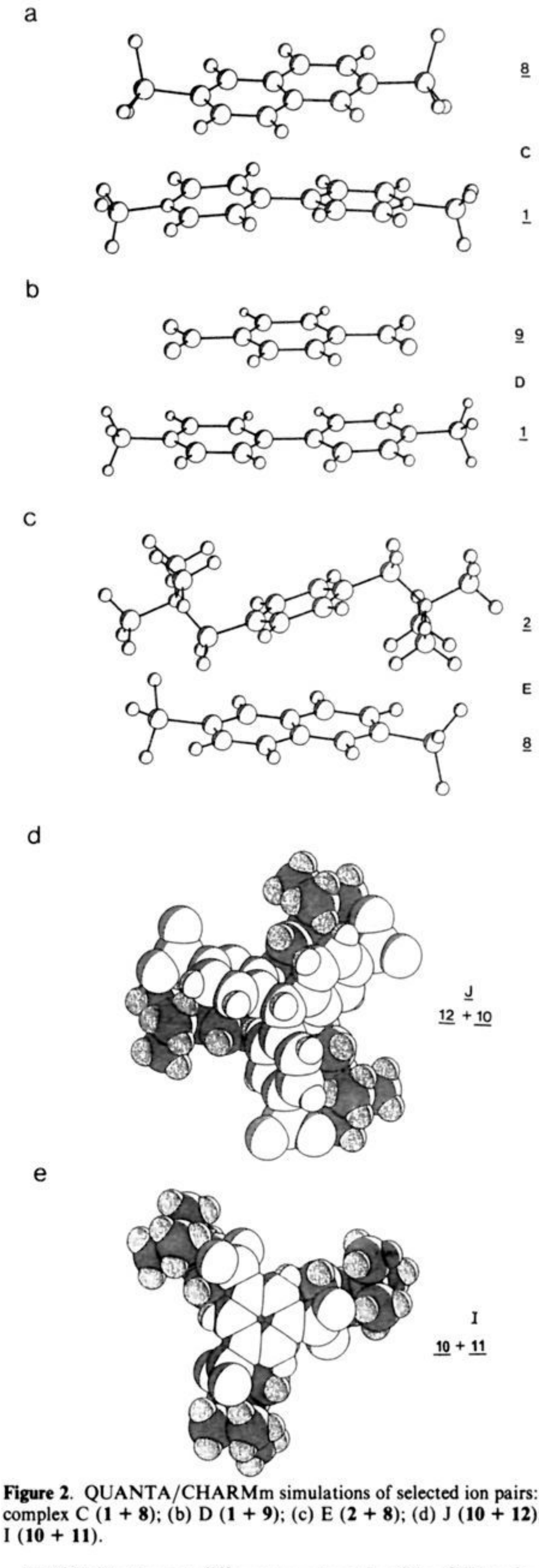


**Figure 2.** QUANTA/CHARMm simulations of selected ion pairs: (a) complex C (**1** + **8**); (b) D (**1** + **9**); (c) E (**2** + **8**); (d) J (**10** + **12**); (e) I (**10** + **11**).

**UV/vis titrations** at different wavelengths of the CT bonds used here yielded wavelength-dependent equilibrium constants $K_{AB}$ based on 1:1 complexes AB (Figure I*, supplementary material). Plots of extinction differences at different wavelengths (Figure II*, supplementary material) showed straight lines indicative of a three-particle system.[20b] Nonlinear numerical curve fitting procedures similar to those described earlier[26] were used to search

Table III. Solvent Effects from UV Spectroscopic $K$ Determinations[a-c]

| | $K_{AB}$ | $K_{AB_2}$ | AB 420 nm | AB 430 nm | AB 440 nm | $AB_2$ 420 nm | $AB_2$ 430 nm | $AB_2$ 440 nm |
|---|---|---|---|---|---|---|---|---|
| | | | | B (1 + 7) | | | | |
| 100% $H_2O$ | 305 | 30 | 170 | 120 | 80 | 200 | 200 | 170 |
| 20% MeOH | 170 | 30 | 170 | 120 | 80 | 225 | 210 | 180 |
| 40% MeOH | 130 | 40 | | 120 | 80 | | 190 | 150 |
| 80% MeOH | 250 | 30 | 130 | 100 | 80 | 820 | 685 | 530 |
| 40% EtOH | 195 | 45 | 165 | 125 | 90 | 230 | 200 | 160 |
| 80% EtOH* | 1100 | | 180 | 150 | 110 | | | |
| 60% acetone* | 330 | 15 | 360 | 270 | 200 | | | |
| 75% dioxane* | 1130 | 350 | 590 | 530 | 420 | 710 | 610 | 605 |
| 80% dioxane* | 3780 | | 260 | 225 | 180 | 420 | 370 | 315 |
| | $K_{AB}$ | $K_{AB_2}$ | AB 370 nm | AB 390 nm | AB 400 nm | $AB_2$ 370 nm | $AB_2$ 390 nm | $AB_2$ 400 nm |
| | | | | C (1 + 8) | | | | |
| 100% $H_2O$ | 250 | 55 | 128 | 62 | 54 | 30 | 55 | 73 |
| 20% MeOH | 114 | 103 | 224 | 118 | 76 | 216 | 167 | 125 |
| 40% MeOH | 111 | 142 | 200 | 112 | 75 | 229 | 159 | 116 |
| 40% EtOH | 118 | 130 | 204 | 161 | 78 | 257 | 180 | 133 |
| 60% acetone | 263 | 324 | 217 | 129 | 88 | 219 | 158 | 117 |

[a,b] See corresponding footnotes to Table II. [c] Errors in $K$ usually ±10%, measurements denoted by *, ±25%; see text.

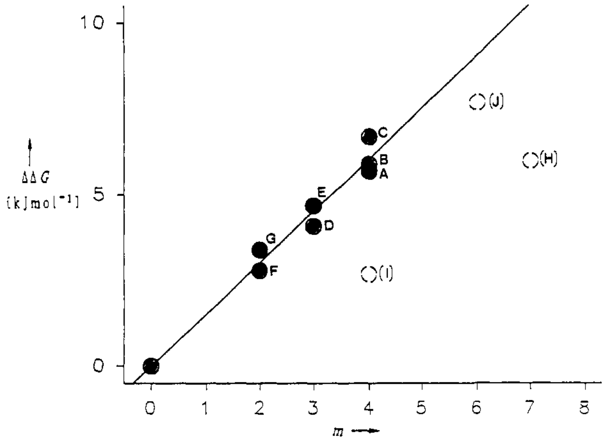


Figure 3. Additional van der Waals interactions in ion pairs A–J as a function of the number of phenyl rings $m$ in the ion pairs (cf. eq 5). The trityl compounds H, I, and J deviate for structural reasons; see text.

for optimal constants $K_{AB}$, $K_{A_2B}$, or $K_{AB_2}$ and for the corresponding extinction coefficients $\epsilon_{AB}$, $\epsilon_{A_2B}$, or $\epsilon_{AB_2}$. Under the conditions that all $\epsilon$ coefficients should be within similar orders of magnitude and should also show a steady dependence on wavelength, it was possible to always eliminate one of the 1:2 (or 2:1) complexes as an unrealistic solution. The best fit values obtained in this way (Table II) shows substantially smaller equilibrium constants for the $AB_2$ compared to the AB ion pairs, as is also expected from the NMR titrations which were based on assumed 1:1 complexes only. In the case of complex A (**1** + **6**), both the small $K_{AB}$ and the relatively large $K_{AB_2}$ value are a consequence of the rather poor geometric fit of the complex and the nonideal contact between anion and cation in this case, as is obvious from model considerations. The relatively strong association observed for the pairs B (**1** + **7**) and C (**1** + **8**) can be due to small additional van der Waals and/or charge-transfer interactions (see below).

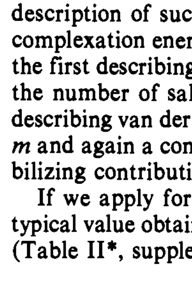
**Solvent effects** were also studied by UV/vis titrations at varying wavelengths, yielding smooth variations of both $K_{AB}$ and $K_{AB_2}$ with water content in the binary solvent mixtures used (Table III). Although the attainable accuracy is severely limited for the more lipophilic mixtures due to the necessarily small concentrations used here and the subsequently small observable absorbances, the results clearly contradict the most simple assumption of a linear dependence of log $K$ on the dielectric constant[15] (Figure III*, supplementary material). This is in line with other observations on solvent effects on ion pair association, which also can reflect dominating entropy contributions.[27] Nevertheless, it is also important for practical applications that the equilibrium constants increase, for example, by a power of magnitude from water to 75–80% dioxane.

We now address the question of additional **van der Waals-type contributions** arising from the aromatic moieties present in different numbers in the ion pairs. Inspection of all $K$ values already indicates an increase with the number of phenyl rings $m$ being part of either the anion, the cation, or both. In the most simple description of such a situation, we can consider the total free complexation energy $\Delta G_t$ as the sum of two independent terms, the first describing the Coulomb-type attraction as a function of the number of salt bridges (eq 4, Figure 1) $n$ and the second describing van der Waals (or other) interactions as a function of $m$ and again a constant increment $\Delta G_V$, which contains the stabilizing contribution of a single aryl unit in an ion pair.

If we apply for the Coulomb increment of 4.8 kJ/mol as a typical value obtained, e.g., from measurements with zinc sulfate (Table II*, supplementary material), we arrive at

$$\Delta G_t = n4.8 + m\Delta G_v \tag{4}$$

A plot of the observed $\Delta G_t$ vs $m$, using $n$4.8 as correction for the Coulombic attraction (eq 2) indeed furnishes a linear correlation (Figure 3) for all measured ion pairs, with the only exception being the trityl or triphenyl complexes H, I, and J in which the geometry of triphenylmethane prevents (as is visible from Dreiding models, for example) an ideal contact between the aromatic unit and its counterpart. More significantly, the *slope* of the linear correlation yields a van der Waals increment of $\Delta G_v \cong 1.5$ kJ/mol, which is in the range of van der Waals interactions observed independently in other models. Thus, the association free energies in the complexes V1 and V2 are 5–6 kJ/mol:[28] in the absence of any permanent electrostatic interactions, the ion X is placed here in a more optimal position opposite the polarized $\pi$-systems, leading to 2.5–3 kJ/mol per X $\pi$-interaction. Furthermore, similar



V1: Y=NH; X=$^+NMe_3$ ΔG=6.0 kJ/mol

V2: Y=NH; X=$SO_3^-$ ΔG=5.3 kJ/mol

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(26) Schneider, H.-J.; Blatter, T.; Simova, S. *J. Am. Chem. Soc.* **1991**, *113*, 1996.

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$\Delta G_V$ contributions have been deduced from the complex formation energies of azacyclophanes with aromatic vs alicyclic substrates[19b] or with diiodomethane vs dichloromethane,[5] which also demonstrate the importance of ionic charges vis-a-vis polarizable groups for such attractive interactions.

**Charge-transfer** interactions[29] could be expected to play a role in ion pairs comprising electron-deficient and electron counterparts, such as in complexes A–E. These indeed show CT bands at typical[29] wavelengths and extinction coefficients (Table III), which were actually the basis for the UV/vis equilibrium titrations. However, *no* additional stabilization is observed in the correlation (Figure 3) for these complexes in comparison to complexes such as F or G, which of course show no CT bands. That CT contributions, even in the presence of typical UV/vis absorptions, are negligibly small (<0.5 kJ/mol) in such supramolecular systems is completely in line with known free association energies of classical CT complexes, which even, for example, for trinitrobenzene + toluene is *negative* with −2 kJ/mol (in $CCl_4$).

## IV. Conclusions

The stabilization of organic ion pairs in water as solvent can be quantified by simple additive increments, not only with respect to the number of salt bridges or Coulombic interactions involved but also with respect to additional van der Waals effects. Together with the evidence from related studies with cyclophanes bearing alternatively $N^+$ atoms or no charges in the vicinity of well-polarizable substrates, the results indicate a stabilization of $\Delta G_V \approx 2$ kJ/mol for the interaction of *either* a cation or an anion with a phenyl ring located in a suitable vicinity opposite the charges by induced dipoles in the $\pi$-systems. The results also show that hydrophobic stacking only contributes to a minor degree: systems like, for example, F and G as well as V1 and V2 show similar "extra" van der Waals stabilizations, although they lack the presence of aryl units positioned properly for $\pi$–$\pi$ stacking interactions. Given a minimum of conformational mobility systems comprising charged groups, aromatic—or other easily polarized—units obviously arrange in geometries which allow a maximum of Coulombic contacts as well as attractions by induced dipoles. Under conformational constraints, as in crystals for example, $\pi$-$\pi$ interactions are often characterized by mutual displacements[30] of aromatic systems in order to avoid actually repulsive electrostatics and also to enable permanent dipole–dipole or dipole–quadrupole interactions. These findings have an impact on protein structures, which are often characterized by aromatic rings (e.g., from phenylalanine) perpendicular to $N^+$ groups (from basic amino acids[6]). While X-ray studies of many structures can provide statistically meaningful information about the geometric consequences of such nonbonded interactions,[6] the measurement of host–guest equilibria can deliver experimental numbers for these. It is hoped that NMR shielding data and nuclear Overhauser effects will in the future also give insight into the solution geometries.

## V. Experimental Details

Compounds were, if not commercially available, prepared by literature methods (**3**[31], **6**[32]) or by modified procedures.

**1,4-Xylylenebis(trimethylammonium iodide) (2).**[33] Xylylenediamine (10 g, 0.073 mol) and 21 g (0.15 mol) of potassium carbonate were mixed in 200 mL of methanol, and 36 mL (0.57 mol) of methyl iodide was added while chilling. After 20 h of stirring at room temperature, the mixture was worked up by filtering washing, and recrystallizing from water; yield, 19.5 g (56%) of colorless powder, mp >300 °C dec: $^1H$ NMR ($D_2O$) $\delta$ (ppm) 3.16 (s, 18 H, $CH_3$), 4.59 (s, 6 H, $CH_2$), 7.73 (s, 4 H, aromatic).

**1,3,5-Tris(4-sulfophenyl)benzene (5)** was obtained by modification of a known procedure[34] from 5 g (16.4 mmol) of 1,3,5-triphenylbenzene and 15 g (0.150 mol) of concentrated sulfuric acid heated to 110 °C for 16 h. After cooling, the material was filtered, taken up with ether, filtered again, and dissolved in 100 mL of water. Excess sulfuric acid was removed by adding barium hydroxide; after filtration from $BaSO_4$, the material was converted with ion-exchange resin to the sodium salt to yield, after several precipitations with ethanol, 5.5 g (55%) of a colorless powder, which is stable to 350 °C: $^1H$ NMR ($D_2O$, ppm) 7.43 (s, 3 av H), 7.86 (d, 6 av H), 7.47 (d, 6 av H).

**Tris[4-(trimethylammonio)phenyl]methane triiodide (10).** Tris[4-(dimethylamino)phenyl]methane (5 g, 0.008 mol) (see below) was stirred with 25 mL (0.4 mol) of methyl iodide in 250 mL of acetonitrile for 20 h at room temperature; after filtration, the residue was dissolved in water and acetone was added to precipitate 6.0 g (93%) of colorless crystals, mp 260 °C dec: $^1H$ NMR ($D_2O$, ppm) 3.73 (s, 27 H, $CH_3$), 5.89 (s, 1 H, CH), 7.78/7.95 (AB with $J$ = 10.1 Hz, 12 av H).

**Tris[4-(dimethylamino)phenyl]methane.** Bis[4-(dimethylamino)-phenyl]methanol (25 g, 0.092 mol), 44.8 g (0.37 mol) of *N*,*N*-dimethylaniline, and about 1 g of *p*-toluenesulfonic acid were refluxed in 300 mL of toluene for 12 h. After washing with water and removal of toluene and excess dimethylaniline in vacuo, the residue was treated with acetone until 32.6 g (95%) of a colorless material was obtained: $^1H$ NMR ($CDCl_3$, ppm) 2.90 (s, 18 H, $CH_3$), 5.26 (s, 1 H, CH), 6.67/7.22 (AB, with $J$ = 9.3 Hz, 12 av H).

**Tris(4-sulfophenyl)methane (12)** was obtained in a manner similar to **5** by stirring 12.2 g (0.05 mol) of triphenylmethane with 25 mL of sulfuric acid for 6 days at room temperature. In spite of several precipitations with water/ethanol, the material remained contaminated by ~10% inorganic salts and ~5% isomeric acids: $^1H$ NMR ($D_2O$, ppm) 5.74 (s, 1 H), 7.19/7.69 (AB, $J$ = 10.1 Hz, 12 av H).

**NMR and UV/vis** spectroscopic measurements and equilibrium titrations were performed and evaluated as described earlier.[22,26] Purity and content of the salts were controlled by quantitative NMR spectra prior to use; concentrations of the stock solutions for the titrations were accurate to ±3% on the average. Errors for $\Delta G$ from the equilibrium titrations (tables I–III) were estimated by comparison of values from single NMR shifts or from single wavelengths to be, on the average, ±0.5 kJ/mol.

**Molecular modeling** studies were carried out with QUANTA/CHARMm[16] (from POLYGEN) on an IRIS 3130 (Silicon Graphics) workstation; energy minimizations, which were used only for checking the geometries, were carried out under gas-phase conditions.

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**Supplementary Material Available:** Tables of additional equilibrium constants for ion pairs (Tables I*–III*), mostly from the literature, and corresponding plots (Figures I*–III*) (5 pages). Ordering information is given on any current masthead page.

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