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Ion-Pair Binding: Is Binding Both Binding Better?

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Abstract: It is often tempting to explain chemical phenomena on the basis of intuitive principles, but this practice can frequently lead to biased analysis of data and incorrect conclusions. One such intuitive principle is brought into play in the binding of salts by synthetic receptors. Following the heuristic concept that "binding both is binding better", it is widely believed that ditopic receptors capable of binding both ionic partners of a salt are more effective than monotopic receptors because of a cooperative effect. Using a newly designed ditopic receptor and a generalized binding descriptor, we show here that, when the problem is correctly formulated and the appropriate algorithm is derived, the cooperativity principle is neither general nor predictable, and that competition between ion binding and ion pairing may even lead to inhibition rather than enhancement of the binding of an ion to a ditopic receptor.

Keywords: affinity descriptors · cooperative effects · ion binding · ion pairs · receptors

Introduction

Cooperativity is a concept that is often invoked to explain phenomena that are not well understood and appear to produce effects beyond expectation. One such phenomena that has recently been gaining in popularity is cooperativity in the binding of an ion pair by synthetic ditopic receptors, which can simultaneously binding the anion and the cation of a salt with higher affinity than is observed toward each of the partners.[1,2] The underlying heuristic principle is that "binding both is binding better". This intuitively plausible concept rests, however, on ambiguous evidence, which does not allow a clear-cut assessment of true cooperativity. In fact, the current literature on binding of ion pairs to ditopic receptors is essentially based on 1) crystallographic evidence,[3–11] which demonstrates the existence of ion-pair complexes but not of cooperative effects, 2) transport through membranes[7,12–15] or extraction from aqueous solutions,[4,16–21] which is not necessarily or solely dependent on cooperativity, and 3) binding measurements in solution,[5,6,10,11,22–40] which suffer from a number of inconsistencies that do not allow a convincing and unambiguous assessment of cooperativity. This drawback is caused by the common practice of comparing the association constant of an ion pair with a ditopic receptor, usually measured by ^{1}H NMR spectroscopy in organic solvents through a single signal of a single reagent, to the association constant of the ditopic receptor with the investigated anion or cation in the presence of an innocent counterion, but neglecting other equilibria (ion pairing, higher stoichiometry association, etc.) that may occur in solution; in addition, in all cases experimental data are fitted to a 1:1 association model for both the ion and the ion-pair complexes. Such a simplified approach is inconsistent for several reasons: 1) systems containing multiple species and/or higher stoichiometry complexes cannot be fitted to a 1:1 binding isotherm; 2) the comparison is conceptually ill defined, because the ternary ion pair/receptor complex and the binary ion/receptor complex are incommensurable, having different dimensionality; 3) a three-reagent species like an ion-pair complex cannot obviously fit into a two-reagent 1:1 model; 4) the counterion is not inert and cannot be neglected. It is in fact little appreciated that even an innocent counterion, although unbound,

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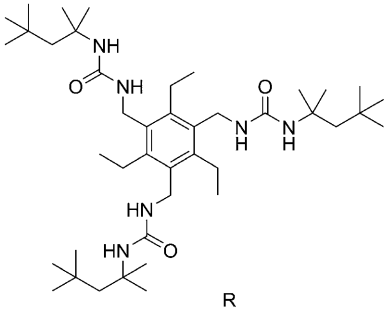
affects binding of the ion under consideration by taking part in ion-pairing equilibria that determine the actual availability of the observed ion.

To find an unambiguous way to ascertain whether cooperativity truly enhances binding of an ion pair, we re-examined the problem from the basic question: "is binding what better than what?". The first requirement for a homogeneous comparison is necessarily the definition of an appropriate reference. Considering that complexes of ions cannot be compared to complexes of ion pairs, the correct reference should be the affinity of the reactant (the ion) rather than that of a product (the ion pair), so a dimensionally correct approach consists of comparing the affinities of individual reacting ions in the presence and absence of a co-bound counterion. This requires taking into account all equilibria involving bound species, measuring the corresponding formation constants, and translating them into a global affinity of the ion under consideration, since in multi-equilibrium systems the overall affinity is not adequately described by any of the constants alone. Positive cooperativity will then emerge when the affinity of the ion for a ditopic receptor simultaneously binding the counterion exceeds that found for a corresponding monotopic receptor or for a ditopic receptor in the presence of an unbound (but not inert) counterion. We stress that, except for limiting cases, a simple 1:1 association model is necessarily inadequate to describe the system, because a salt undergoes an ion-pairing equilibrium in solution, especially in organic solvents, and the free ions as well as the ion pair originating from the equilibrium are both, in general, capable of binding to the receptor, whether mono- or ditopic, so that a three-constant model is the minimum required model for treating the binding of salts. The affinity of an ion will therefore be determined by at least three independent, non-negligible association equilibria.



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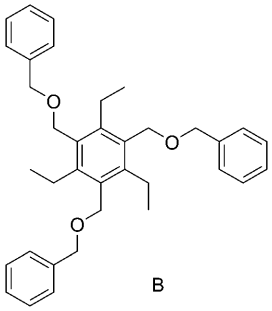


B

Results and Discussion

Searching for a convenient approach to address the issue of cooperativity, we devised a ditopic receptor that could be dissected into the two constituent monotopic binding sites, one exclusively capable of binding the cation and the other the anion of a salt. In this way, the association of each ion of the salt with the ditopic receptor could be investigated and independently compared under the same conditions to that with the corresponding monotopic counterpart, avoiding the presence of "innocent" counterions, while taking into account the ion-pairing equilibrium of the salt and all complexes of free ions and ion-pairs with each of the three receptors. Following this approach, we conveniently employed some tripodal receptors that we had developed for different purposes in our molecular recognition studies.

The tripodal ureidic receptor R, which shows significant binding affinities for glycosides of monosaccharides,[41] was found to effectively bind the chloride anion (X) in $CDCl_3$/CD_3CN (80/20), a medium in which both the salt and the receptor displayed acceptable solubility. Careful analysis of the ^1H NMR titration experiments of tetramethylammonium chloride (QX) with R in the above medium allowed reliable determination of the formation constants of the complex species formed in solution.[42] From the results collected in Table 1 (see the Supporting Information), it can be noted that, besides a small degree of dimerization of the receptor and a non-negligible ion-pair formation constant, which was in excellent agreement with the value of $\log\beta = 4.05 \pm 0.01$ independently measured by a dilution experiment on QX in the same medium,[42] 1:1 and 2:1 receptor:chloride complexes were detected, together with the complex of the monotopic receptor with the whole ion pair. On the contrary, no evidence of binding to the tetramethylammonium (Q) cation could be found by control experiments with the picrate salt. On the other hand, the benzylic receptor B, which was employed in the course of our studies on the cation–π interaction, was found to bind to Q in the above medium with moderate but measurable affinity. The formation constants of the species formed with QX in the above solvent mixture are collected in Table 2 (see the Supporting Information).

As for R, complexes of the receptor with both the free and the ion-paired Q cation were detected, together with ion-pair formation. The corresponding value of the constant

Table 1. Cumulative formation constants β with standard deviations σ for complexes of ureidic receptor R with tetramethylammonium chloride (QX).[a]

Species	β	$\lg\beta$
RQX	$(1.32\pm0.02)\times10^{6}\,M^{-2}$	6.121 ± 0.010
RX	$(8.83\pm0.02)\times10^{2}\,M^{-1}$	2.946 ± 0.008
R_2	$(6.06\pm0.06)\times10^{0}\,M^{-1}$	0.783 ± 0.027
R_2X	$(3.25\pm0.11)\times10^{4}\,M^{-2}$	4.513 ± 0.046
QX	$(1.23\pm0.01)\times10^{4}\,M^{-1}$	4.090 ± 0.005

[a] Measured by ^1H NMR (400 MHz) from titration experiments at $T=298$ K in $CDCl_3/CD_3CN$ (80/20) on 0.13/1.06 mmol L^{-1} solutions of QX using receptor concentrations up to 22 mmol L^{-1}. Formation constants were obtained by simultaneous nonlinear least-squares fit of the shifts of all available signals from two independent titrations run at different salt concentrations. Global standard deviation of the fit $\sigma=0.00027$ ppm (RMS weighted residual = 0.00025). Data are reported from ref. [42].

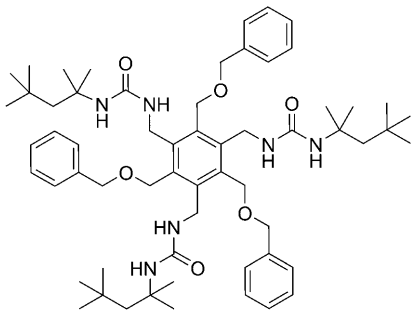
Table 2. Cumulative formation constants β with standard deviations σ for complexes of benzylic receptor B with tetramethylammonium chloride (QX).[a]

Species	β	$\lg\beta$
BQX	$(5.85\pm0.05)\times10^{4}\,M^{-2}$	4.767 ± 0.021
BQ	$(2.36\pm0.02)\times10^{1}\,M^{-1}$	1.373 ± 0.007
QX[b]	$(1.23\pm0.01)\times10^{4}\,M^{-1}$	4.090 ± 0.005

[a] Measured by ^{1}H NMR (400 MHz) from titration experiments at $T=298$ K in $CDCl_3/CD_3CN$ (80/20) on 0.185/1.03 mmol L^{-1} solutions of QX with receptor concentrations up to 59 mmol L^{-1}. Binding constants were obtained by simultaneous nonlinear least-squares fit of the shifts of the only available Me signal from two independent titrations run at different salt concentrations. Global standard deviation of the fit $\sigma=0.00055$ ppm (RMS weighted residual = 0.00051). [b] The ion-pair formation constant was taken from Table 1 and kept invariant in the refinement.

of the latter from Table 1 was used in the fit and kept invariant in the refinement.

In the next step, the two monotopic receptors R and B were combined into the architecture of ditopic receptor D, designed for the independent binding of both ionic partners of QX.



D

Indeed, due to steric gearing, the alternate topology of substituents[43] is expected to allow the cation and the anion to bind to opposite sides of the aromatic ring of D, in such a way that each side would closely mimic its monotopic counterparts R and B. The synthesis of receptor D was accomplished in seven steps from mesitylene with an overall unoptimized yield of 10% (see the Supporting Information). Following the methodology described for R,[42] a reliable set of formation constants could be accurately measured for the complex species detected in the association of ditopic receptor D with QX in $CDCl_3/CD_3CN$ (80/20) at 298 K (See Supporting Information). The results are reported in Table 3 as cumulative formation constants.

As expected, besides the complexes of the free ions, complexes with one and two ion pairs were also formed, whereas dimerization of the receptor was negligible. As for B, the value of the ion-pair formation constant from Table 1 was used in the fit and kept invariant in the refinement. The six-constant model, although quite complex, is the only model giving an excellent fit with experimental data, far better than any other model tested, so it can be confidently considered a reliable description of the system.[44]

Table 3. Cumulative formation constants β with standard deviations σ for complexes of ditopic receptor D with tetramethylammonium chloride (QX).[a]

Species	β	$\lg\beta$
DQX	$(2.35\pm0.04)\times10^{5}\,M^{-2}$	5.371 ± 0.017
DQ_2X_2	$(1.15\pm0.04)\times10^{12}\,M^{-4}$	12.061 ± 0.018
D_2[b]	$(1.55\pm0.02)\times10^{0}\,M^{-1}$	0.189 ± 0.006
DQ	$(9.61\pm0.05)\times10^{0}\,M^{-1}$	0.983 ± 0.022
DX	$(1.36\pm0.05)\times10^{2}\,M^{-1}$	2.132 ± 0.020
QX[c]	$(1.23\pm0.01)\times10^{4}\,M^{-1}$	4.090 ± 0.005

[a] Measured by ^{1}H NMR (400 MHz) from titration experiments at $T=298$ K in $CDCl_3/CD_3CN$ (80/20) on 0.24/1.08 mmol L^{-1} solutions of QX at receptor concentrations up to 54 mmol L^{-1}. Formation constants were obtained by simultaneous nonlinear least-squares fit of the shifts of all available signals from two independent titrations run at different salt concentrations. Global standard deviation of the fit $\sigma=0.00016$ ppm (RMS weighted residual = 0.00015). [b] The formation constant was kept invariant in the final refinement. [c] The ion-pair formation constant was taken from Table 1 and kept invariant in the refinement.

Assessing affinities: Having the formation constants of all the complex species available for the three receptors, in the next step we need to assess the affinities of X for receptors R and D, and of Q for receptors B and D. The question arises how to evaluate affinities for systems of three reagents involving more than one binding constant in which complex species of different stoichiometry are present. It may be tempting to compare the formation constants of corresponding ternary complexes, such as RQX and DQX. Following this approach, we can easily appreciate that the cation-binding site does not enhance the affinity of the ditopic receptor for the anion. However, such an approach is misleading, because the affinities of the receptors do not rely solely on ternary complexes; indeed, other species may compensate the contribution from the ternary complexes. Rather, what we need is to convert the set of association constants into a parameter describing the overall affinity. We have addressed this issue by using the median binding concentration (BC_{50}) parameter,[41] which we have shown to be a generalized binding descriptor[45] useful for comparing heterogeneous binding data and which we have recently extended to include the binding of salts.[46] The BC_{50} parameter, which is defined as the total concentration of a reagent (e.g., a receptor or a ligand) necessary for binding 50% of an observed species (e.g., a ligand or a receptor), is calculated from the measured formation constants[47] and is best expressed as a function of the fraction of bound reagent (i.e., the reagent for which we want to evaluate the affinity), which represents the saturation degree of the reagent itself. Considering that for 1:1 complexes, when the fraction of bound reagent is zero, BC_{50} coincides with the dissociation constant K_d,[41] the BC_{50} parameter can be visualized as a global dissociation constant. Affinities assessed through the BC_{50} parameter are thus related to dissociation constants and, consequently, to binding free energies. The BC_{50} value is a convenient and practical affinity descriptor, as 1) it takes into account the contribution from all the complex species involved but is independent of the association model, 2) it can be used for direct comparison of heteroge-

neous systems because it has the units of a concentration in all cases, and 3) its usage is straightforward as, in analogy to the widespread IC_{50} parameter, the lower the BC_{50} value, the higher the affinity. In the present study, the appropriate approach will consist of calculating the BC_{50} values of each ion toward the ditopic receptor from the sets of formation constants in Tables 1–3 and comparing these values to those calculated toward the respective monotopic receptors. Considering that the actual affinity varies with the saturation of the reagent, the comparison is best accomplished by plotting the BC_{50} values against the fraction of bound reagent in the entire complexation range. Thus, from comparison of the BC_{50} curves, the occurrence of binding cooperativity, if any, exerted by the ditopic receptor can be easily evidenced and quantitatively assessed.

To define a three-reagent system, BC_{50} calculation requires fixing, besides the conditions for the two binding partners, the concentration of the counterion;[42] this can be done by imposing the condition that the electroneutrality of the solution must be maintained. Such a condition is satisfied by choosing, for each value of the fraction of bound reagent, a free concentration of the counterion that will maintain the total concentration of the cation equal to that of the anion. Using the "BC_{50} calculator" program,[47] BC_{50} values were thus calculated for both ions under these conditions and the results are reported in Figures 1 and 2 (see the Supporting Information). Examination of the affinity profiles of Q for the monotopic receptor B and the ditopic receptor D depicted in Figure 1a reveals for the BC_{50} parameter a hyperbolic trend featuring saturation behavior for both receptors, with values asymptotically approaching the infinite for complete complexation.

At the other end, the curves intersect the BC_{50} axis for $x_{\text{bound cation}}=0$ (BC_{50}^0), where the unbound cation is forming the first complex molecule, giving the intrinsic affinities for the two receptors. The corresponding BC_{50}^0 values were $1.95(9)\times10^{-1}$ mol L^{-1} (B) and $1.19(3)\times10^{-2}$ mol L^{-1}(D). Clearly, the curve of the ditopic receptor lies below the curve of the monotopic receptor in the whole complexation range, including the BC_{50}^0 value, that is, Q indeed binds more effectively to the ditopic than to the monotopic receptor at any degree of saturation. Considering that the cation can bind to only one side of the ditopic receptor, which is identical to the monotopic receptor, it is evident that the cation "feels" a cooperative contribution from simultaneous binding of the anion, whatever complex species is involved in the association. A quantitative assessment of cooperativity can be obtained from the ratio of the BC_{50} curves, shown in Figure 1b, which shows a 16-fold preference of Q for the ditopic with respect to the corresponding monotopic receptor up to 80% complexation, in terms of cation required for binding 50% of receptor. The preference decay exhibited for larger extents of complexation clearly shows that the BC_{50} ratio is not constant along the complexation range. This effect is due to the variable contribution to the BC_{50} parameter made by complex species involving the counterion, which depend on the (variable) concentration of the latter imposed by the electroneutrality condition.[42] The intrinsic affinity parameter BC_{50}^0 therefore cannot be used for direct comparison as in two-reagent systems,[45] since these contributions vanish when the concentration of the counterion (along with the fraction of bound cation) is zero.

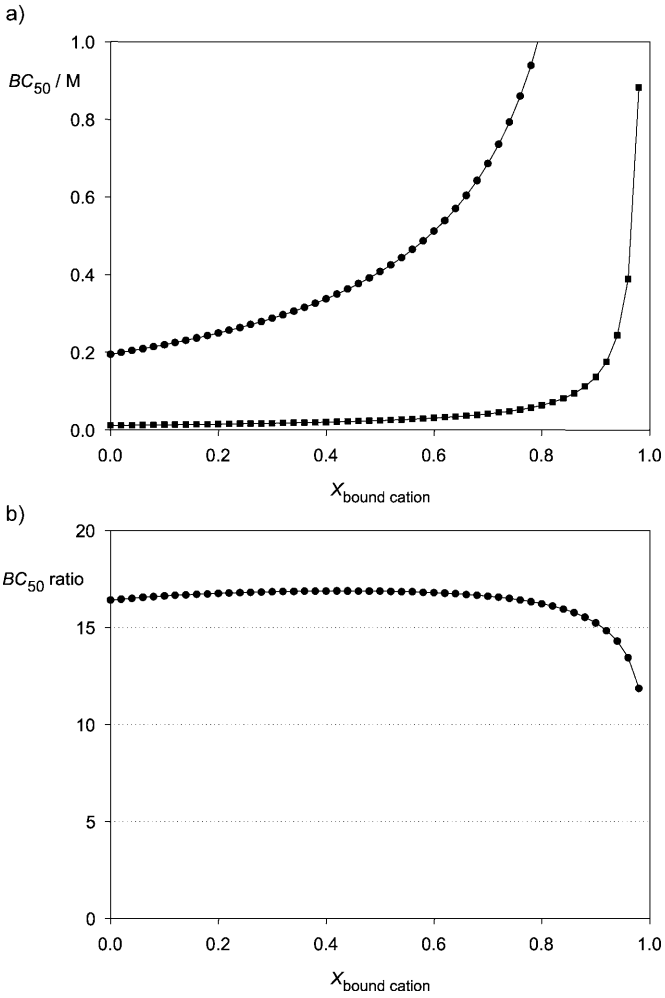


Figure 1. a) Plot of the BC_{50} [mol L^{-1}] curves calculated for Q toward monotopic receptor B (●) and the ditopic receptor D (■) at total concentration $T_X=T_Q$ as a function of the fraction of bound cation. BC_{50} values were calculated from the formation constants of Tables 2 and 3 as described in ref. [42], by using the BC_{50} calculator program.[47] Limiting BC_{50}^0 values are: $1.95(9)\times10^{-1}$ mol L^{-1} (B) and $1.19(3)\times10^{-2}$ mol L^{-1} (D). b) Plot of the BC_{50}(B)/BC_{50}(D) ratio at $T_X=T_Q$ as a function of the fraction of bound cation.

A different situation is apparent when considering the binding of the anion to the mono- and ditopic receptors (Figure 2). Up to nearly 85% complexation the curve of the ditopic receptor lies above that of the monotopic receptor, that is the chloride anion binds to the monotopic receptor with a modest but unambiguous preference. Such a preference can be quantified through the BC_{50} ratio (Figure 2b), which shows an intrinsic twofold advantage in binding to the monotopic with respect to the ditopic receptor, an advantage that decreases with increasing saturation and vanishes at 85% complexation, inverting to a preference for the ditopic

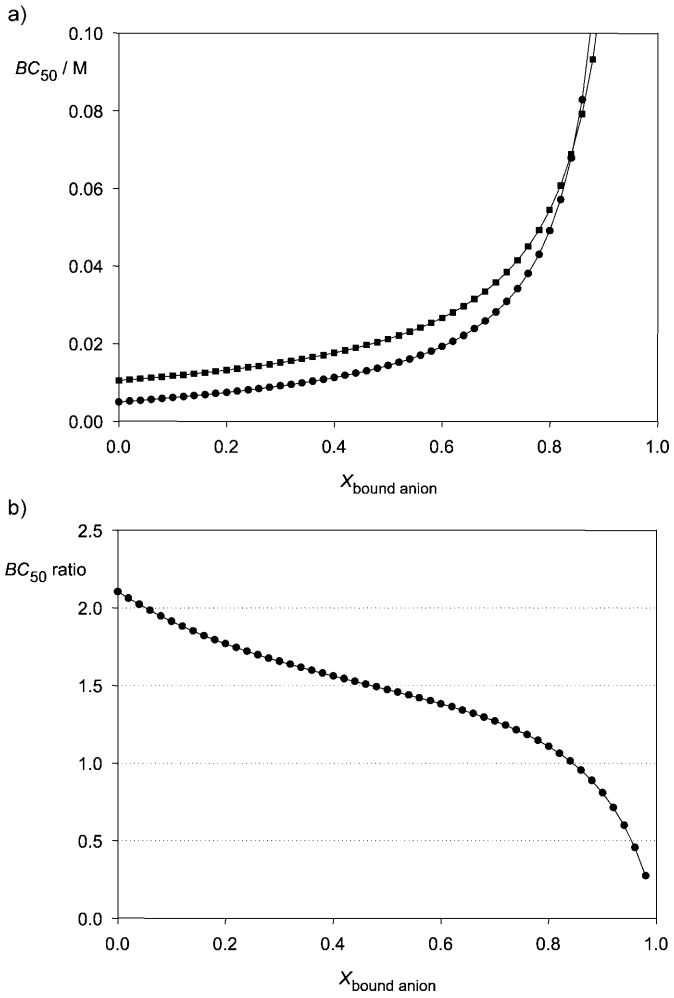


Figure 2. a) Plot of the BC_{50} [mol L^{-1}] curves calculated for X toward monotopic receptor R (●) and ditopic receptor D (■) at total concentration $T_Q = T_X$ as a function of the fraction of bound anion. BC_{50} values were calculated from the formation constants of Tables 1 and 3 as described in ref. [42], by using the BC_{50} calculator program.[47] BC^0_{50} values are $5.0(1)\times10^{-3}$ mol L^{-1} (R) and $1.05(2)\times10^{-2}$ mol L^{-1} (D). b) Plot of the BC_{50}(D)/BC_{50}(R) ratio at $T_Q = T_X$ as a function of the fraction of bound anion.

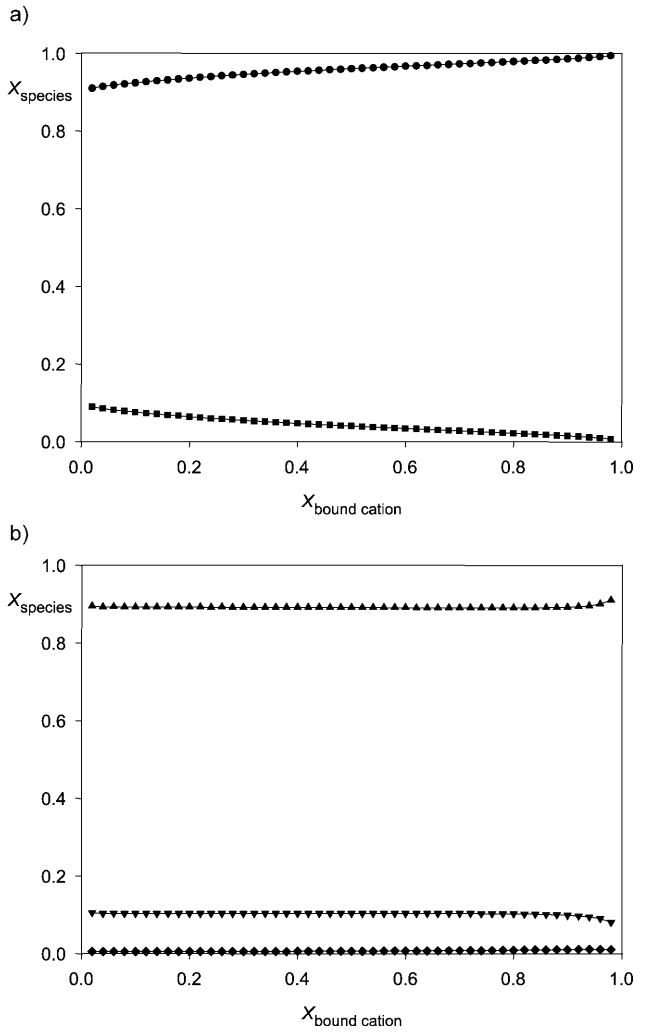


Figure 3. Plot of the distribution of complex species of a) receptor B and b) receptor D with QX, expressed as fraction of the total complexed cation, versus the fraction of bound cation. Distributions were calculated at $T_X = T_Q$ from the formation constants of Tables 2 and 3. a) BQX (●), BQ (■); b) DQ_2X_2 (▲), DQX (▼), DQ (◆).

receptor above this value. In this case, for most of the complexation range an inhibiting effect is evident, rather than cooperative participation of the simultaneously bound cation. It must be concluded that, in contrast to the cation, binding of the anion suffers from an anticooperative effect from concomitant binding of the counterion, that is, not only is cooperativity not the rule, but it also may operate in opposite directions for the two partners of an ion pair.

The observed behavior may be understood by examining the distribution of the complex species responsible for the affinity profiles (Figures 3 and 4, Figures S1 and S2 in the Supporting Information). Concerning the cation, in Figure 3a it is apparent that the species largely determining the global affinity of Q for B is the complex of the receptor with the ion-paired cation, with very limited contribution from the complex of the free cation. Likewise, the distribution depicted in Figure 3b for Q binding to D shows a predominant contribution from the complex of the ditopic receptor with two ion pairs, with a minor (10%) contribution from the complex with a single ion pair and a negligible contribution from the complex of the free cation. The strongly preferred binding of two ion pairs accounts for the observed cooperativity. Although the global affinity is determined by a balance of the actual thermodynamic stabilities of the complexes formed, it is not surprising that, on a purely stoichiometric basis, the ditopic receptor is more effective than the monotopic in binding the cation. It is noteworthy, however, that for both receptors the observed affinity is due to complexes of ion-paired species rather than of free cation, in contrast to what is generally assumed. In contrast, a different picture is apparent for binding of the anion: while the species distribution for the ditopic receptor D is very similar to that of the cation (Figure 4b), with a slightly larger contribution from the complex of the free anion, for the mono-

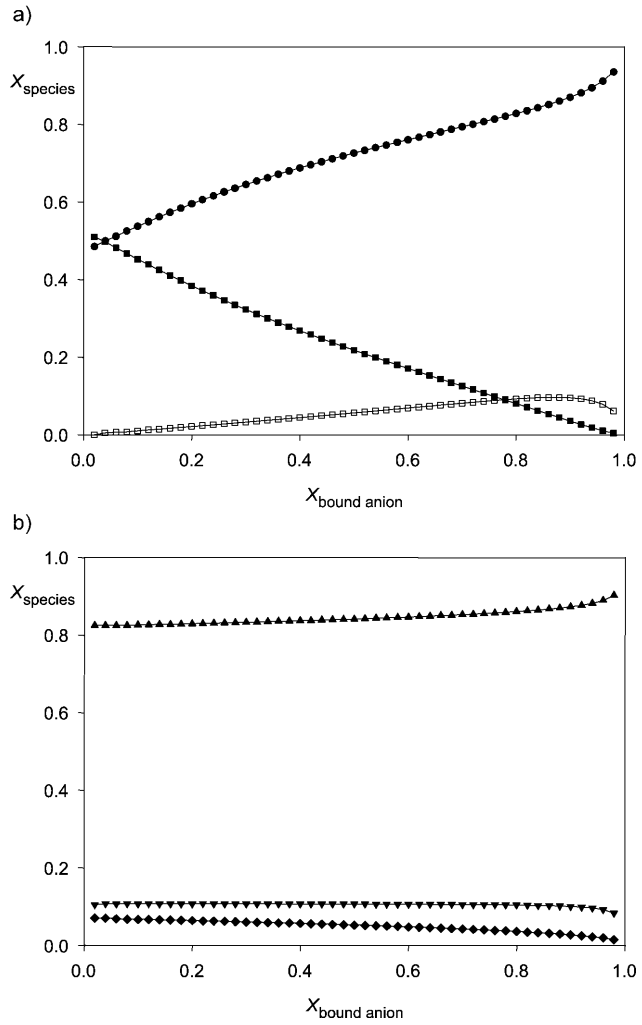


Figure 4. Plot of the distribution of complex species of a) receptor R and b) receptor D with QX, expressed as fraction of the total complexed anion, versus the fraction of bound anion. Distributions were calculated at $T_Q = T_X$ from the formation constants of Tables 1 and 3. a) RQX (●), RX (■), R_2X (□); b) DQ_2X_2 (▲), DQX (▼), DX (◆).

topic receptor R the contributions from complexes of the free and the ion-paired anions are equivalent at low complexation (Figure 4a); the complex of the ion-paired anion is increasingly predominant for higher complexation, whereas the R_2X complex is below 10% in the whole complexation range. Considering that complexes of the ion pair are apparently less effective than those of the free anion in contributing to the affinity,[42] in agreement with previous findings showing that electrostatic attraction of the counterion weakens the interaction of the ion with the receptor,[48,49] the affinity profile showing a preference of the anion for the monotopic versus the ditopic receptor up to 85% complexation may be related to a significant weight of the RX complex in the balance of the thermodynamic stabilities of the complexes contributing to the overall affinity. Thus, the net outcome appears to be the loss for the ditopic receptor of the advantage of binding the free anion when the extent of complexation increases.

Conclusions

Is binding both really binding better? We have provided a quantitative and methodologically correct answer to this question by conceptually re-examining and experimentally testing the binding of an ion pair to a ditopic receptor. When the appropriate algorithm is applied, it is clear that cooperativity is neither general nor predictable and may even operate in opposite directions for the two partners of the ion pair. Several general aspects were focused on in this analysis: 1) Complexes of ions and of ion pairs are incommensurable; comparison between commensurable entities (ions) is mandatory. 2) The 1:1 association model is inadequate to describe the binding of salts, because ion pairing and ion-pair binding cannot, in general, be neglected. 3) Binding of the whole ion pair is equally feasible for both the ditopic and the monotopic receptor. 4) Affinities of ions cannot be assessed directly by comparing binding constants, because multiple equilibria are always involved; for this purpose, the BC_{50} can be used as a general and convenient descriptor of global affinity. Hopefully, these aspects will be taken into consideration in future studies.

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