Partitioning the electrostatic interaction energy between two charge distributions

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Abstract

Treating the interaction between two charge distributions as a joint venture, we explore here the possibility of quantifying the extent of participation of each charge distribution. By introducing the concept of reduced charge analogous to reduced mass, we show that the interaction energy expression between two charges separates into a sum of two terms, one for each charge. This partitioning, in addition to facilitating a graphical representation of atom-based interaction energy components on complementary surfaces involved in a binding reaction, provides additional insights into the mechanism of interaction and binding. We further introduce the idea of representing molecular electrostatic potentials in the interaction view, i.e. potentials at each atom site of charge distribution I due to charge distribution II and vice versa and demonstrate the graphical equivalence of the potentials thus computed with the energy partitioning proposed here. The method is illustrated with applications to a few test cases and binding reactions of small molecules in vacuum and complexation of biomolecules in aqueous medium. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The Coulomb interaction energy between two charges q_i and q_j separated by a distance r_{ij} in a medium of dielectric constant ϵ is given (in units of kcal/mol) as

$$E_{ij} = \frac{332 q_i q_j}{\epsilon r_{ij}} \tag{1}$$

Treating this interaction energy as a joint investment by the two charges q_i and q_j to maintain the configuration r_{ij} in the dielectric medium under consideration, it is of practical interest to know as to what the contribution of each partner is to this joint fund. Some questions of common concern are: is j attracted by i or is it the reverse; is one a reluctant partner or are they both equal partners; in an interaction between two chemical systems which one could be modified chemically to optimize the interactions for kinetic and mechanistic reasons? Prima facie, there is no indication from Coulomb's law that i and j are unequal partners, i.e. the interaction energy of i with j is the same as that of j with i. Traditionally, molecular electrostatic potentials are used to depict complementarities via visual representations of surface potentials. These, however, do not immediately convey the attendant energetics. A scheme addressing the extent of participation of each charge in the interaction in a quantitative manner, is of considerable theoretical and practical interest especially in scanning a multitude of

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candidate molecules aimed at a fixed receptor site and in designing lead compounds. In the following, we propose a partitioning of the electrostatic interaction energy and examine its consequences with some prototypical charge distributions and come to some fascinating conclusions. We further define the molecular electrostatic potentials in the interaction view and show them to be consistent with the energy partitioning. Finally we illustrate this methodology with applications to some enzyme-inhibitor and protein–DNA complexes.

2. Theory

We introduce a reduced charge q_r between charges q_i and q_j analogous to reduced mass as

$$q_r = \frac{q_i q_j}{|q_i| + |q_j|} \tag{2}$$

The Coulomb interaction energy can now be split as

$$E_{ij} = E_i + E_j \tag{3}$$

$$E_i = \{332 q_r |q_i|/r_{ij}\}; \quad E_j = \{332 q_r |q_j|/r_{ij}\} \tag{4}$$

This separation takes advantage of the fact that the electrostatic potential varies linearly with charge. This partitioning is the equivalent of weighting the interaction energy in proportion to the charge.

$$\frac{332 q_i q_j}{r_{ij}} = \frac{332 q_i q_j}{r_{ij}} \left[\left\{ \frac{|q_i|}{|q_i| + |q_j|} \right\} + \left\{ \frac{|q_j|}{|q_i| + |q_j|} \right\} \right] \tag{5}$$

The expression in square brackets turns out to be unity. Extension of this formula to the interaction between two arbitrary charge distributions I and II is straightforward:

$$E_{\text{I–II}} = \sum_{i=1}^{m} \sum_{j=1}^{n} \frac{332 q_i q_j}{r_{ij}} = E_{\text{I}} + E_{\text{II}} \tag{6}$$

$$E_{\text{I}} = \sum_{i=1}^{m} E_i^{\text{I}}; \quad E_i^{\text{I}} = \sum_{j=1}^{n} \frac{332 q_i q_j}{r_{ij}} \left[\frac{|q_i|}{|q_i| + |q_j|} \right] \tag{7}$$
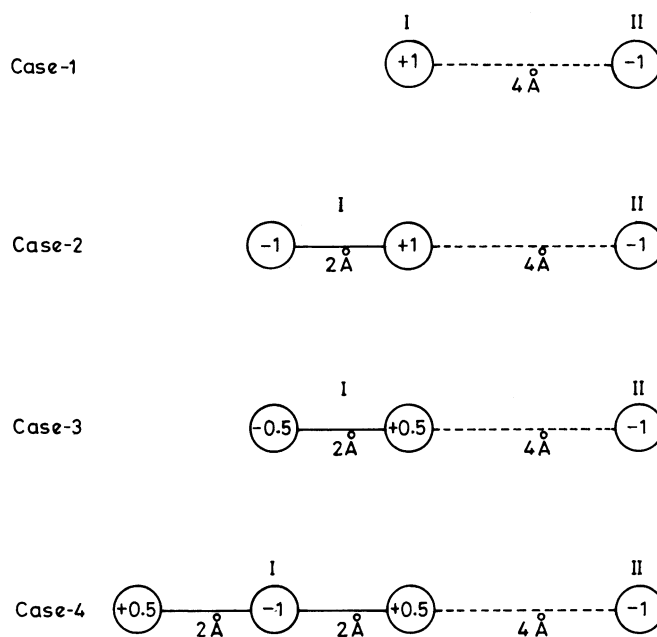

Fig. 1. Some prototypical cases considered in the text for partitioning the interaction energy between two charge distributions, I and II. Case-1 represents the interaction of two ions. Case-2 depicts the interaction of an ion pair (I) with an ion (II). Cases 3 and 4 represent the interaction of an idealized neutral molecule (I) with an ion (II). Formal charges are adopted in case-2. Partial charges are introduced in cases 3 and 4.

Table 1
A partitioning of the Coulomb interaction energy (in kcal/mol) between two charge distributions

	E_I	E_{II}	E_{net} ($E_I + E_{II}$)
Case-1	−41.5	−41.5	−83.0
Case-2	−13.8	−13.8	−27.6
Case-3	−4.6	−9.2	−13.8
Case-4	+6.9	−13.8	−6.9

$$E_{II} = \sum_{j=1}^{n} E_j^{II}; \quad E_j^{II} = \sum_{i=1}^{m} \frac{332 q_i q_j}{r_{ij}} \left[\frac{|q_j|}{|q_i| + |q_j|} \right] \quad (8)$$

where m and n are the number of charges in distributions I and II, respectively, E_I and E_{II} the contributions of distributions I and II to the total electrostatic energy E_{I-II}.

3. Results and discussion

Consider now a few simple cases shown in Fig. 1. From cases 1 and 2, we find that $E_i = E_j = 0.5 E_{ij}$, i.e. the interaction energy is distributed equally between the charges if they are of equal magnitude (see Table 1 for results). Matters change once partial charges are introduced. Case-3 indicates that the contributions of the neutral molecule (species I) and the ion (species II) are not equal. Although not obvious from Coulomb's law, it does seem intuitive that a neutral molecule carrying partial atomic charges should contribute less than an ion to the total interaction energy. Case-2 situation is what is normally envisaged. Case-3 illustrates the results with unequal charges, a situation that is closer to reality in most bimolecular complexes. Case-4 dramatically presents the consequences of a model partial charge distribution (I) interacting with an ion (II). Here the charge distribution I makes a positive contribution to the interaction energy while the contribution of the

Table 3
Atomic contributions to the total electrostatic interaction energy (in kcal/mol) between methylamine and acetate

Methylamine			Acetate		
Atom	Charge	Energy	Atom	Charge	Energy
C	0.2677	−6.6	CH	−0.2952	−4.7
HC1	−0.0089	0.0	HC1	0.0289	+0.1
HC2	−0.0089	0.0	HC2	0.0289	+0.1
HC3	−0.0089	0.0	HC3	0.0289	+0.1
N	−0.8774	+54.5	C	0.9217	+25.2
HN1	0.3182	−13.5	O	−0.8566	−27.8
HN2	0.3182	−13.5	O	−0.8566	−27.8
Total	0.0	+20.9		−1.0	−34.9

moiety II dominates the net energetics. This exemplifies a situation where the charge distribution II drives the binding with I acquiescing in view of the net gain. This process is distinct from the common expectation based on the net interaction energy that both species I and II are attracted to each other. A picturization of binding in case-4 would involve a freely diffusing species I being pulled by II.

To illustrate the partitioning scheme further, we present results with a sodium ion, ammonium ion and methylamine interacting with an acetate ion (see Table 2). The structures were generated with the InsightII modeling software from MSI. Partial atomic charges employed for computing the interaction energies were adopted from Ref. [1]. In the cases of sodium and ammonium ions, which carry a net charge opposite to that of acetate (cases 5 and 6), the electrostatic contributions (with the dielectric constant set at unity) to the interaction energies are individually favorable. In the case of methylamine–acetate interaction (case-7), where methylamine is neutral, although the net interaction energy is favorable, methylamine disfavors binding with acetate facilitating the binding process (Table 2). Table 3 presents in detail the atomic contributions to the total energy

Table 2
Interaction energies (in kcal/mol) partitioned into individual contributions

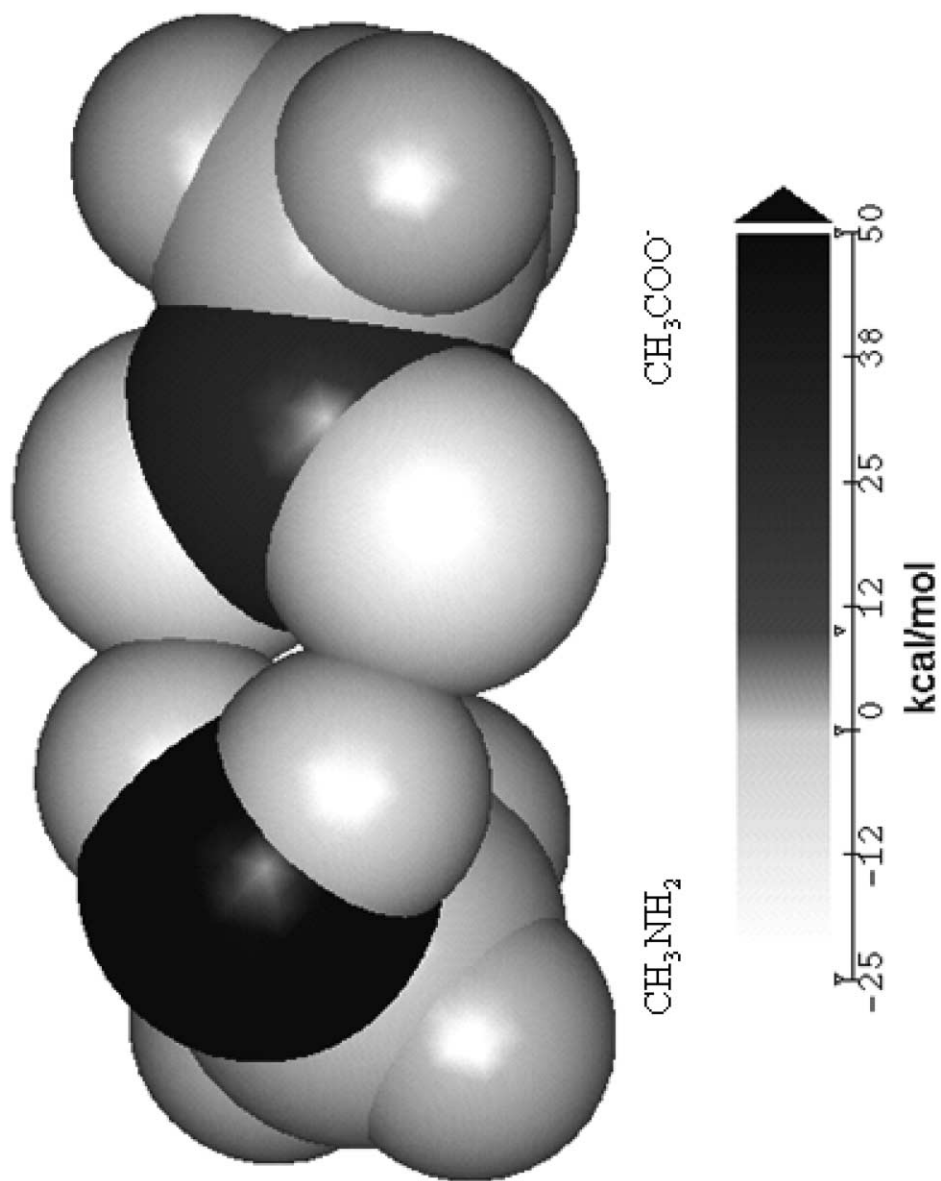|	$Na^+/NH_4^+/CH_3NH_2$	CH_3COO^-	Total	Coulomb
Case-5 Na^+:CH_3COO^-	−93.6	−70.6	−164.2	−164.2
Case-6 NH_4^+:CH_3COO^-	−42.5	−108.6	−151.1	−151.1
Case-7 CH_3NH_2:CH_3COO^-	+20.9	−34.9	−14.0	−14.0

Fig. 2. Methylamine bound to acetate (case-7 of Table 2), with atoms shaded according to their individual contributions to the net interaction energy (Table 3) following the partitioning described in the text. This figure can be viewed with better detail in color at http://jayaramb.tripod.com/partition.htm.

computed via Eqs. (7) and (8). These atom-wise energies are depicted graphically in Fig. 2.

Despite the overall consistency, a case can be made that any charge-wise energy partitioning is by nature arbitrary. Total energy may be divided in any number of ways among participating charges as apparently there are no constraints. That the partitioning based on reduced charges is not so arbitrary but has built-in constraints can be justified on two counts. First, the interaction energies vary linearly with the magnitude and sign of the charges and this is incorporated in the division scheme here. Secondly, the individual energy contributions must be consistent with the potentials in the "interaction view"; where the reacting species are put in the field of each other. Fig. 3 (generated with InsightII) shows the potentials around methylamine and acetate ion *due to the field of each other*, which we call the *interaction view*. This is obtained by discharging one of the molecules and calculating the potentials at and around its atoms due to charges on the other molecule. The potentials in the vicinity of methylamine due to the acetate ion show that the interactions of the amine hydrogens with acetate, characterized by positive charges (dark) and negative

potentials (light) on hydrogens (Fig. 3), are favorable. The nitrogen atom, negatively charged in a negative potential, makes an unfavorable contribution. This is exactly what shows up quantitatively in our partitioning scheme (Table 3 and Fig. 2). If we examine the interaction from acetate point of view (Fig. 3), the potentials due to ammonia at its charge sites show that the oxygens and the methyl carbon participate in a favorable interaction, while the carbon attached to the oxygens is unfavorable, the methyl hydrogens making a negligible contribution. These atom-wise attributes to interaction are again reflected in the energy partitioning (Table 3 and Fig. 2). Thus the scheme proposed here is not merely consistent with the net electrostatic interaction energies and forces originating in Coulomb's law but brings an extra element of clarity in a molecular level grasp of the binding process, in addition to facilitating atom-based visual representations of the interaction energies.

Extension of this partitioning scheme to incorporate electrostatics of desolvation [1] is easy, since the reaction potential due to solvent also varies linearly with charge. To illustrate an atom-wise partitioning of the Coulomb as well as solvation effects in the net
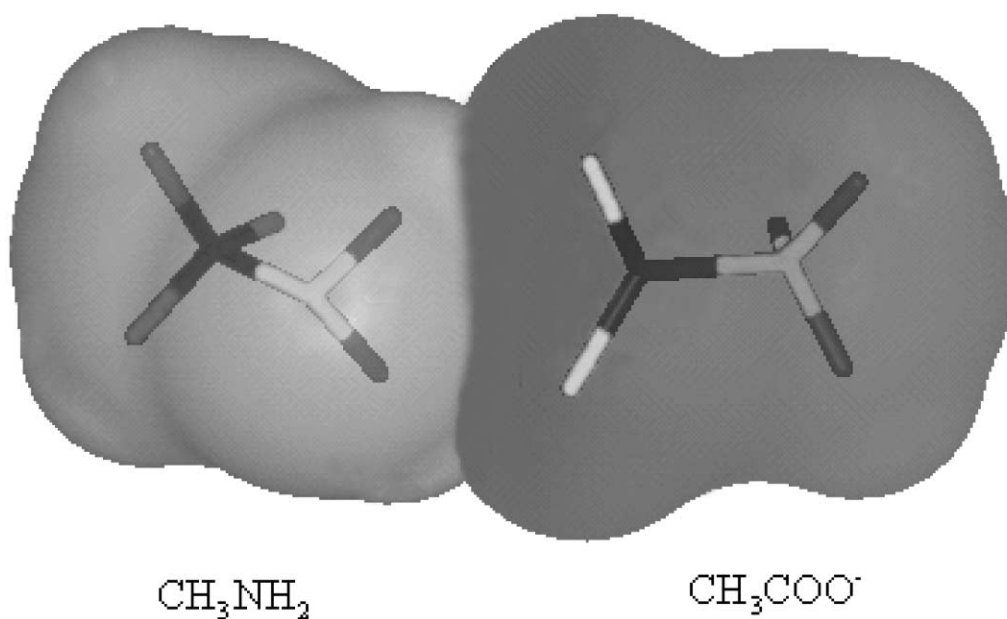

Fig. 3. Potentials around methylamine and acetate due to the field of each other (*interaction view*). The darker shade represents positive potentials and the negative potentials are shown in lighter shade. The atoms are shaded according to charge with positive charges in black and negative charges in light shades. A more informative color figure can be viewed at http://jayaramb.tripod.com/partition.htm.

Table 4
Interaction energies (in kcal/mol) for pencillopepsin–pepstatin analogue complexes (1APT, 1APU) and 434cro-OR1 protein–DNA complex (PDR001)

PDB code	Enzyme/Protein				Inhibitor/DNA				Net
	Charge	E_{coul}	E_{solv}	E_{el} (E_I)	Charge	E_{coul}	E_{solv}	E_{el} (E_{II})	(E_I+E_{II})
1APT	−19	−1594.2	1558.7	−35.5	+1	1061.0	−1072.6	−11.6	−47.1
1APU	−19	−205.4	201.8	−3.6	0	144.8	−145.7	−0.9	−4.5
PDR001	+13	10289.1	−10070.0	219.1	−36	−17586.9	17349.3	−237.6	−18.5

electrostatics of binding, we take two enzyme-inhibitor complexes (the aspartic proteinase pencillopepsin with two of its inhibitors; see Ref. [2] and references therein) and a protein–DNA complex [3] (434cro protein–OR1 operator DNA). The electrostatic free energies of solvation are estimated using the modified generalized Born model described in Ref. [1]. The total electrostatic interaction energy between two molecules I and II with m and n atoms, respectively, in a polarizable medium is expressed as the sum of the Coulomb energy in vacuum and a solvent shielding term:

$$E_{el} = E_{coulomb} + E_{solv} \qquad (9)$$

$$E_{solv} = -166\left(1 - \frac{1}{\epsilon}\right)\sum_{i=1}^{m}\sum_{j=1}^{n}\frac{q_i q_j}{f_{mGB}} \qquad (10)$$

f_{mGB} is an effective distance parameter described in Ref. [1]. The Coulomb energy is partitioned as described in Eqs. (6)–(8) and the shielding energy can be partitioned in a similar manner:

$$E_{solv} = E_I^{solv} + E_{II}^{solv} = -166\left(1 - \frac{1}{\epsilon}\right)\sum_{i=1}^{m}\sum_{j=1}^{n}\frac{q_i q_j}{f_{mGB}}$$

$$\times \left[\frac{|q_i|}{|q_i| + |q_j|} + \frac{|q_j|}{|q_i| + |q_j|}\right] \qquad (11)$$

Additional details on the solvation parameters used and the procedure for evaluating the electrostatics interactions in macromolecular systems are provided elsewhere [1–3]. Results of the energy partitioning between the reacting molecules are shown in Table 4. The enzyme and the inhibitor both attract each other with the enzyme (charge −19) displaying a stronger contribution. The positively charged inhibitor (1APT) makes a greater contribution to the interaction energy than the uncharged one (1APU). In contrast, in the case of the 434 cro protein–OR1 DNA complex, although the two species are oppositely charged, DNA favors binding while the protein is disinclined

to do so. This is due to the fact that the positive charge on the protein is spread over a large area leading to a lower charge density relative to DNA. In protein–DNA binding, where species II (DNA) is a highly charged polyanion, cases 4 and 7 (shown in Fig. 1 and Tables 1 and 2) portray the general rule. DNA acts as an attractor to pull the freely diffusing protein which tends to disfavor complexation, but acquiesces in view of the DNA.

4. Conclusions

We present here a novel scheme of pooling atom-wise contributions to the interaction energy between two molecules. We show the equivalence of this method for generating electrostatic potentials in the interaction view with quantification of atomic level energy contributions as an additional information. Atom-wise contributions to the interaction energy readily convey a knowledge of substitutions to be attempted on the ligand for achieving optimal binding with the receptor.

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