Vol. 126, No. 1, 1985 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
January 16, 1985 Pages 247-253

A SCREENED ELECTROSTATIC POTENTIAL MODEL OF HYDRATION FOR CONFORMATIONAL ANALYSIS OF BIOMOLECULES

O.L. OLATUNJI AND S. PREMILAT

Laboratoire de Biophysique Moléculaire
ERA CNRS N° 828, Faculté des Sciences
Université de Nancy I, B.P. N° 239
54506 Vandoeuvre les Nancy, France

Received August 2, 1984

Summary. A screened electrostatic potential model of hydration which could avoid the time consuming Monte-Carlo procedures is derived from the study of the dielectric effect of a water molecule in the vicinity of two charges. It is shown that the molecular dielectric constant depends on the distance, sizes and signs of the interacting charges. The model is used to evaluate the hydration energy of the tetrapeptide (TYR-GLY-GLY-PHE) conformations. Results are in good agreement with Monte-Carlo calculations.

Introduction. Theoretical conformational analysis using semi-empirical energy functions has become a useful tool in the characterization of macromolecules. However it is well known that the behaviour of macromolecules of biological interest in aqueous solutions is influenced considerably by the solvent itself (1-3). The role of aqueous solvent could be considered in a simple way be modifying the value of the dielectric constant (4). However there is a little in the litterature concerning the reasonableness of the fundamental asumptions implicit in the Coulomb's law ($E_{el} = Cq_iq_j/\varepsilon^* r_{ij}$) when attemping to account for the solvent effect. Since the role of the solvent is simulated by the constant ε^*, the value of this constant can be crucial at the molecular level. For instance, value of ε^* ranging between 1 to 10 are used without satisfactory justification. The concept of dielectric constant at molecular level has been discussed by Hopfinger (5-6) and there are some attemps to characterize the spatial variability of ε^* for uncharged systems (6-7).

Here, in order to contribute to this problem a simplified model which retains the basic philosophy of the simulation approaches is presented. Our main interest is the study of the dielectric screening effect of a water molecule in the vicinity of two charges. Hence one has to evaluate the microscopic electrostatic energy contribution in order to provide some insight into the mecanism of the electrostatic energy balance of charge separation in water. The present study is mainly devoted to the following problem : is the

0006-291X/85 $1.50

"dielectric constant" at a molecular level function of the types of the interacting charges ? More precisely, do the values and the signs of the charges have some importance on the screening effect of the water molecules ? A positive answer to these question induced to search for charge dependent "dielectric constants" (in the area of short atomic distances). A preliminary application of this hydration model is used for the study of the conformational stability of the tetrapeptdie (TYR-GLY-GLY-PHE).

METHODS. 1) A specific local interaction is said to exist between two atoms i and j in water if these atoms are in contacts, or more quantitatively if the distance between them r_{ij}, satisfies the relation :

$$r^o_{ij} < r_{ij} < r^o_{ij} + 2r_{H_2O} \qquad (1)$$

where r^o_{ij} and r_{H_2O} are the sum of the Van-der-Waals radii of atom i, j and water molecule respectively. This nearest neighbor interaction model (1) has been shown to be useful for approximate connection between hydrophobic interaction and experimental quantities (3,8).

The conformational energy of the system can be written as :

$$E(x_{\alpha\beta},\theta,\varphi,\psi) = \sum_{i=1}^{NAT} \sum_{j=1}^{NAT} \left(-\frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} + \frac{Cq_iq_j}{r_{ij}}\right) - \frac{1}{2} \sum_{i=1}^{NAT}{}' \alpha_i \vec{E}_i^2 \qquad (2)$$

where NAT is the number of atoms in the systems, x_α = x,y,z, refer to the Cartesian coordinates and β = 1,2,3 refer to the two solute atoms and the oxygen atom of the water molecule (arbitrarily treated as the center of the molecule). The three Euler angles (θ,φ,ψ) specifies the orientation of the water molecule.

The first two terms in the double summation are the classical attractive and repulsive terms represented by a two parameters Lennard-Jones potential. The third term is the electrostatic energy between charges q_i and q_j, C is a constant used to get the energy in kcal/mole. The second summation is the non-additive polarization energy, α_i being the polarizability of atom i, and $\vec{E}_i$ the electrostatic field acting on atom i and calculated with the partial charges q_i of all others atoms of the system. All energetic parameters are taken from references (9,11). The average electrostatic energy is obtained by calculating :

$$<E_{el}> = \frac{\sum_\theta \sum_\varphi \sum_\psi E_{el}(x_{\alpha\beta},\theta,\varphi,\psi) \exp\left[-E(x_{\alpha\beta},\theta,\varphi,\psi)/kT\right]}{\sum_\theta \sum_\varphi \sum_\psi \exp\left[-E(x_{\alpha\beta},\theta,\varphi,\psi)/kT\right]} \qquad (3)$$

where k is the Boltzman factor, and T the absolute temperature. For a given distance $r_{ij} = r^o_{ij} + \delta$ $(0 \leqslant \delta \leqslant 2r_{H_2O})$ the average physical quantities are calculated at 20° angular intervals with T = 298°K. The molecular dielectric screening factor for charge-charge interaction is defined as :

$$S(r_{ij}, q_i, q_j, \varepsilon_b) = \frac{E^o_{el}}{<E_{el}>} \qquad (4)$$

where E^o_{el} is the electrostatic interaction energy in the medium with average dielectric constant ε_b. The value of the molecular dielectric constant ε^*

can be extracted from Eq(4).

$$\varepsilon^* = \varepsilon_b \, S(r_{ij}, q_i, q_j, \varepsilon_b) \qquad (5)$$

The formulas (2-5) allows one to compute average quantities in particular the screening factor S for various configurations of the system.

2) A second order of approximation involving Monte-Carlo calculation is used in order to test the influence of the nearby solvent molecules on the stability of the charges-water complex derived from the three body interaction model.

Starting with a configuration of 512 SPC water molecules (11) in a cubic box, a representative sample of water molecules is chosen to fill a sphere of 10.7 Å radius. This configuration is generated from the cubic box by deleting all water molecules situated outside of the sphere. The resulting system of 160 water molecules is partitioned into a reaction zone consisting of molecules within the sphere of radius 7.6 Å and the boundary zone of solvent molecules making up a rigid wall. This sample of SPC molecules has a density near to 0.0331 molecules/$Å^3$ which is appropriate for water at 298°K and 1 atm.

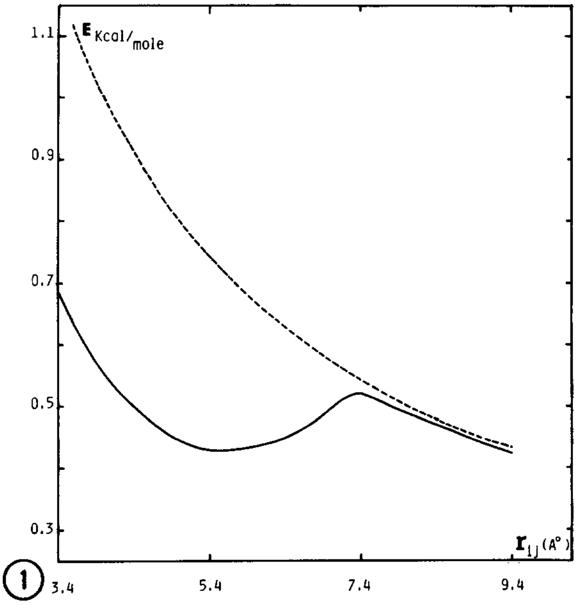
The solute is placed in the spherical box so that its center of gravity coïncides with the origin of the coordinates axes. Then every solvent molecules which overlapps a solute atom is deleted. The Monte-Carlo procedure is based on the well known Metropolis algorithm (12). The generation of random configurations is realized as usually by allowing the solvent molecules to be moved by translational and rotational displacements. However according to the model, only rotational displacements are allowed to solvent molecules of the wall. Approximate boundary conditions for the model system must be defined as the usual periodic boundary conditions which work well to simulate an infinite fluid with short range interactions are not adapted to the study of solutions in polar solvents. To overcome this difficulty the image boundary conditions proposed by Friedman (13) is presently used.

The above Monte-Carlo procedure provides a powerful tool to evaluate the solvation energy of charges species and for studying the energy balance of charges separation in water. But in this preliminary work this procedure is not applied exhaustively as the actual purpose is simply to test the influence of the nearby solvent molecules on the stability of the charges-water complex.

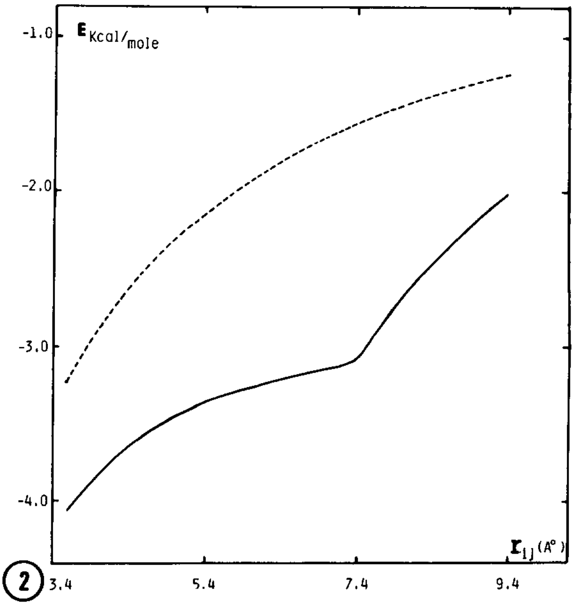
RESULTS AND DISCUSSION. Results obtained from the present calculations lead to the following remarks.

1) For charges of like sign, the average electrostatic energy $\langle E_{el} \rangle$ is smaller than its simple Coulombic value, i.e. the screening effect of water molecule decrease the repulsive energy between the two charges. The factor S is generally greater than unity for identical charges but can become negative when one of the two charges is small compare to the other. For charges of like sign one observes a deep minimum in the average electrostatic energy at distances r^*_{ij} satisfying $r_{ij} < r^*_{ij} < r^o_{ij} + 2r_{H_2O}$ (fig.1). The position r^*_{ij} is closely related to the value of the bulk dielectric constant ε_b, r^*_{ij} approaches the limit value $R = r^o_{ij} + 2r_{H_2O}$ when ε_b increases.

2) For charges of opposite signs, the average electrostatic energy (negative value) $\langle E_{el} \rangle$ is smaller than its Coulombic value, i.e., the screening effect of water molecule increases the attractive energy between the two charges. The screening factor S is allways smaller than unity. One observes



①



②

Fig.1 (———) Average electrostatic energy of two charges $C^{\beta}(q_i = q_j - 0.110$ e.u.) and a water molecule as a function of charges distance r_{ij}. The dielectric constant of the bulk medium is $\varepsilon_b = 1$.

(-----) Direct $C^{\beta} - C^{\beta}$ charge-charge interaction.

Fig.2 (———) Average electrostatic energy of two charges $C^{\alpha}(q_i = 0.318$ e.u.), $C^{\beta}(q_j = -0.110$ e.u.) and a water molecule as a function of charges distance r_{ij}. The dielectric constant of the bulk medium is $\varepsilon_b = 1$.

(----) Direct $C^{\alpha} - C^{\beta}$ charge-charge interaction.

two minima in the average electrostatic energy (fig.2). The first one at Van-der-Waals contact and it is obvious that the lowest value of the energy is obtained when the atoms are in contact. The second one, at a larger distance, position corresponding to an unstable energy minimum of the system.

3) The results of Monte-Carlo runs show that the stability of the charges-water complex is not much affected by the solvent environment.

What the above results suggest is that some useful and nontrivial information concerning the dielectric screening effect of a water molecule in the vicinity of two charges can be obtained from the simple three body model. The oscillations and positions of the minima of the average electrostatic energy $< E_{el} >$ show the possibility of relatively stable charge-pair configurations where charges are separated by one solvent molecule (water-bridges) (14). The most interesting feature of the obtained results is the "distance and charges dependent" dielectric constants (see table 1 for some examples). More precisely one observes that the values and the signs of the charges have some importance on the dielectric screening effect of the water molecule.

TABLE I

Example of molecular "dielectric constant" for different charges and distances (distance between charges = $r_i + r_j + \delta, \varepsilon_b = 3.5$)

Atom type		N	H^β	C^α	O
Charge (e.u.)		- 0.202	0.046	0.318	- 0.422
Van-der-Waals radii (Å)		1.55	1.20	1.70	1.52
N	$\delta = 0$ Å	4.25	3.00	3.35	4.25
	$\delta = 2$ Å	4.00	3.50	3.00	4.50
	$\delta = 4$ Å	3.55	2.00	2.50	4.00
H^β			4.00	5.00	3.00
			4.00	6.00	2.00
			4.00	6.25	2.00
C^α				4.00	3.35
				4.00	3.00
				3.60	3.00
O					4.00
					4.00
					3.60

Hence, is should be pointed out that the idea of a bulk dielectric constant, generally used for pairwise short-range interactions in conformational energy calculations is, at best a crude representation of reality. Moreover, accurate calculations of bound moments and partial charges are meaningless for the electrostatic energy calculation if there is a large error in the dielectric constant. However there is empirical and computational support (15-16) for systems where the solvent (water) is not explicitly included in the conformational energy calculations. It is the main objectif of the present work to improve this approach and fortunately computational investigations reported here will allow one to account for a part of solvent effects through "charge dependent" molecular dielectric constants.

As an example of application of this hydration model the relative stability of different conformations of the tetrapeptide (TYR-GLY-GLY-PHE) in water are considered. A Monte-Carlo procedure described by Hagler et al. (17) has been used recently to study the aqueous solution of this tetrapeptide (18). The results obtained provide a useful test for the screened Coulombic potential model of hydration described here. Calculations were performed on three different tetrapeptide conformations (table II). Rx is the crystal conformation (19), conformations Mt and Mu are obtained by a Monte-Carlo method described previously by Premilat et al. (20-21).

TABLE II

(φ, ψ, χ) [x] Dihedral angles and energy E* (kcal/mole) of three tetrapeptide conformations

Confor mations	TYR$_1$					GLY$_2$		GLY$_3$		PHE$_4$				Conformational energy		
	φ_1	χ_1	χ_1^2	χ_1^3	ψ_1	φ_2	ψ_2	φ_3	ψ_3	φ_4	χ_4^1	χ_4^2	ψ_4	E* (a)	E*(ε_b) (b)	E*(ε*) (b)
Mt	-74	-163	-102	136	146	-172	128	73	-146	-150	-113	92	166	-130.0	-21.10	-141.7
Mu	-129	-162	-140	175	-176	109	37	133	- 99	- 81	55	91	-15	- 95.1	- 7.8	-126.4
Rx	-106	63	70	-40	170	74	11	90	0	- 71	168	70	-35	-126.8	- 9.15	-129.1

(a) Monte-Carlo results (18)

(b) This work E*(ε_b) calculated with $\varepsilon_b = 3.5$; E*(ε*) calculated with the molecular dielectric constant $\varepsilon^*(r_{ij}, q_i, q_j, \varepsilon_b)$

x IUPAC-IUB conventions

The conformational energy of these three conformations are calculated and the solvent effect is taken into account by using the "charge dependent" molecular dielectric constants in the electrostatic component of the conformational energy. Results are qualitatively and quantitatively in good agreement with Monte-Carlo calculations (Table II). Moreover they give a good insight on the mecanism of the electrostatic balance of charges separation in water. Hence, as the electrostatic energy is a major factor determining the structure of the system, effects arising from differences in sizes and signs of the interacting charges play an important role in this organisation. Even if the present model of hydration is relatively simple, one can see that it provides useful information on the effect of solvent on molecular structures. Moreover by this way on could avoid the time consuming Monte-Carlo procedures which actually cannot be used confidently for the study of large molecule-water systems particularly when calculations involve comparison of different solute conformations.

REFERENCES

1. NEMETHY, G., SCHERAGA, H.A., (1977), Q. Rev. Biophys., 10, 239
2. WARSHEL , A., (1979), J. Phys. Chem., 83, 1640
3. BEN-NAIM, A., (1980), "Hydrophobic Interactions", Plenum Press
4. RICHARDS, W.G. and ELLIOT, R.T., (1983), In "Topic in Molecular Pharmacology", BURGEN, A.S.V., and ROBERTS, G.C.K., Eds, Elsevier Science, 53
5. HOPFINGER, A.J., (1973), "Conformational Properties of Macromolecules", Academic Press
6. HOPFINGER, A.J., (1974), In "Peptides, Polypeptides and Proteins", BLOUT, E.R., BOVEY, F.A., GOODMAN, M. and LOTAN, N., Eds, Willey, 71
7. GREENBERG, D.A., BARRY, C.D. and MARSHALL, G.R., (1978), J. Am. Chem. Soc., 100, 4020
8. PRATT, L. and CHANDLER, D., (1977), J. Chem. Phys., 67, 3683
9. SCHERAGA, H.A., (1968), Adv. Phys. Org. Chem., 6, 103
10. BERNAL, J.D., and FOWLER, R.H., (1933), J. Chem. Phys., 1, 515
11. BERENDSEN, H.J.C., POSTMA, J.P.M., VAN GUNSTEREN, W.F., and HERMAN, J., (1981), In "Intermolecular Forces", PULLMAN, B. Ed., REIDEL, D., 331
12. METROPOLIS, N.A., ROSEMBLUTH, A.W., ROSEMBLUTH, M.N., TELLER, A.H., TELLER, E., (1953), J. Chem. Phys., 21, 1087
13. FRIEDMAN, H.L., (1975), Mol. Phys., 29, 1533
14. CHAN, D.Y.C., MITCHELL, D.J. and NINHAM, B.W., (1978), J. Chem. Phys., 70, 2946
15. ORCHARD, R.T., TAN T.S., and HOPFINGER, A.T. (1984), Macromolecules, 17, 169
16. WIPFF, G., DEARING, A., WEINER, P., BLANEY, J., and KOLLMAN, P., (1983), J. Am. Chem. Soc., 105, 997
17. HAGLER, A.T., and MOULT, J., (1978), Nature, 272, 222
18. DEMONTE, J.P., (1984), Ph.D. Thesis, Laboratory of General Chemistry, Free University of Brussels, Belgium
19. FOURNIE-ZALUSKI, M.C., PRANGE, T., PASCARD, C., and ROQUES, B.P., (1977), Biochem. Biophys. Res. Comm., 79, 1199
20. PREMILAT, S. and MAIGRET, B., (1977), J. Chem. Phys., 66, 3418
21. PREMILAT, S. and MAIGRET, B., (1980), J. Phys. Chem., 84, 293