An Intermolecular Potential Function for Cyclen-Water Derived from Ab-Initio Molecular Orbital Calculations

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An interaction pair potential function for 1,4,7,10-tetraaza-cyclododecane (cyclen) and water has been derived from ab-initio molecular orbital computations. The 250 computed points of the energy surface for the water-cyclen interaction have been fitted with an analytical potential of the form

$$\Delta E \ (\text{kcal} \cdot \text{mol}^{-1}) = \sum_{i=1}^{3} \sum_{j=1}^{32} \{- \, |A_{ij}^{\mathrm{ab}}| \, /r_{ij}^{6} + |B_{ij}^{\mathrm{ab}}| \, /r_{ij}^{12} + q_i \, q_j (1/r_{ij}) \, (|C_{ij}^{\mathrm{ab}}| + |D_{ij}^{\mathrm{ab}}| \, /r_{ij})\},$$

where A, B, C, and D are constants, and q_i and q_j are the atomic charges of the i-th atom of water and the j-th atom of cyclen at infinite separation.

Introduction

During the last few years, computer simulation methods such as Monte Carlo (MC) [1] and molecular dynamics (MD) [2] techniques have turned out to be valuable tool in the study of pure liquids and solutions. The significance and liability of the results of such simulations depends strongly on the quality of the analytical pair potential function in use. The obvious way to obtain this function is to use quantum chemical calculations, and this approach has been pioneered by Clementi and coworkers [3]. Another possibility to obtain this function is to use experimental data. One well-known result of such an approach is the ST2 potential function for water [4].

A certain lack in solute-solute- and solute-solvent potential functions seemed long to have been the main obstacle for a rapid progress of simulation techniques in solution chemistry. An effective procedure to obtain and test the quality of an intermolecular potential function, proposed by Beveridge et al. [5] has been an important step to encourage further work in this field.

Recent investigations of the "macrocyclic effect" [6] − the extra stability of metal complexes with cyclic ligands compared to analogous non-cyclic ligands − prompted us to investigate the feasibility of developing pair potential functions for such

ligands interacting with water and ions. Margerum et al. [6, 7] have suggested that this macrocyclic effect arises from a lower degree of solvation of the cyclic ligands, whereas some other groups [8, 9] showed that these desolvation effects were over-estimated. To give a theoretically based answer to this question and to calculate properties and structure of water surrounding the cyclic ligand, an extension of our quantum chemical studies [10, 12] to MC and MD simulation was needed.

In this work, we report an intermolecular potential function for 1,4,7,10-tetraaza-cyclododecane with water (Fig. 1), derived from 250 positions of the ab-initio computed energy surface for this interaction.

Method

The cyclen and the water molecule were treated as rigid throughout the calculations. The geometry of the ligand molecule was taken from our previous optimization [10−12], and for the water molecule experimental data [13] were used. The cyclen molecule is in the alternate conformation [11, 12] and has C_{2v}-symmetry (Figure 1). Considering the data from the population analysis according to Mullikan [14], the hydrogen atoms of cyclen were distinguished into three groups: H_N for the hydrogen atoms binding to the N atoms, and H_C and H_C' for the hydrogen binding to the C atoms in plane and perpendicular to the molecular plane, respectively.
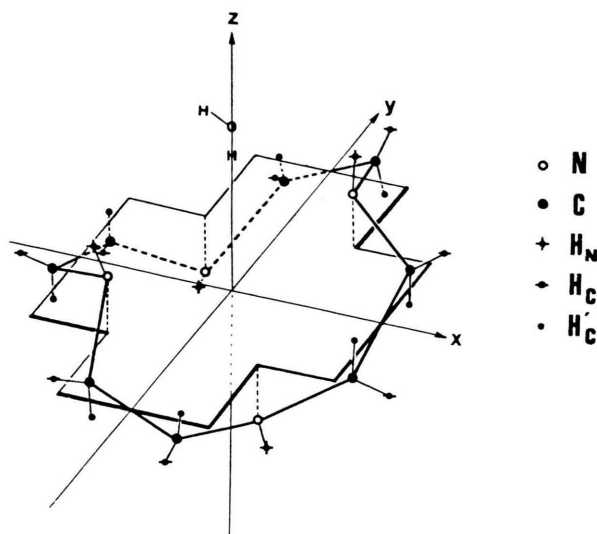
Fig. 1. The optimized position for a water molecular interacting with the 1,4,7,10-tetraaza-cyclododecane ligand (alternate conformation).

The ab-initio MO SFC calculations have been performed with a minimal Gaussian lobe basis set [15] for 250 cyclen-water configurations (each point took about 45 minutes of computer time on a Cyber 74 computer). The size of the system under consideration did obviously not allow the use of a more extended basis set because of the unreasonable computation time that would have required. The basis set dependence of the Monte Carlo results has been investigated by Jorgensen [16], with the result that minimal basis sets are quite sufficient for the determination of the potential functions, so that the use of our basis size should also be only a minor methodical problem.

Results and Discussion

The calculated values of the pair interaction energy, $\Delta E(L, W)$, were fitted, using a multidimensional non-linear least-squares procedure, to functions of the following form, consisting of a Lennard-Jones and a "Coulombic" expression:

$$\Delta E(L, W) = \sum_{i=1}^{3} \sum_{j=1}^{32} \{- |A_{ij}^{ab}|/r_{ij}^{6} + |B_{ij}^{ab}|/r_{ij}^{12} + q_i q_j (1/r_{ij})(|C_{ij}^{ab}| + |D_{ij}^{ab}|/r_{ij})\}, \quad (1)$$

where, A_{ij}, B_{ij}, C_{ij}, and D_{ij} are the fitting constants (absolute values) and r_{ij} is the distance between an atom i of water (W) and an atom j of the ligand (L). q_i and q_j are the net charges of the atom i and j in atomic units, obtained from the population analysis [14] of the isolated molecules.

These charges lead to a smaller than the experimental dipole moment of H_2O (1.61 D instead of 1.87 D). However, this deviation seems to be acceptable for reasons of methodical consistency (use of data obtained for ΔE and dipole moment from the same basis set), since the adjusted parameters can easily compensate for the deviation. Superscripts a and b indicate that we did not only distinguish between atoms of different atomic number (e.g. hydrogen and carbon) but also between atoms of equal atomic number but different environmental conditions, for example H_N from H_C and H_C'.

As only absolute values were allowed for the parameters, A and B represent attractive and repulsive interactions of atoms i and j, respectively, while C and D correspond to either repulsive or attractive interactions, according to the sign of q_i and q_j.

Some comments should be made concerning the addition of the second Coulombic term, D. This term was essentially introduced in order to obtain a better numerical fitting. For larger distances r_{ij}, this parameter plays only a minor part in the fitting procedure, similar to potentials obtained for water-amino acid interactions [17−20]. However, when a water molecule approaches close to the ligand molecule, the actual values of the atomic charges should vary as a function of the distance and the orientation of water relative to ligand, due to mutual polarization effects. The product $q_i q_j$ of the atomic charges − constant in our approaches − can be made a distance dependent product $q_i' q_j'$ introducing a power series of r_{ij}^{-1} [20]:

$$q_i' q_j' = q_i q_j (1 + C_{ij}^{ab}/r_{ij} + D_{ij}^{ab}/r_{ij}^{2} + \dots), \quad (2)$$

where $C, D, \dots$ are constants. This procedure led to the second (Coulombic) term in our potential (1).

As we assign a set of parameters A, B, C, and D for each pair of atoms, we actually construct a combination of five different pair potentials, describing the interaction of C, N, H_N, H_C, and H_C' atoms of the ligand with the oxygen atom, and five additional different pair potentials describing the interaction with the hydrogen atoms of water. Therefore, ten

sets of parameters A, B, C, and D (= 40 parameters) entered in our calculations.

The fitting procedure started with 150 points of the energies calculated for various water positions and orientations relative to the ligand. These 150 points have been selected using 15 different trajectories pointing to various binding centers of the molecule, within one of the 8 equivalent configuration spaces around the ligand. The resulting analytical potential functions with the best fit for this set of the initial data, gave a standard deviation of $\sigma = \pm 1.58$. Then, additional 25 randomly chosen points outside the initial data set were added. With the first analytical potential, the energy for these additional 25 points was calculated, leading to a standard deviation of $\sigma_{test} = \pm 3.64$, as given in Table 1.

Now, the 25 test points were included into the final procedure and a new set of parameters A, B, C, and D with a standard deviation $\sigma = \pm 1.72$ were obtained. Another 25 points were again tested and then included. This procedure was repeated until

constancy of the fitting parameters was obtained within a range of $\pm 5\%$ [21] and the standard deviation was satisfactory compared with the accuracy of the MO calculations. An additional criterion of convergency is the coincidence of σ_{test} and σ_{values} (cf. Table 1). The results of this procedure are shown in Table 1, indicating that 250 points of the energy surface were sufficient to accomplish this convergency. The final parameter values are summarized in Table 2.

In Fig. 2, potential energy curves for the SCF energies (E_{MO}) for various water orientations are shown and the lowest curve is compared with the corresponding curve E_{FIT} from (1) with the final optimized parameter values. The correlation between E_{MO} and E_{FIT} for all 250 data points is plotted in Figure 3. In order to illustrate the quality of the fitting for various interaction energy ranges, their standard deviations were evaluated separately and listed in Table 3. Compared to other works, the final standard deviation in our case is quite satisfactory (for example $\sigma_{WL} = 0.23$, 1.57, 2.00 and 2.57, when W = water and L = formaldehyde [5], methanol [22], urea [23], and butanol [24], respectively).

In this context also the influence of the small basis set used in our SCF calculations should be considered. Due to basis set superposition errors, some artificial stabilisation will occur especially for short water-ligand distances. An analytical potential, whose energies are somewhat "too high" for these short distances is not necessarily bad, therefore, and might even correct for some of the basis set superposition error.

Table 1. Characteristics of optimization process according to (1). N: number of ab-initio data; $\pm \sigma$: standard deviation in $kcal \cdot mol^{-1}$; $\pm \sigma_{test}$ see text.

Step	N	$\pm \sigma$	N_{test}	$\pm \sigma_{test}$
1	150	1.58	25	3.64
2	175	1.72	25	2.17
3	200	1.46	25	1.93
4	225	1.84	25	2.06
5	250	1.94	–	–

Table 2. Final optimization parameter values for N, C, H_N, H_C, and H_C' atoms for 1,4,7,10-tetraaza-cyclododecane interaction with oxygen (a) and hydrogen (b) atoms of water ($q_0 = -0.38$, $q_H = 0.19$). Interaction energies have been evaluated in hartree and converted into $kcal \cdot mol^{-1}$, r has been considered in atomic length units.

|	Atom		Parameter			
	X	q_X	A	B	C	D
(a)	N	− 0.52	0.7088242199 E + 04	0.1356347727 E + 10	0.6290222862 E + 03	0.5125715435 E + 03
	C	− 0.21	0.1258444167 E + 06	0.2326464596 E + 10	0.6280239668 E + 03	0.5148098836 E + 03
	H_N	+ 0.26	0.3271823805 E + 03	0.2667838093 E + 07	0.6254469452 E + 03	0.4812850289 E + 03
	H_C	+ 0.14	0.5838662961 E + 04	0.7094557693 E + 06	0.6291925770 E + 03	0.5048285948 E + 03
	H_C'	+ 0.20	0.2292557115 E + 03	0.3322617153 E + 07	0.6317168600 E + 03	0.4974500330 E + 03
(b)	N	− 0.52	0.2271841049 E + 04	0.2173738501 E + 05	0.6246459916 E + 03	0.4830482097 E + 03
	C	− 0.21	0.1730465573 E + 02	0.4774781017 E + 08	0.6262451527 E + 03	0.4823037170 E + 03
	H_N	+ 0.26	0.6584947492 E + 02	0.4826953244 E + 04	0.6303361748 E + 03	0.5300506155 E + 03
	H_C	+ 0.14	0.5523938519 E + 03	0.1066351656 E + 05	0.6282850595 E + 03	0.5070445377 E + 03
	H_C'	+ 0.20	0.1288102693 E + 04	0.7042391127 E + 05	0.6220563999 E + 03	0.4920909411 E + 03
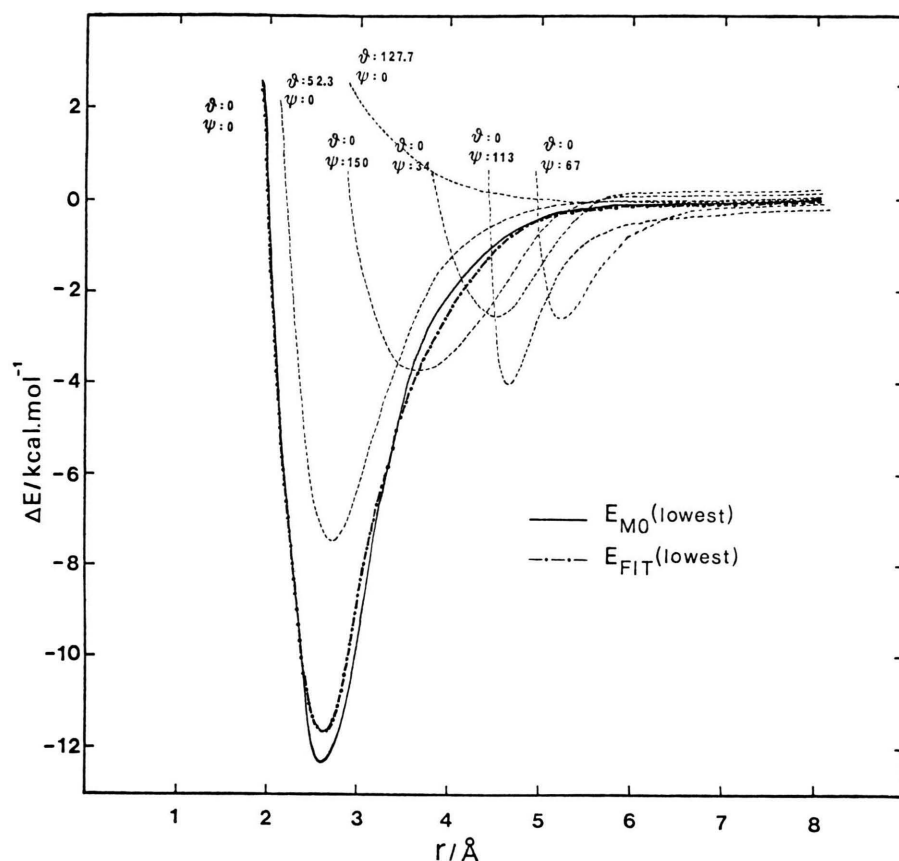
Fig. 2. Angular dependence of interaction potential: Ψ is the angle between the z-axis and the vector r pointing toward oxygen, ϑ is the angle between vector r and the O–H bond of water. For the case of the lowest potential curve, the comparison between SCF-data and the fitted analytical potential (–·–·–) is illustrated.
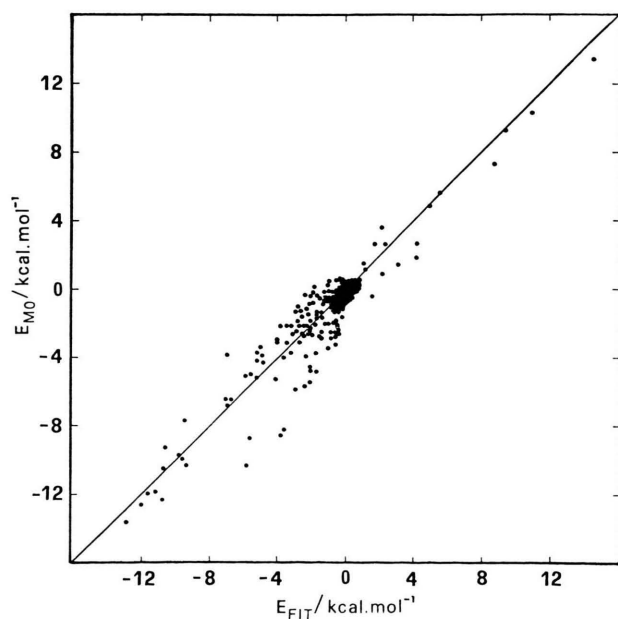

Table 3. Standard deviations $\pm\,\sigma$, calculated from (1) for different interaction energy ranges.

	Total	$\Delta E < -5$	$\Delta E < 0$	$\Delta E < 5$	$\Delta E > 5$ (kcal · mol^{-1})
$\pm\,\sigma$:	1.94	2.26	1.29	1.12	1.00

Fig. 3. Energy data from MO calculations versus those obtained by (1) with optimized parameters.

Finally, absolute energies are not too important for the subsequent MC and MD simulation, as long as the relative shape of the energy surface is reflected well.

First MC simulations using the analytical potential function presented in this paper, have led to quite encouraging results [25].

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