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Computer simulation studies of spherands, crowns and porphyrins: application of computer graphics, distance geometry, molecular mechanics and molecular dynamics approaches

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Abstract - We present the results of simulations on spherands, crown ethers and hemes, using computer graphics, distance geometry, molecular mechanics and molecular dynamics. In the spherand calculations, we show how a combined use of distance geometry, computer graphics and molecular mechanics led to the prediction of a new spherand isomer with high Li^+ and Na^+ affinity. In the area of crowns, we simulated the relative cation affinities of dibenzo 18-crown-6 and dibenzo 30-crown-10, using molecular dynamics and free energy perturbation theory and found good agreement with the relative experimental free energies of ion binding. For the hemes, we simulated the relative free energy of association of CO and O_2 in different porphyrins using molecular dynamics and free energy perturbation approaches and found a reasonable agreement between the calculated and experimental relative CO/O_2 affinity.

INTRODUCTION

Computer simulation methods are proving of increasing use in understanding the specificity of intermolecular interactions in complex molecules. These methods include model building approaches such as computer graphics and distance geometry and numerical based methods such as molecular mechanics and dynamics. The former two are used to construct representative structures of molecular systems and the latter two to evaluate their energetic feasibility.

These methods have been applied to a variety of molecules of organic and biochemical interest, including ionophores, proteins and nucleic acids. In this paper, we focus on the molecules of organic chemical interest, in particular ionophores and heme models. We first describe our calculations on anisole spherands, [1] in which we used a combination of computer graphics and distance geometry to create models of such structures, and then molecular mechanics to evaluate their energies and interaction energies with alkali cations. The calculations successfully rationalize the ion specificity of these molecules as well as predicting the properties of a new isomer of a spherand with the highest known Li^+ and Na^+ affinity.

A second set of calculations on dibenzo crown ethers uses a new approach to evaluating free energy differences between closely related molecules, free energy perturbation theory. [2] This approach is described by Singh [3] and Bash [4] and the focus of our studies here is to rationalize the relative affinities of alkali cations for dibenzo 18-crown-6 and dibenzo 30-crown-10 in methanol. To do so, we describe simulations in which we "mutate" one alkali cation into another in a cluster of methanol molecules and when bound to the crown. We are able to show how the relative crown-cation affinity is a delicate balance between solvation and binding free energies.

A large number of heme models of oxygen binding proteins have been synthesized and characterized [5]. In addition to the porphyrin ring, these systems have ligands to represent the proximal histidine in myoglobin and hemoglobin, as well as organic "straps" on the distal (O_2 binding) side of the heme. These systems have a wider range of relative CO and O_2 affinities, presumably due to differences in steric effects coming from the fact that the optimal Fe - C ≡ O angle is 180° and the Fe - O - O angle near 130°. Although one cannot evaluate the chemical bonding contribution to the relative CO and O_2 affinities, by mutating CO into O_2 in different heme models, we can gain insight into the role of steric and electrostatic effects in influencing these affinities.

METHODS

The computer graphics, distance geometry and molecular mechanics methodologies used in the spherand studies are fully described in ref. [1] and an overview given in ref. [6]

In all the molecular mechanics and dynamics calculation, the AMBER program [7] was used, with an energy function of the form:

$$E_{total} = \sum_{bonds} \frac{K_r}{2}(r - r_{eq})^2 + \sum_{angles} \frac{K_\theta}{2}(\theta - \theta_{eq})^2 + \sum_{dihedrals} \sum_{n} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] \quad (1)$$

$$+ \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}}\right] + \sum_{i<j}{}_{1\text{-}4\ terms} \left[\frac{1}{2}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}}\right]\right]$$

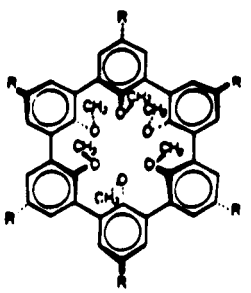
$$+ \sum_{H\text{-}bonds} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}}\right]$$

$$+ \sum_{i<j} \left[\frac{q_i q_j}{\varepsilon R_{ij}}\right] + \sum_{i<j}{}_{1\text{-}4\ terms} \left[\frac{1}{EEL_{scale}}\left[\frac{q_i q_j}{\varepsilon R_{ij}}\right]\right]$$

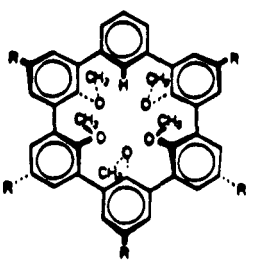
The molecular mechanical parameters and the starting geometries used in the dibenzo crown study are described in ref. 2.

The molecular mechanical parameters for the heme models were developed by simulating the stereochemistry around the iron atom in four heme complexes whose X-ray crystal structures are known. These four systems are the following. a) "picket fence" (1-MeIm)(O_2), [(1-Methylimidazole)-meso-tetra(α,α,α,α-o-pivalamidophenyl)porphyrinatoiron(II) (O_2) [8] b) picket fence(2-Meim)(O_2) [9] c) picket fence (2-MeIm) [8] and d) pyridine-TPP-CO, [(Pyridine)-meso-tetra(α,α,α,α-phenyl)porphyrinatoiron(II) (CO)] [10]. Starting values for the parameters were obtained elsewhere [11], or were taken from the AMBER force field.

The quality of fit between calculated and known structures was assessed based on the agreement between specific geometric features. These features included the following: a) The direction and extent of the displacement of the iron atom from the planes defined by, the four pyrrole nitrogens (Fe-Ct), and all of the 24 atoms of the porphyrin core (Fe-Core). b) The iron proximal-nitrogen bond distance (Fe-NB). c) The bond distance between the iron atom and the sixth ligand (Fe-L1). d) The average iron-pyrrole nitrogen bond length (Fe-Np). e) The size of the pyrrole-nitrogen "hole" (Ct-Np). f) The extent of "pyrrole-tilting" (Ct_{beta}-Ct). This feature is determined in two ways. i) There are four sets of symmetry-related atoms in the porphyrin core; the four pyrrole nitrogens, the four *meso* carbons, the eight *alpha-pyrrole* carbons and the eight *beta-pyrrole* carbons. Each of these four groups can be considered to form a "circle" with its own "center" and "radius". The amount of "pyrrole-tilting" can be evaluated by the computing the difference between the "centers" of the pyrrole-nitrogen "circle" (Ct_N) and the beta-carbon "circle" (Ct_{beta}). If there is no tilting, the difference between these two centers is zero. As the tiling increases these two centers move further and further apart. ii) A second way of determining the extent of "pyrrole-tilting" is to examine the C_{alpha} - C_m - C_{alpha} - N_p dihedral angle. However, the values of these dihedral angles are dependent on the movement of *two* pyrrole groups and as such are not as accurate a determination of the pyrrole tilting. Values of the four calculated models agree reasonably with experiment, the evidence for which will be published elsewhere.



(1a) R = CH_3
(1b) R = H



(2a) R = CH_3
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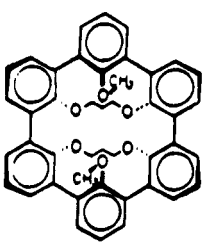
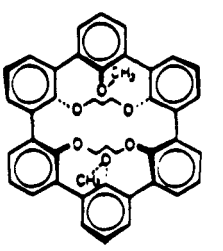
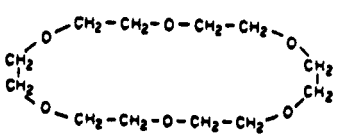


(3a)



(3b)



(4)

RESULTS

Molecular mechanics calculations on spherands [1] **1** - **3** and 18-crown-6 **4**, their Li^+, Na^+ and K^+ complexes and the hexahydrates of these cations have found the following: spherand **1** is calculated to have a large and comparable Li^+ and Na^+ affinity, and a very low K^+ affinity, consistent with experiment and in contrast to calculations and experiments on 18-crown-6 (**4**). The reduction in binding energy due to removal of a single OCH_3 group in (**1**) to lead to (**2**) is calculated to be ~ 14 kcal/mole, in good agreement with the experimental value of ~ 13 kcal/mole. The reduction in Li^+ binding energy in going from (**1**) → (**3a**) is calculated to be ~ 8 kcal/mole, in reasonable agreement with the experimental value for the free energy difference of ~ 7 kcal/mole. The calculations on (3b) suggested it would have a large Li^+ affinity than (1) and that it was more stable than (3a). The fact that (3a) was synthesized in initial experiments by Cram and co-workers was suggested to be due to kinetic factors. A modified synthetic approach by Cram found (3b) and confirmed our prediction that it would have a higher Li^+ affinity than (1).

The above studies used no x-ray data as input, all the structures being created by computer graphics and distance geometry approaches. The calculated structures were found to be in rather good agreement with available x-ray determined structures.

In the studies on dibenzo 18-crown-6 (DB18C6) and dibenzo 30-crown-10 (DB30C10), [2] we evaluated the free energy for perturbing $K^+ \rightarrow Rb^+$, $K^+ \rightarrow Na^+$ and $Rb^+ \rightarrow Cs^+$ when complexed to the crowns, when complexed to the crowns and two methanol molecules and when complexed to six methanol molecules. The calculations corresponded to evaluating ΔG_4 and ΔG_3 in the following cycle and comparing the difference to $\Delta G_2 - \Delta G_1$ determined experimentally.

$$\begin{array}{ccc} & \overset{\Delta G_1}{} & \\ (\text{Host})_{solv} + (\text{Guest-1})_{solv} & \rightleftarrows & (\text{Host.Guest-1})_{solv} \\ \uparrow\downarrow \Delta G_3 & & \uparrow\downarrow \Delta G_4 \\ & \underset{\Delta G_2}{} & \\ (\text{Host})_{solv} + (\text{Guest-2})_{solv} & \rightleftarrows & (\text{Host.Guest-2})_{solv} \end{array}$$

As one can see from Table I, the calculations are successful in reproducing the fact that K^+ is bound most tightly to dibenzo 18-crown-6, with both the smaller cation Na^+ and the larger ones Rb^+ and Cs^+ having lower affinity. For dibenzo 30-crown-10, the calculations (and experiments) find a much larger difference between Na^+ and K^+ affinities than in dibenzo-18-crown-6, with K^+ and Rb^+ of comparable affinities and Cs^+ lower in affinity. Although quantitative agreement with experiment is not achieved with this simple "solvation model", using a few CH_3OH molecules to represent the liquid, the important chemical trends are reproduced.

TABLE 1. Results of the Free Energy Calculations (kcal mol^{-1})[a]

Host	Guest-1	Guest-2	ΔG_4	ΔG_3[b]	ΔG_4-ΔG_3	ΔG_2-ΔG_1[c]
DB18C6	K^+	Na^+	-14.27±0.46	-19.20±1.05	4.93±1.51	0.9
DB18C6	K^+	Rb^+	7.07±0.26	5.86±0.12	1.21±0.38	1.0
DB18C6	Rb^+	Cs^+	6.44±0.13	4.95±0.17	1.49±0.30	1.4
DB18C6.2 MeOH	K^+	Na^+	-17.07±0.80	-19.20±1.05	2.13±1.85	0.9
DB18C6.2 MeOH	K^+	Rb^+	9.07±0.15	5.86±0.12	3.21±0.27	1.0
DB18C6.2 MeOH	Rb^+	Cs^+	8.55±0.33	4.95±0.13	3.60±0.46	1.4
DB30C10	K^+	Na^+	-9.15±0.42	-19.20±1.05	10.05±1.47	3.3
DB30C10	K^+	Rb^+	4.24±0.11	5.86±0.12	-1.62±0.23	-0.1
DB30C10	Rb^+	Cs^+	4.95±0.17	4.95±0.13	0.00±0.30	0.6
DB30C10.2 MeOH	K^+	Na^+	-12.42±0.64	-19.20±1.05	6.78±1.69	3.3
DB30C10.2 MeOH	K^+	Rb^+	5.02±0.27	5.86±0.12	-0.84±0.39	-0.1
DB30C10.2 MeOH	Rb^+	Cs^+	5.17±0.80	4.95±0.13	0.22±0.93	0.6

[a]See the thermodynamical cycle for an explanation of the symbols used. [b]ΔG_3 was calculated by perturbing guest-1.(6 MeOH) into guest-2.(6 MeOH).

In the porphyrin calculations, the relative free energies and enthalpy components for the $O_2 \rightarrow CO$ "mutations" are compared in Table 2. Compared to the reference value (flatheme), the 7,7-durene has little difference in CO and O_2 affinity, whereas the 5,5 pyridine and picket fence hemes have their relative CO affinity greatly reduced. As one can see, for picket fence, the effect is mainly electrostatic, whereas, for the 5,5 pyridine, there is a substantial non-bonded component, presumably due to the unfavorable steric interactions of CO with its Fe - C ≡ O angle of 180°, with the "strap".

TABLE 2. Relative contributions of different components to the enthalpic, and the free energy difference between the dioxygen and carbon monoxide complexes of four heme systems (kcal mol^{-1}.

component	5,5-pyridine heme	picket fence heme	flatheme	7,7-durene heme
EEL	7.384 ± 0.091	8.505 ± 0.092	2.478 ± 0.054	2.110 ± 0.087
NONB	0.773 ± 0.072	-0.013 ± 0.003	-0.040 ± 0.003	0.690 ± 0.009
14NB	0.227 ± 0.001	0.220 ± 0.001	0.139 ± 0.013	0.124 ± 0.007
14EL	-3.398 ± 0.014	-4.347 ± 0.006	-3.502 ± 0.026	-3.446 ± 0.006
BADH	0.788 ± 0.018	1.024 ± 0.033	0.544 ± 0.072	0.329 ± 0.022
TOTL	5.931 ± 0.349	5.392 ± 0.130	-0.381 ± 0.115	-0.197 ± 0.116
GIBBS	5.780 ± 0.065	5.424 ± 0.319	-0.353 ± 0.087	-0.233 ± 0.049
exp[a]	-1.56 [5]	-4.94 [5]	-5.91 [5]	-6.38 [12]

[a] values = -RTln(M) at 20-25 degrees.

SUMMARY AND CONCLUSIONS

The applicability of computer simulation methods to the study of ionophores and porphyrins has been demonstrated here. Such methods have been able to reproduce ion selectivity of spherands and crowns and give clear physical explanations for this selectivity. Insights into the reasons for the relative CO/O_2 selectivity of porphyrins have also emerged from our calculations.

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