Electrostatic Interactions in Aliphatic Dicarboxylic Acids: A Computational Route to the Determination of pK_a Shifts

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Abstract: pK_a shift calculations on a series of dibasic aliphatic dicarboxylic acids are reported. The structures of the molecules are determined with the MM2 force field, and pK_a shifts are evaluated using the finite difference Poisson–Boltzmann methodology. Both the structures generated and the pK_a shifts calculated solely via computer modeling a priori are in good agreement with experiment.

I. Introduction

Calculating the pK_a values of dibasic aliphatic acids has been a problem of longstanding interest.[1-5] More than 50 years ago, Kirkwood and Westheimer used classical electrostatics to approach the problem, treating the solute as a low dielectric spherical cavity. The need for a proper geometric description of the acid and uncertainties as to the placement of charges within the cavity limited the accuracy of the results that were obtained.[5] The availability of numerical solutions to the Poisson–Boltzmann equation and the success of this approach in treating a variety of electrostatic phenomena in aqueous solution[6-10] suggest that a reinvestigation of dibasic acids would be of value. In this work we have carried out pK_a shift calculations on a series of dibasic aliphatic acids by first obtaining the structures of the molecules with the help of the MM2 force field[11] and then evaluating the pK_a shifts via the finite difference Poisson–Boltzmann (FDPB) method.[8-10]

II. Background

Consider the following ionization equilibrium of a dibasic aliphatic acid:

$$\underset{\mathbf{A}}{^-OOC(CH_2)_nCOOH} + H_2O \rightleftharpoons \underset{\mathbf{B}}{^-OOC(CH_2)_nCOO^-} + H_3O^+$$

The electrostatic repulsions between the two negative charges are expected to render **B** unstable relative to **A** and shift the equilibrium to the left. This manifests itself as an increase in pK_a, indicating less facile dissociation.

If it were feasible to evaluate the electrostatic potentials accurately at a given site (r_i) of charge q_i due to other charges q_j in the system, the pK_a shift of the functional group containing charge q_i could be determined as

$$\Delta pK_i = q_i\phi(r_i)/(2.303RT)$$

pK_a shifts yield valuable information on intramolecular interactions affecting the ionization equilibrium of the functional group of interest. Studies such as these encounter two difficulties. One concerns the structure assumed by the molecule under given experimental conditions, and the other relates to the accuracy of the electrostatic model employed to estimate the pK_a shifts. Several force fields and computer programs/packages[11-15] for geometry optimization and molecular modeling have been developed over the years, and the computational procedures are now well established for generating structures. Similarly, several numerical schemes such as the finite difference Poisson–Boltzmann method, the finite element Poisson–Boltzmann method, etc. have since been reported.[8,16-20] Their predictive abilities on the pK_a values of side chains in proteins are now well chronicled.[16-22] In the present work, we have combined these two techniques, namely, the geometry optimization (using the MM2 force field) and the FDPB method, for the evaluation of the electrostatic contribution to intramolecular interactions for a reappraisal of pK_a shifts of dicarboxylic acids. This work gives us an opportunity to critically evaluate the performance of the above computational techniques on structural and thermodynamic predictions vis-à-vis experiment.

III. Calculations

Initial structures of the dicarboxylic acids were generated using computer modeling with the anionic groups farthest apart. These structures were then subjected to extensive energy minimization using MM2 force field (with a tolerance value of gradient 0.0001 kcal/Å mol). To circumvent the local minimum problem, several random conformations were generated via random numbers in torsional space, and the resultant

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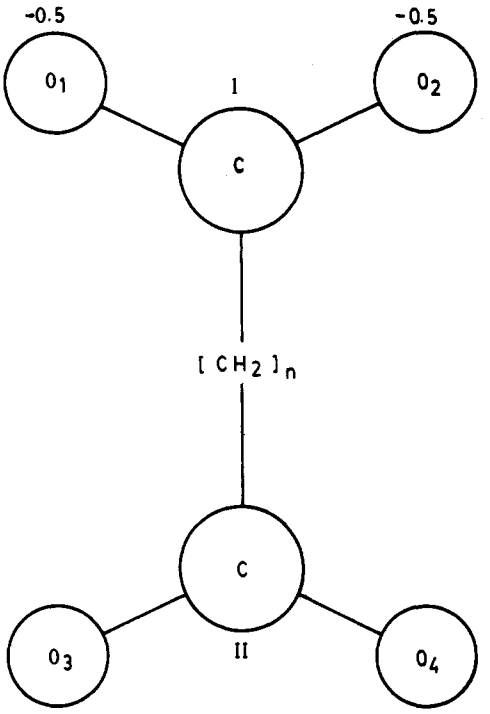

Figure 1. Schematic representation and charge assignment scheme of the aliphatic dibasic carboxylic acids studied. A charge of –0.5 is assumed to O_1 and O_2 of carboxylate group I for calculating potentials at sites O_3 and O_4 of carboxylate group II using the FDPB method. n represents the number of intervening methylene groups (n = 0, for oxalic acid; n = 1, malonic acid; n = 2, succinic acid; n = 3, glutaric acid; n = 4, adipic acid; n = 5, pimelic acid; n = 6, suberic acid; n = 7, azelaic acid).

structures were optimized. The lowest energy conformation for each molecule was taken as the starting structure for subsequent ΔpK_a determination.

Electrostatic potentials due to a negative charge on the carboxylate group I (Figure 1) at the sites of the oxygens of carboxylic acid group II were estimated using the FDPB method. The details of the FDPB method have been described previously.[8-10] The molecule was mapped onto a 65 × 65 × 65 point cubic lattice with a resolution of 2 grids/Å. The surrounding solvent was treated as a continuum of dielectric constant of value 80. A dielectric constant of 2 was assigned to the region enveloped by the van der Waals surface of the solute molecule. OPLS parameters[23] were used for van der Waals radii. Methyl and methylene groups were treated as united atoms. The negative charge on the carboxylate group I was evenly distributed on both of the anionic oxygens. We used a very simple formal charge description in our calculations. A charge of –0.5 was assigned to each anionic oxygens (labeled O_1 and O_2; see Figure 1). The potentials at the sites of oxygens (labeled O_3 and O_4) of the carboxylate group II were determined via the FDPB method. The pK_a shifts are then obtained as

$$\Delta pK_a = [(\phi_1 + \phi_2)/2]/2.303$$

where ϕ_1 and ϕ_2 are potentials (in kT/e units) on target oxygens (O_3 and O_4).

The FDPB calculations were repeated for the structures obtained from X-ray crystallography.[24]

IV. Results and Discussion

The energy minimized structures obtained by using the MM2 force field, are compared with X-ray structures in Figure 2. Distance between the two carboxylate groups in each molecule is plotted against the number of intervening methylene groups (distance here refers to the distance between the midpoints of oxygens of each carboxylate group in the molecule). The linearity

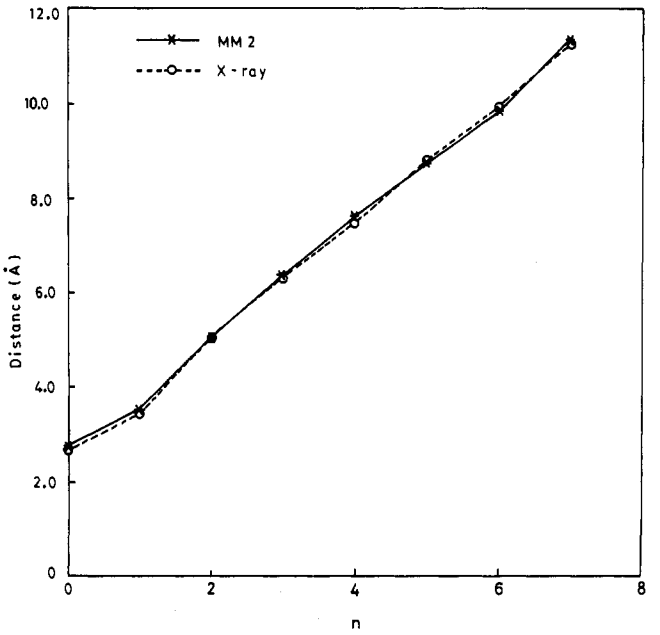

Figure 2. Distances between the two carboxylate groups in each molecule plotted against n, number of intervening methylene groups for X-ray and MM2 structures.

Table 1. Calculated pK_a Shifts of Some Diabasic Carboxylic Acids

	pK_a shifts				
		X-ray	MM2		
systems (n)[b]	exptl[a]	FDPB	FDPB	$\epsilon = 80$	$\epsilon = r$
oxalic acid (0)	2.36	5.41	4.04	0.98	25.49
malonic acid (1)	2.26	2.42	2.47	0.83	18.47
succinic acid (2)	0.84	0.82	0.84	0.58	9.00
glutaric acid (3)	0.47	0.49	0.48	0.47	5.98
adipic acid (4)	0.38	0.37	0.36	0.40	4.14
pimelic acid (5)	0.34	0.30	0.31	0.35	3.15
suberic acid (6)	0.28	0.27	0.27	0.31	2.49
azelaic acid (7)	0.26	0.24	0.24	0.27	1.89
methylmalonic acid (1)	1.89		2.34	0.77	15.54

[a] Experimental values taken from ref 3. [b] n is the number of intervening methylene groups between the two carboxylate groups.

of the plot appears to imply that the structures are mostly governed by electrostatic repulsions. Overall, the X-ray and MM2 structures are identical (correlation coefficient, r = 0.99) and superimposable. These results indicate the level of accuracies attained by the MM2 force field in these systems. One must, however, note that MM2 calculations are done on isolated systems in the gas phase, while X-ray results refer to the solid phase.

Results on pK_a shifts are collected in Table 1. Experimental values are shown in the first column against each dicarboxylic acid. The number of intervening methylene groups is given in parentheses adjacent to each dicarboxylic acid. The FDPB results on pK_a shifts for X-ray and MM2 structures are given in the second and third columns, respectively. pK_a shifts obtained by the simple Coulombic model with ϵ = 80 and those with $\epsilon = r$ (distance-dependent dielectric screening function) are listed in the fourth and fifth columns, respectively.

pK_a shifts calculated using the FDPB method may be seen to be in close correspondence with experimental values for all the systems studied except for oxalic acid (Figure 3). Other models, such as the Coulombic and the distance-dependent dielectric function, are not so satisfactory. An inspection of the results with $\epsilon = r$ suggests that $\epsilon = 10r$ may be more apt for these systems. The FDPB calculations on oxalic acid were repeated with another set of van der Waals radii[25] (R_C = 1.87 Å, R_O = 1.48 Å, and R_{CH_2} = 1.90 Å) for the purposes of defining the van der Waals surface,

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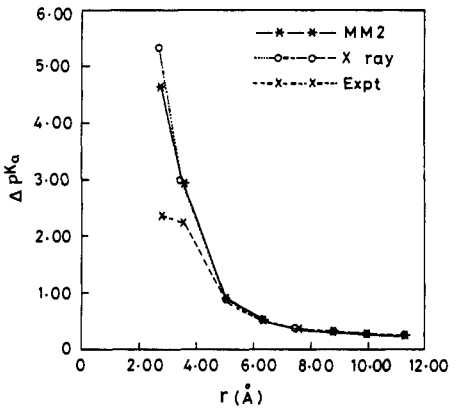

Figure 3. Calculated ΔpK_a versus r, distance between the two carboxylate groups: FDPB for X-ray structures, FDPB for MM2 structures, and experimental.

and a pK_a shift of 2.55 was obtained, which again accords well with experiment. This indicates that when the charges are close as in oxalic acid, the sensitivity of the results to the radii and other parameters increases. A study of the dependence of the pK_a shift on the probe radius indicates that ΔpK_a values for oxalic and malonic acid increase by about 0.4 units when the probe radius is increased from 0 (corresponding to the van der Waals surface of the molecule) to 1.4 Å (corresponding to accessible surface of the molecule for solvent water). The variations are much less significant for other systems. Overall, the agreement between theory (FDPB) and experiment is good.

An issue of relevance in assessing the role of electrostatic interactions is the structure adopted by the molecular system and whether an ensemble of structures has to be considered as opposed to a single structure. Some recent work on electrostatics of macromolecules has underscored the importance of conformational averaging in theoretical estimates of ΔpK_a values.[20,26,27] For the small systems considered here, where the structures are largely governed by electrostatic repulsions as may be inferred from Figure 2, conformational averaging is not expected to yield a large spread in pK_a shifts. To probe this further, we have carried out molecular dynamics simulations[28] on each system and collected about 10 structures spaced at 1-ps intervals. The pK_a shifts were then calculated for these 10 structures in each case. The standard deviations (2σ values) vary from 0.26 units for oxalic acid to 0.02 units for azelaic acid, suggesting that conformational averaging may not affect the estimated ΔpK_a values significantly in these dicarboxylic acid systems.

It may be recalled that in the present study the structures were generated using molecular mechanical force field, and pK_a shifts were obtained via numerical solutions to the Poisson–Boltzmann equation. Further refinements may include a consideration of the solution structure of the dicarboxylic acids (as obtainable from molecular dynamics simulations), a more realistic partial charge distribution in FDPB calculations, and inclusion of nonelectrostatic contributions. But these do not seem to be required for the systems under study. Both the structures and the pK_a shifts are in agreement with available experimental data.

V. Conclusions

We have shown that the FDPB method used in conjunction with energy minimization (MM2) protocols for molecular structure predicts accurately the pK_a shifts of dicarboxylic acids. Other electrostatic models (with $\epsilon = 80$ or $\epsilon = r$) either underestimate or overestimate the observed pK_a shifts. The results presented here indicate the power of geometry optimization coupled with the dielectric continuum approach in estimating free energy differences and hence pK_a shifts in aqueous solutions.

It is of interest that the experimental results are reproduced with a continuum model that assumes that the solvent dielectric constant is 80 near the surface of the solute. Thus, the effects of dielectric saturation due to the charged groups seem to be minimal. This is in keeping with studies of solvation free energies,[29] where dielectric saturation effects have also been found to be small. Finally, our results suggest that the observed pK_a shifts in dibasic acids are due entirely to charge–charge interactions between the acidic groups. Thus, the original Kirkwood–Westheimer treatment provided the correct physical description of the phenomenon, although the absence of an accurate geometric model for the solute limited the utility of the theory and the extent of agreement with experiment.

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