

Extension of the Kirkwood–Westheimer Model of Substituent Effects to General Shapes, Charges, and Polarizabilities. Application to the Substituted Bicyclo[2.2.2]octanes¹

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Abstract: The Poisson equation of electrostatics is solved by the finite element method for solute models of arbitrary shape, charge density, and polarizability distribution. The method overcomes the earlier limitation of the Kirkwood–Westheimer theory to configurations for which analytic solutions could be obtained. The $-N^+(CH_3)_3$, $-Br$, and $-COOH/COO^-$ 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids were considered with the assumption of axial symmetry. The ΔpK data (relative to the H substituent) were closely reproduced with realistic molecular sizes and shapes, and with reasonable dielectric constants in different regions of the molecule and the adjacent solvent. The results were particularly sensitive to the dielectric constant at the solute–solvent interface, but all three substituents could be fitted using a single value. An initial inability to calculate more than $2/3$ of the Br ΔpK was overcome when it was realized that the theory required embedded rather than vacuum dipole moments. (All earlier calculations used vacuum moments for dipolar substituents.) $COOH$ and COO^- charge distributions were estimated from SCF–INDO molecular orbital calculations, and correction of the dipolar part for embedding considerably improved the fit.

The electrostatic theory of substituent effects was formulated 40 years ago for molecules of spherical and spheroidal shape.^{2,3} The molecule was represented as a region of uniform low dielectric constant in a solvent of uniform (usually higher) dielectric constant. For reasons of mathematical convenience, calculated results were limited to configurations with site and substituent at equal depth within the molecule. In the spheroidal case, the charge or dipole positions were further restricted to the foci. As might be expected, agreement of the theory with the data was only fair, discrepancies of a factor of 2 being typical. In spite of the difficulty of performing realistic calculations, it is generally believed that the theory can account for the substituent effects, at least in the case of saturated molecules.⁴

The site–focus coincidence requirement in the spheroidal model has recently been removed.⁵ However, many mathematical difficulties still impede a proper test of the electrostatic model against the data. An attempt to explore some of these difficulties by considering toroidal and spherical shell models by analytic means⁶ suggests that a more general approach to the problem would be of value. It is the purpose of the present paper to show that a suitable method does now exist for a realistic test of the model against the data. The present work may be considered to build on that of Ehrenson,⁵ who provided a review of earlier work.

In the past 10–15 years, structural engineers have developed the finite element method, an extension of the variation method for solving partial differential equations such as the Poisson equation of electrostatics. An initial application of this method to problems of molecular electrostatics⁷ demonstrated that difficulties caused by irregular molecular shape, or by variable dielectric constant and charge density, can now be overcome.

The calculations presented in the following sections attempt to reproduce the ΔpK data of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acid derivatives by generalized Kirkwood–Westheimer calculations. The substituents considered are $-N^+(CH_3)_3$, $-Br$, and $-COOH/-COO^-$, corresponding to charge, dipole, and mixed charge–dipole, respectively. Although the mathematical restrictions have been removed, it is still necessary to decide on a suitable assignment of dielectric constants, charge densities, and other factors as input to the calculations. To explore these variables, the initial calculations

have been limited to the approximation of axially symmetric molecular shapes, for which the problem is essentially two-dimensional. Full three-dimensional calculations are planned as the next step of the investigation. The substituted octane acids seem ideal for the present purposes because they are saturated, rigid, and deviate only slightly from ellipsoidal shapes. In addition, they have been used as model systems for testing the Kirkwood–Westheimer theory for the past 25 years.

It is worthwhile to summarize and briefly comment on the earlier work relating to the specific compounds of interest. The first Kirkwood–Westheimer calculations for dipolar substituents of the octane acids, including $-Br$ and $-CN$, accounted for only about half of the observed ΔpK s.⁸ In a later study of ten dipolar substituents, it was found that Tanford's modification of the Kirkwood–Westheimer theory⁹ also gave low predictions for the ΔpK s of the dipolar substituents relative to hydrogen or alkyl substituents, but better agreement was obtained for comparisons among the dipolar substituents themselves.¹⁰ The first data on the $-N^+(CH_3)_3$, $-COOH$, and $-COO^-$ substituents were interpreted to give an effective depth of the positive charge in the case of $-N^+(CH_3)_3$, and an effective dipole in the case of COO^- .¹¹ Extensive data and calculations were reported for the octane analogues of the above compounds,¹² with results supporting the earlier findings. Finally, Ehrenson⁵ has been able to separate site and focus positions in the spheroidal model.

Several aspects of the earlier calculations require some comment. The site position within the ionizing carboxyl has generally been taken as the proton position, implying neglect of charge redistribution upon ionization. With two exceptions,^{11,12} the same assumption seems to have been made for the carboxyl substituent. It is interesting to note that a negative charge at the proton position² is roughly equivalent to a negative charge between the oxygen atoms, plus a dipole of about 3.5 D.^{11,12}

For the dipolar substituents such as $-Br$, it has been customary to use the vacuum dipole moments, μ_v . Thus μ_v for CH_3Br has been used for the difference between the dipoles of a C–H bond and a C–Br bond. However, it has not been recognized in earlier calculations that the theory requires embedded rather than vacuum dipoles. Since the embedded dipole might be 20–40% greater than the vacuum dipole (de-

pending on the vapor molecule),¹³ it is clear that a significant fraction of the discrepancy of the earlier calculations is due to this effect in the case of dipolar substituents. Further discussion of this problem will be given in the following sections.

Theoretical Background

The Coulomb law of force between point charges can be transformed mathematically into the Poisson partial differential equation for ϕ , the electrostatic potential:

$$\frac{\partial}{\partial x_\alpha} \left(\epsilon_{\alpha\beta} \frac{\partial \phi}{\partial x_\beta} \right) = -4\pi\rho \quad (1)$$

where ρ is the free charge density, $\epsilon_{\alpha\beta}$ is the dielectric constant, and x_α is a Cartesian coordinate component. (Summation is implied over a Greek symbol that appears twice in a symbol or product of symbols.) Once ϕ is found by solving eq 1, it may be used to calculate all electrostatic quantities of interest, such as fields, polarizations, and energies.

To solve eq 1, it may be mathematically converted into an integral whose value is stationary to small variations of ϕ from its true functional form. Approximate solutions are then obtained in terms of a trial solution depending on a set of n parameters $\{c_i\}$. By setting the n first derivatives of the variation integral with respect to the c_i equal to zero, a set of equations is obtained that may be solved for the c_i . This technique, known as the variation method, is widely used in quantum chemistry to solve the Schroedinger equation for the wave function.

For present purposes, a recent extension of the variation method known as the finite element method is ideally suited for molecular electrostatics problems. Let

$$\phi = \sum_{i=1}^n c_i \phi_i \quad (2)$$

be a trial function consisting of a linear combination of known functions ϕ_i . Then the ϕ_i may be taken as simple polynomial functions in small regions (finite elements) of space. If the c_i represent values of the potential at particular points (or nodes) of the elements, then the ϕ_i can be chosen to serve as interpolating functions within the elements. The equations to be solved are linear, banded (because off-diagonal coefficients occur only between nodes in the same element), and well conditioned (roundoff errors are small). In addition, any reasonable geometry and dielectric or charge density functions may be used. The finite element method is well known in engineering,¹⁴ and has recently been adapted for problems in molecular electrostatics.⁷

The electrostatic energy of an array of charges in a dielectric may be expressed in several equivalent ways.¹⁵ For two point charges, q_1 and q_2 , it is $q_1\phi_1$ or $q_2\phi_2$, where ϕ_1 is the potential of q_2 at q_1 , and ϕ_2 is similarly defined. This result is expressed symmetrically as $1/2(q_1\phi_1 + q_2\phi_2)$. Note that the "self-energy" of forming q_1 and q_2 is not included. For continuous charge distributions, the electrostatic energy, including self-energy, is

$$W_i = \frac{1}{2} \int_V \rho \phi dv \quad (3)$$

The interaction energy of one charge distribution with a second nonoverlapping charge distribution is

$$W_i = \int_{V_1} \rho_1 \phi_2 dv \quad (4)$$

where ϕ_2 is the potential of the second charge distribution at the first. The integral is carried out over the first charge distribution, and does not include self-energies. The energy may also be expressed in a well-known field formulation involving a volume and a surface integral. This form is not as useful as eq 3 and 4 for the present considerations and will not be discussed further, except for the comment that the volume inte-

gral has been considered and calculated. Most of the following results are obtained by eq. 4.

The charge density ρ_q of a charge q associated with an atom or more general point (x_0, y_0, z_0) of a molecule is represented by a Gaussian function in the finite element calculations:

$$\rho_q(x, y, z) = \frac{q}{(2\pi)^{3/2}\sigma^3} e^{-\frac{1}{2}(r/\sigma)^2} \quad (5)$$

where

$$r = [(x - x_0)^2 + (y - y_0)^2 + (z - z_0)^2]^{1/2} \quad (6)$$

and σ is the spread or standard deviation parameter. If the charge is along the z axis, $x_0 = y_0 = 0$. The analogous representation of the charge density of a point dipole along the z axis is

$$\rho_{\mu_z}(x, y, z) = \frac{\mu_z z}{(2\pi)^{3/2}\sigma^5} e^{-\frac{1}{2}(r/\sigma)^2} \quad (7)$$

The behavior of these representations in finite element calculations has been explored.⁷ With cubic interpolating functions, it is necessary that the element size be no larger than σ in the vicinity of the Gaussian function.

When ρ_q and ρ_μ refer to charge immersed in a polarizable medium, they represent the "embedded" charge or dipole in the sense that in an infinite medium of dielectric constant ϵ , the potential is the same as that of ρ_q/ϵ or ρ_μ/ϵ in vacuum. The charges appear to be reduced because of the polarized bound charges of the medium that partially shield them.

When a point charge q is embedded at the center of a dielectric sphere of radius a , the shielding charge at q is canceled by the bound charge of opposite sign on the outer surface of the sphere. The potential in the vacuum outside the sphere is therefore the same as that of the embedded charge q . A different result is obtained for a point dipole μ embedded in a dielectric sphere. In this case, the potential in the vacuum outside the sphere is that of a dipole of magnitude $3\mu/(\epsilon + 2)$. This result is obtained by straightforward solution of the Poisson equation inside and outside the dielectric sphere:¹³

$$\phi_{\text{in}} = \frac{\mu z}{\epsilon r^3} - \frac{2\mu z}{\epsilon a^3} \frac{1 - \epsilon}{2 + \epsilon} \quad (8)$$

and

$$\phi_{\text{out}} = \frac{3}{\epsilon + 2} \frac{\mu z}{r^3} \quad (9)$$

where μ is assumed to be aligned with the z axis. Equation 9 gives the relation between μ and μ_v , the vacuum dipole moment for a polar molecule represented by this model:

$$\mu_v = \frac{3}{\epsilon + 2} \mu \quad (10)$$

This result may also be derived by adding $\int P dv$, the integral of the polarization vector over the molecule, to μ . Thus

$$\mu_v = \mu - \frac{\epsilon - 1}{3\epsilon} \mu - \frac{2(\epsilon - 1)^2}{3\epsilon(\epsilon + 2)} \mu = \frac{3}{\epsilon + 2} \mu \quad (11)$$

The negative (second and third) terms of eq 11 are obtained from the first and second terms of eq 8, respectively. The singularity contribution was evaluated indirectly by Fröhlich¹³ in a closely related derivation.

It should be emphasized that eq 10 or 11 give μ_v/μ only for the model of a point dipole in a uniform dielectric sphere. A different relation would be expected in the more likely case of a separated charge dipole off-center in a nonspherical molecule with a nonuniform polarizability distribution. Kirkwood-Westheimer calculations require μ rather than μ_v . Although μ may be appreciably greater than μ_v , all earlier calculations seem to have used μ_v . This choice is undoubtedly responsible

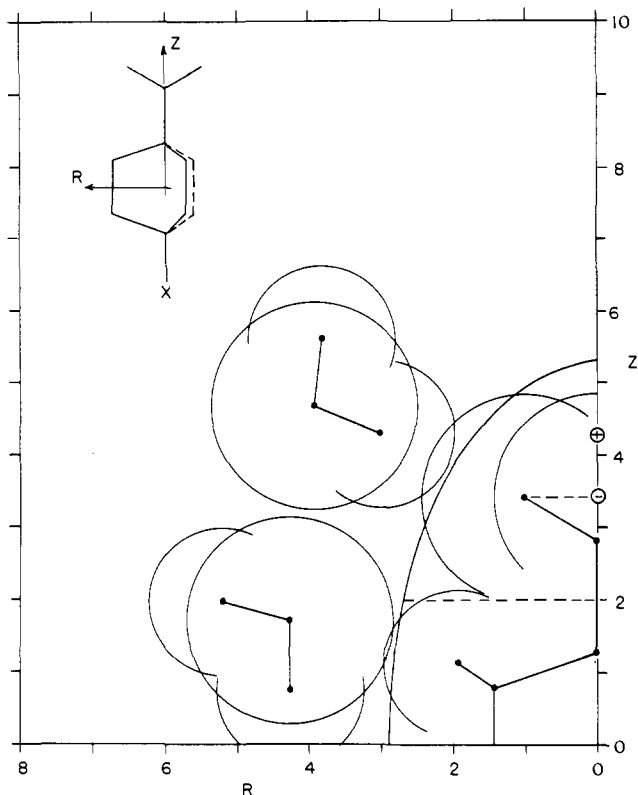
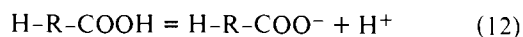


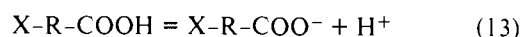
Figure 1. Molecular geometry and van der Waals radii for the acid site end of the molecule in cylindrical coordinates. Radii are shown for 90° rotations of the carboxyl oxygens. The ellipse approximates the molecular size and shape. The water molecules suggest possible solvent molecule positions. The diacid has reflection symmetry in the $z = 0$ plane.

for a significant part of the discrepancies that have been noted.^{8,10}

The chemical equilibria associated with substituent effects in carboxylic acids are



and



where R is the bicyclo[2.2.2]octane group (1,4 substituted) and X is $\text{N}^+(\text{CH}_3)_3$, Br, COOH, or COO^- in the present paper. If the thermodynamic dissociation constants for eq 12 and 13 are K_H and K_X , then from general thermodynamics and $\Delta pK = -\log(K_X/K_H)$, we obtain

$$2.303RT\Delta pK = N_A\Delta w \quad (14)$$

where N_A is Avogadro's number and Δw is the average reversible work at constant temperature and pressure to transfer a proton from the X-substituted acid to the H-substituted (reference) acid. If X is COOH or COO^- , then we take K_X equal to $\frac{1}{2}K_1$ or $2K_2$, the statistically corrected first or second ionization constant.

In the generalized Kirkwood–Westheimer theory, Δw is assumed to be the difference in the electrostatic energies of the four species in the difference of eq 12 and 13. Thus,

$$\Delta w = \Delta w_X - \Delta w_H \quad (15)$$

where

$$\Delta w_X = w(\text{X-R-COO}^-) - w(\text{X-R-COOH}) \quad (16)$$

$$\Delta w_H = w(\text{H-R-COO}^-) - w(\text{H-R-COOH}) \quad (17)$$

The energy change on ionization, Δw_X , is typically calculated

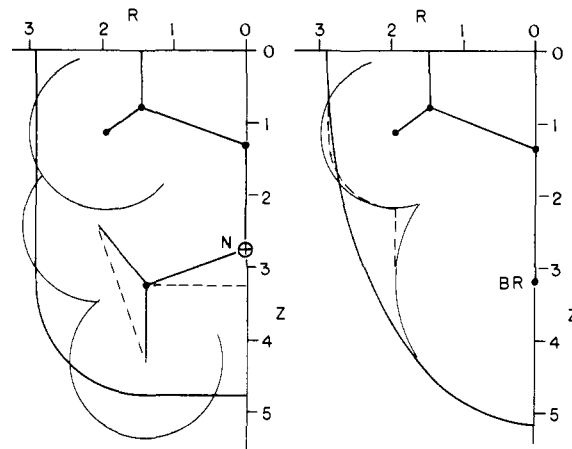


Figure 2. Molecular geometry for the substituent ends of the molecule for $-\text{N}^+(\text{CH}_3)_3$ and $-\text{Br}$. The curves used to represent the molecular size and shape are shown. Only one rotation of the methyl group is shown for $-\text{N}^+(\text{CH}_3)_3$. The dashed curve on the Br drawing was used for exploring the effect of shape variation.

in the present paper by solving the Poisson equation for the electrostatic potential due to the X-substituted charge distribution as a first step; then Δw_X is calculated by eq 4 as the interaction energy of this potential with a negative charge distributed over the carboxyl group (representing the change of the carboxyl charge distribution on ionization). As Holtz and Stock¹⁰ have pointed out, if the substituent dipole can be estimated independently of the C–H dipole (of the reference acid), then it makes sense to calculate Δw_H relative to a hypothetical reference acid with a zero-dipole C–H bond. This refinement has not been included in the present calculations, in which Δw_H is not explicitly calculated. Another potential error in the above procedure is the neglect of the change in size of the molecule upon adding the substituent.¹⁰ Thus a large polarizable substituent could also contribute to Δw by changing the ionization energy. This effect will be shown to be almost negligible for the largest substituent, $-\text{N}^+(\text{CH}_3)_3$, by separate calculations involving eq 3.

Calculation Preliminaries

The development of the calculation methods for application of the finite element method to molecular problems has been described.⁷ The substituent effect calculations required the addition of new programs for the calculation of the electrostatic energy. Since integrals of the type in eq 3 were already available for generating the finite element method equations, only minor innovations were required. The volume integral of the field energy expression was similarly available.

To test the energy programs, the potential of a unit dipole in vacuum ($\epsilon = 1$) and in a spherical cavity in a medium of dielectric constant 4 was calculated as described previously.⁷ The difference of the $\rho\phi$ energy integral (eq 3) and the field energy volume integral was less than 0.01% for each of the two cases ($\epsilon = 1, 4$), suggesting that the field energy surface integral was almost negligible in these cases. The difference of the $\rho\phi$ integrals for the two calculations differed by only 0.04% from the theoretical $-\frac{1}{2}\mu R$, where μ is the dipole moment and R is the reaction field.¹⁵ Since the difference was $\frac{1}{30}$ of the numbers subtracted, the agreement is quite good. It is felt that all of the directly calculated interaction energies obtained below (by eq 4) are reliable to at least 0.1%. The greatest uncertainty in the results is in the choice of input data.

In order to develop suitable meshes for the substituent effect calculations, the experience gained in the earlier reaction field calculations⁷ was utilized. The molecular geometry and van der Waals radii were drawn as shown in Figures 1 and 2. Bond

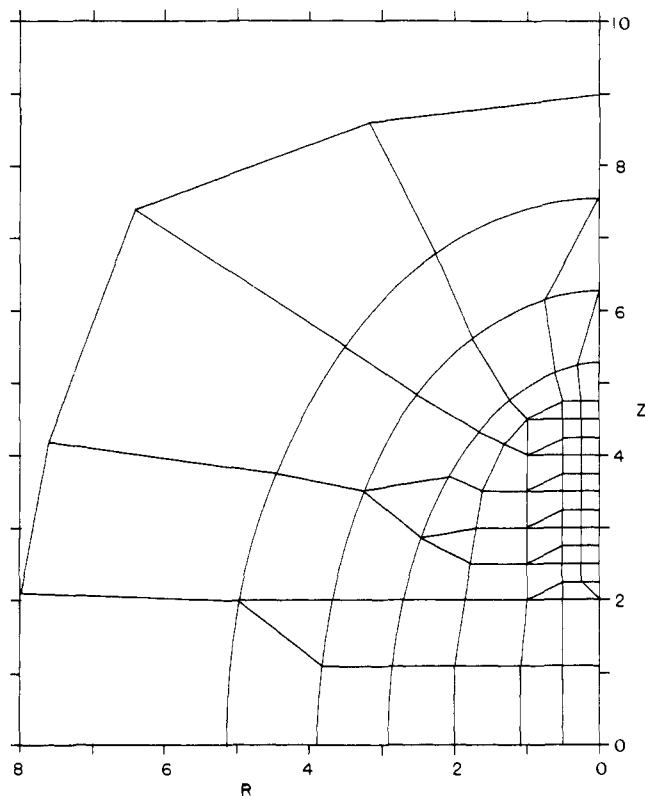


Figure 3. Element geometry in a two-dimensional section of the acid or site end of the molecule. Only the elements of the inner region are shown. The inner ellipse coincides with the ellipse of Figure 1. The mesh was doubled by reflection in $z = 0$ for the diacid.

lengths, angles, and radii were taken from standard sources.^{16,17}

In Figure 1, the ionizable proton position was assigned in the usual way (assuming axial symmetry),² and was found to be at $z = 4.27$ Å. The midpoint of the O atoms was at $z = 3.42$ Å, and the carboxyl carbon was at $z = 2.82$ Å. The axes of the half-ellipse approximating the molecular shape were $a, b = 5.27, 2.90$ Å, respectively. Note that rotatable solvent dipoles do not occur in a shell of about 1 Å thickness outside the van der Waals radii.

In Figure 2, a nonellipsoidal shape was chosen for the $N^+(\text{CH}_3)_3$ substituent. The N^+ atom was at $z = -2.75$ Å. The Br substituent was reasonably fitted by a half-ellipse with $a, b = -5.14, 2.90$ Å, respectively. The Br atom was at $z = -3.19$ Å, the length of the C-Br bond being 1.91 Å. Note that the C-Br bond penetrates the bicyclooctane region.

Figure 3 shows the mesh developed for the acid site end of the molecule. Since the proton position was only 1 Å from the surface of the molecule, it was necessary to take $\sigma = 0.25$ Å in eq 5 to have all of the charge within the molecule. This requirement forced the use of small 0.25 Å elements where charge distributions might occur. (The same σ value was also used for all of the other charges and dipoles.) Two spheroidal shells were provided outside the van der Waals radius to allow variation of the dielectric constant in this interesting region. The mesh also allowed easy variation of the dielectric constant in the carboxyl and bicyclooctane regions. Figure 4 shows the outer region, extending to a cylindrical surface at $r = 40$ Å and $z = \pm 40$ Å. Nodes on the outer boundary were assigned limiting charge and dipole potentials in the calculations. The outer region was essentially the same for all of the calculations. The outer rectangular elements had quadratic interpolating functions; all other elements had cubic functions.

Mesheres for the substituent end of the molecule are shown in Figures 5-7. The simplicity of Figure 5 reflects the as-

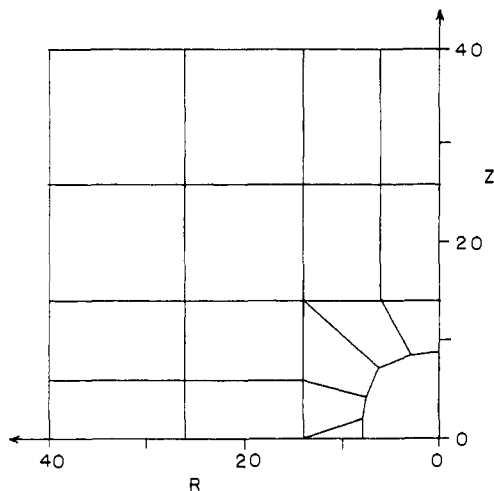


Figure 4. Element geometry in the outer region. There is reflection symmetry in the $z = 0$ plane.

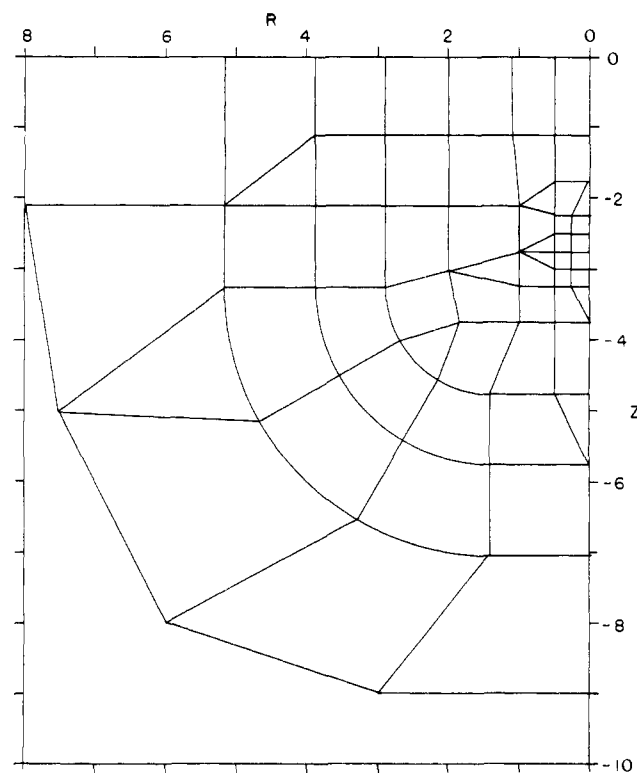


Figure 5. Element geometry for the trimethylammonium substituent. The site end of the molecule is shown in Figure 3.

sumption of a simple charge. In Figure 6, the length of the C-Br bond and the interest in point dipole vs. separated charge dipole representations required a more complex mesh. Figure 7 shows a distortion of Figure 6 providing a better fit of the molecular shape without changing the topology of the mesh.

To test the mesh and calculation procedures, the diacid mesh of Figure 3 was distorted to the geometry of Ehrenson's recent calculation¹⁸ so that the middle ellipse had $a, b = 5.87, 4.51$ Å, corresponding to foci at $z = \pm 3.75$ Å. The potential of a negative charge at the substituent carboxyl proton position ($z = -4.27$ Å) was then calculated using $\epsilon = 2$ within the cavity and $\epsilon = 50$ for the solvent (50% wt ethanol-water). The interaction energy of this potential with a negative charge at the ionizing carboxyl proton position, $z = 4.27$ Å, was then calculated. The result was approximately 1% greater than Ehrenson's value. This small difference is not surprising, since

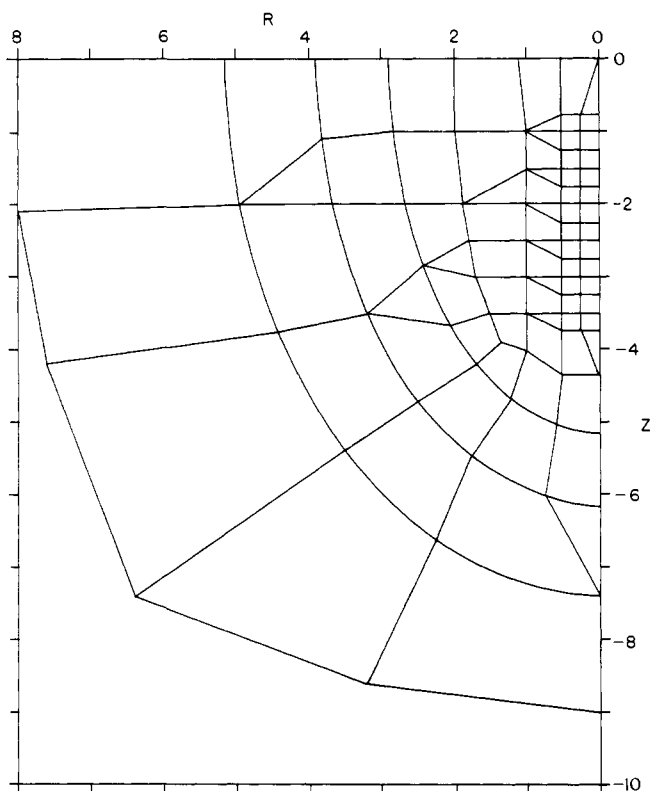


Figure 6. Element geometry for the Br substituent. The site end of the molecule is shown in Figure 3.

the present calculation used distributed rather than point charges. As a further check on the reliability of the results, contour plots of the calculated potentials were generated by the computer in most cases. As previously discussed,⁷ these plots were very useful for diagnostic purposes.

Calculations and Results

The Poisson equation can now be solved by the finite element method for any reasonable set of parameters, essentially removing the earlier difficulties of testing the electrostatic theory against the data. However, the proper choice of parameters is not immediately obvious. In fact, it will be seen that the calculations are extremely sensitive to some of the parameters, making it easy to fit a small amount of data. For this reason, the $-N^+(CH_3)_3$ substituent was considered first because it is the simplest, and is well represented by a localized positive charge in a hydrocarbon environment. It therefore has the smallest number of adjustable parameters.

For exploratory axially symmetric calculations of the type described in this paper, uniform dielectric constants, ϵ_i , have been assigned to the various regions as follows: (1) bulk solvent; (2) carboxyl group; (3) bicyclooctane disk; (4) substituent; (5) first outer shell; and (6) second (larger) outer shell. The size of the cavity (taken as the surface between the first and second shells) may also be varied. For subsequent refined calculations, variable dielectric constants may be appropriate, particularly in the two shells at the molecule-solvent interface.

Another important input parameter involves the charge redistribution in the carboxyl site upon removal of the proton. When the proton is removed, the electron cloud surrounding it undoubtedly shifts toward the oxygen atoms. For present purposes, the charge redistribution parameter is taken as the fraction of a positive charge removed from the proton site, with the assumption that the remainder of the charge is removed from the midpoint of the oxygen atoms, with no change at the carbon atom.

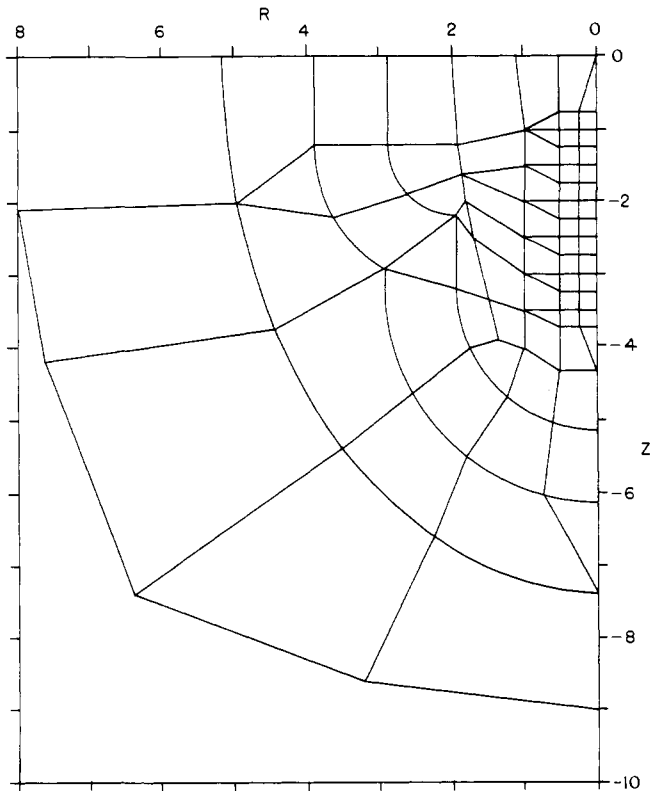


Figure 7. The mesh of Figure 6, distorted to provide a better fit to the molecular shape, as suggested by Figure 2.

Trimethylammonium. Using the meshes shown in Figures 3-5 and the parameters in Table I (the dielectric constants ϵ_i for regions 1-6 and the indicated ratio of charge removal, H/O), the calculated $|\Delta pK|$ was 5% greater than the experimental value. Since the result is very sensitive to the first outer shell dielectric constant and moderately sensitive to the cavity size, a perfect fit could easily be obtained by a small adjustment of one or both of these parameters. Since the cavity size effect is less, the inner part of the first shell must be more important than the outer part. The carboxyl dielectric constant was taken to be that of liquid CO_2 .¹⁹ The result is sensitive to this choice, but the range of likely values is limited. The H/O charge removal ratio is suggested by the O-H bond length of $\sim 1 \text{ \AA}$ and bond dipole moment of approximately 1.6 D,²⁰ and is further justified in the discussion of the substituent carboxyl given below. The calculation is relatively insensitive to this ratio, at least for the carboxyl at the ionizing site. The results for parameter variation given in Table I (and subsequent tables) require a cautionary comment: They are often nonlinear in the varied parameter, and are sometimes dependent on the values of other parameters.

The varied dielectric constant of the bicyclo disk in Table I was chosen to qualitatively represent the effect of adding a double bond (to convert the octane to octene). Experimentally, this modification increases $|\Delta pK|$ by 14%.¹² The dielectric constants of liquid cyclohexane and cyclohexene are 2.02 and 2.22, respectively.¹⁹ For present purposes, this increment should be increased to take care of anisotropy and concentration effects. The calculated effect is in the same direction as the data, but is too small. Perhaps the electrostatic theory does not adequately represent the full effect of a double bond. It is interesting that an increased dielectric constant in a slab between the site and substituent increases the interaction, essentially by extending the higher values of the potential. This effect contrasts with the reduction of the interaction when site and substituent are immersed in a generally higher dielectric constant.

Table I. Parameters for the $-N^+(CH_3)_3$ Substituent ΔpK Calculation

Parameter ^a	Value for close fit ^b	Varied value ^c	% change of $ \Delta pK $
ϵ_1 solvent	50		
ϵ_2 COOH/COO ⁻	1.6	2	-9
ϵ_3 bicyclo disk	2	2.5	+3
ϵ_4 substituent	2		
ϵ_5 1st shell	4	2.3	+36
ϵ_6 2nd shell	50	20	+4
Ionized charge, H/O	33/67	42/58	-5
Cavity size		-0.2 Å	-6

^a See text for descriptions. ^b $\Delta pK(\text{exptl}) = -1.50 \pm 0.02$ (ref 12); $\Delta pK(\text{calcd}) = -1.57$ (5% too large). ^c All other values from the preceding column.

Table II. Parameters for the $-Br$ Substituent ΔpK Calculation

Parameter ^a	Value for close fit ^b	Varied value ^c	% change of $ \Delta pK $
ϵ_1 solvent	50		
ϵ_2 COOH/COO ⁻	1.6		
ϵ_3 bicyclo disk	2	1.3 ^d	-5
ϵ_4 substituent	3		
ϵ_5 1st shell	4	2.3	+24
ϵ_6 2nd shell	50		
Ionized charge, H/O	33/67	42/58	-6
Cavity size		-0.2 Å	-5
Cavity shape	Spheroid ^e	Indented ^e	-1
Dipole moment, D	3.15 ^f	3.15 ^g	-15
		3.15 ^h	-3

^a See text for descriptions. ^b $\Delta pK(\text{exptl}) = -0.74 \pm 0.03$ (ref 12); $\Delta pK(\text{calcd}) = -0.74$. ^c All other values from the preceding column. ^d ϵ_3 was changed only in a central cylinder of $r = 0.5$ Å from $z = +1.1$ to -0.75 Å. ^e See Figures 2, 6, and 7. ^f Separated embedded charges at the C and Br atom centers. ^g Point (Gaussian) embedded dipole at the midpoint of the C-Br bond. ^h Separated charges, like note *f*, but the negative charge is at $z = z_{Br} - 0.1$ Å.

To investigate the direct effect of the polarizability of the substituent (relative to H) in changing the energy of ionization of the carboxyl, a preliminary calculation was carried out for both the H and the uncharged $N(CH_3)_3$ substituents, evaluating the total energy of the ionized acids by eq 3. The difference between the two calculations gave a ΔpK of less than +0.01, which is similar to the data for alkane substituents.¹² It is also small enough to neglect in the present considerations.

Bromide. The meshes of Figures 3, 4, and 6 were used, along with the same dielectric constants as in the trimethylammonium substituent calculation, except for the substituent region. Since $\epsilon = 3.1$ and $n^2 = 2.8$ for liquid bromine,¹⁹ a value of $\epsilon_4 = 3$ was chosen for the bromine atom.

The vacuum moment was taken as 2.1 D,⁸ and the embedded moment was calculated on the assumption that the vacuum moment corresponded to a nearly spherical molecule (such as CH_3Br) with nearly uniform polarizability distribution, so that eq 10 could be used. Taking $\epsilon = 2.5$, the average of the hydrocarbon and bromine values (2 and 3), eq 10 predicted $\mu/\mu_v = 3/2$. This value is clearly very approximate, and could only be improved by a more careful analysis of the moments of the alkyl bromide molecules in the vapor state. Presumably, such an analysis would require both quantum mechanical and finite element calculations.

A close fit of the ΔpK data was obtained for the parameters shown in Table II. The 15% decrease in going from a separated charge dipole to a point dipole is of interest, since the correct charge distribution is probably between these two limits. However, when the negative charge is moved beyond the Br

Table III. Atomic Charges for Acetic Acid and Its Ion^a

Form	H ₃	C	C	=O	-O	H
Acid	+0.055	-0.045	+0.495	-0.397	-0.305	+0.197
Ion	-0.148	-0.041	+0.453	-0.632	-0.632	

^a From SCF-INDO calculations (ref 22).

Table IV. Axial Representations of Carboxyl Charges

	Total charges			Embedded charges		
	C	O ₂	H	C	O ₂	H
COOH	+0.5	-0.7	+0.2	+0.8	-1.1	+0.3
COO ⁻	+0.4	-1.3	-0.1	+0.7	-1.7	0.0
$\Delta(\text{COO}^- - \text{COOH})$	-0.1	-0.6	-0.3	-0.1	-0.6	-0.3

atom (to represent a "lone-pair" contribution), there is also a decrease in the substituent effect, as may be seen from Table II. The substituent interaction may therefore pass through a maximum for separated charges at less than the bond length.

The sensitivities to other parameters are similar to but not identical with those in Table I. The effect of the change at the center of the bicyclo disk is consistent with the opposite type of change made in Table I. The insensitivity to cavity shape near the substituent atom is surprising, and probably indicates a cancellation of specific effects in this particular case.

Carboxyl. The meshes of Figures 3 (doubled to negative z) and 4 were used, along with the dielectric parameters of Table I, except that both site and substituent are now carboxyl. In order to carry out meaningful calculations, it was necessary to assign charge densities to the $-COOH$ and $-COO^-$ groups. For this purpose, molecular orbital calculations of the SCF-INDO type²¹ were carried out for acetic acid and its ion in the vapor state,²² using geometry from microwave spectroscopy.²³ The results were obtained as net charges associated with each of the atoms and as two dipole moments: μ_a , the moment calculated from point charges at the atom centers, and μ_t , the total moment of the molecule. μ_a and μ_t differ because of the asymmetry of the charge densities allowed by the calculations at atom centers other than H.

For acetic acid (un-ionized), μ_a and μ_t were 1.53 and 1.60 D. The angle of μ_t to the line from the methyl carbon to the carboxyl carbon was 110.6° (taking the sense of μ_t as minus to plus), on the $-C-O-H$ side of the molecule. This result is in good agreement with Smyth's bond dipole estimate of 1.4 D and 112° for a cis planar structure, and with the experimental magnitude of 1.7 D.²⁰

For the acetic acid ion, μ_a and μ_t were 1.97 and 3.63 D, along the negative C-C bond as defined above. Since the dipole moment of a charged species depends on the choice of coordinate origin, the absolute values are not directly useful. However, the difference between μ_a and μ_t suggests considerable asymmetry of the atomic charges. The oxygen atom lone-pair electrons seem likely to be the main source of this effect.

The calculated atom charge values are summarized in Table III. Axial representations of these charges are shown in Table IV. The total charges were taken from Table III, redistributing the methyl charge of the ionic species over the C, O₂, and H positions. The embedded charges will be discussed below. Table V shows the results of three calculations and the corresponding data for the first and second ionization constants of the diacid, and the difference of the two. In the first calculation, the first and second ionization values, ΔpK_1 and ΔpK_2 , were in poor agreement with the data, but the difference, ΔpK_{2-1} , was in good agreement. In the second calculation, the charge at the

Table V. ΔpK Calculations for the Carboxyl Substituent

Calculation	ΔpK_1	ΔpK_2	ΔpK_{2-1}
1. Total charges ^a	-0.13	0.68	0.81
2. O ₂ ⁻ charges shifted	-0.23	0.49	0.72
3. Embedded charges ^a	-0.38	0.31	0.67
Experimental data ^b	-0.47	0.30	0.77

^a See Table IV. ^b Reference 12.

O₂ midpoint was shifted 0.3 Å toward the H position to represent a lone-pair effect. The agreement of ΔpK_1 and ΔpK_2 was improved somewhat, and the difference stayed relatively constant. Since the difference represents the net charge effect, these results suggested that the neutral or dipolar charges should be corrected for embedding, but not the net or ionic charges. (This situation is discussed in the Theoretical section above.)

In the third calculation, the COOH charges were multiplied by $\epsilon = 1.6$ as a crude way of estimating the embedded charges (see Table IV). The net ionic charges of the difference, $\Delta(\text{COO}^- - \text{COOH})$, were left the same, and the corrected total charges for COO⁻ were deduced by adding the corrected COOH charges to the net charges. The 0.3 Å shift introduced in the second calculation was retained. The results indicate considerably improved agreement for ΔpK_1 and ΔpK_2 , while ΔpK_{2-1} remains close to the data. It is then reasonable to conclude that the embedding effect is also important in this mixed charge-dipole case. Further calculations on the carboxyl substituent should probably be in three dimensions, since the axial representation must cause some error in the calculation of the oxygen atom effects.

Discussion

The preceding calculations suggest that the generalized Kirkwood–Westheimer electrostatic model is capable of explaining substituent effect data in the bicyclooctane series with realistic shapes, dielectric constants, and charge distributions. Now that the mathematical limitations of the earlier analytic approach can be circumvented, attention may be directed to the development of a more accurate molecular description. For this purpose, it is desirable to extend the calculations to the full three-dimensional case. The carboxyl problem can then be more realistically analyzed, and other systems, such as substituted benzoic acids, can be explored. In the latter case, of course, an electrostatic theory could explain only part of the observed effects.

The calculations have demonstrated the importance of the solvent layer immediately outside the solute molecule. It would be of interest to develop and test a more theoretically based

continuously variable dielectric distribution for this region. The initial inability to fit the ΔpK data of the Br substituent led to the realization that the theory required embedded rather than vacuum dipole moments. The present analysis of this situation was limited to the case of a point dipole at the center of a uniformly polarizable molecule. However, the problem of obtaining more precise characterizations of the embedded moments of a series of vapor phase molecules would be of interest both for itself and for advancing the substituent effect calculations, which are sensitive not only to the magnitude of the moment, but also to the manner in which the constituent charges are distributed. The finite element approach, coupled with quantum mechanical calculations, should also lead to new insights in this area.

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References and Notes

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