Substituent Bulk Effects on Solvation[1]

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Prolate ellipsoidal cavity models appear able, within the context of Kirkwood–Westheimer solvation theory, to rationalize the lack of bulk effects observed on the acidities of p-$CH_2NR_3^+$-substituted benzoic acids. The crucial feature appears to be whether increased bulk can and does substantially increase the distances of the interacting sites from the solvent in all directions.

A major criticism leveled at the Kirkwood–Westheimer (KW) continuum solvent theory for reactivities concerns its presumed inability to explain why only relatively small and perhaps even inverse (from the intuitively expected) effects are observed upon substantial increase of bulk around substituent sites. After all, it may be argued, putting more low-dielectric material between the substituent pole site and cavity wall should increase the relative depth of this site, the average depth of both interacting sites within the cavity, and hence substantially decrease the effective dielectric experienced in their interaction. This, in turn, should result in a significantly increased substituent effect, all else being equal (which is, of course, assumed).

The best evidence that such bulk effects in nature are very small is due to Wepster and his group[2] from data mainly on p-$CH_2NR_3^+$-substituted benzoic acid ionizations. Supporting evidence has been obtained by Edward et al.[3] from various amino acid dissociations. Both groups stress the apparent inconsistencies of their data with the theory.[4]

It is the purpose of this short report to examine whether such inconsistencies do in fact exist, and if so what features of the theory are responsible. Recent results obtained in the course of successive refinements of KW theory[5] suggest that at least two assumptions bearing on how such polar sites as NR_3^+ would be located within the cavity, and how increases in the size of the group R might be reflected in cavity shape as well as size changes, may be critical in theoretical representation of bulk effects.

In KW theory, the substituent effect upon reactivity is ultimately related to the electrostatic work difference arising from the differential interaction between the substituent and reaction-center sites.[6] That is,

$$\log K/K_0 \equiv \Delta = \left[\frac{(-e)^2}{2.303RT}\right]\frac{1}{\rho\epsilon_{\text{eff}}} = 243/\rho\epsilon_{\text{eff}}$$

when both the reaction and substituent sites are (positive) poles separated at a distance ρ, and, for the latter relation, where the reactions (substituted and standard in the same environment) take place at 298 K and ρ is in angstroms.

For strictly rigid or averageable conformation systems where the interaction distances are known, the problem of evaluating solvent influence on substituent effects in the context of KW theory becomes one entirely of estimation of the effective dielectric constant, ϵ_{eff}, mediating the interaction. Since such structural averageability plausibly pertains for all p-$CH_2NR_3^+$-substituted benzoic acids and their conjugate bases upon ionization, this system seemed most appropriate for detailed evaluation of the merits of the theory.

Wepster's value of 8 Å for ρ for these species can be readily adopted.[2,7] Some other details of the KW-type model used, from which the expectations of substantial bulk effects arise, are, however, less easily rationalized. One is whether assumption of spherical cavities for obviously elongated molecules (which become increasingly elongated with increase in the size of R) is justified. Another concerns specification of imbedding distances of the substituent and reaction-center sites; e.g., are 1 and 1.5 Å distances physically reasonable respectively for an acid proton to hydroxylic solvent H bond and for the positive charge (presumably mainly on nitrogen) through the trimethyl pyramid to nonbonding solvent interaction?

The answer to the first, regarding cavity shape, is probably not (spherical), to the second, almost certainly not, as these distances appear much too short for any physical system. That these are very closely connected matters has been recently demonstrated,[8] wherein experimental ΔpK_a values for dicarboxylic and otherwise substituted acids could be satisfactorily reproduced by employing either ellipsoidal cavities with realistic substrate to cavity-wall distances *or* spherical cavities with such shorter distances as were discussed above.[9] In light of these results, and more recent developments where individual (nonaveraged) cavity site location forms of KW theory especially pertinent to the present systems have been made available, quantitative reassessment of the bulk effect phenomenon appeared in order and was carried out.

Figure 1 illustrates schematically the location of p-$CH_2N(Me)_3^+$-substituted benzoic acid within the spherical cavity as specified in ref 2 and within an ellipsoidal cavity where d_H is 1.6 Å, d_+, 4.2 Å, and b, the minor axis half-

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[2] Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *J. Org. Chem.* **1978**, *43*, 4720, particularly section 10.(2.a.).

[3] Edward, J. T.; Farrell, P. G.; Hallé, J. C.; Kirchnerova, J.; Schaal, R.; Terrier, F. J. *J. Org. Chem.* **1979**, *44*, 615. These data, obtained for entirely independent purposes, are perhaps more tenuous for present comparisons, on the one hand, because of the flexibility of the framework separating the interacting sites. They are, on the other hand, better because of the closer proximity of these sites.

[4] See as well: Hoefnagel, A. J.; Wepster, B. M. *J. Org. Chem.* **1982**, *47*, 2318.

[5] For the most recent in a series of reports on refinements of continuum solvent theory, and in particular KW theory, see: Ehrenson, S. *J. Am. Chem. Soc.* **1982**, *104*, 4793.

[6] Kirkwood, J. G.; Westheimer, F. H. *J. Chem. Phys.* **1938**, *6*, 506. Westheimer, F. H.; Kirkwood, J. G. *Ibid.* **1938**, *6*, 513.

[7] This value is apparently obtained upon free rotational averaging about the ring-substituent carbon bond and the otherwise usual assumptions about locations of the acid proton and substituent charge entirely on nitrogen. The vector ρ, it is usefully recognized, becomes a rotational symmetry axis for all species under these and the further assumptions of free rotation about the C–N bond.

[8] Ehrenson, S. *J. Am. Chem. Soc.* **1976**, *98*, 7510.

[9] Many of the criticisms leveled at KW theory, which employs (often unreasonable) imbedding distances as adjustable parameters,[10] should be satisfied upon their physical specification.

[10] Cf.: Tanford, C. *J. Am. Chem. Soc.* **1957**, *79*, 5348. Siegel, S.; Komarmy J. M. *Ibid.* **1960**, *82*, 2547.

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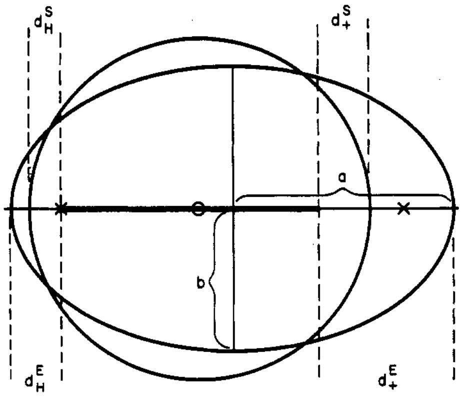

Figure 1. Illustration of how rotationally averaged p-$CH_2N(CH_3)_3^+$-benzoic acid (heavy line on major axis) occupies spherical cavity, dimensions as in ref 2, and prolate ellipsoidal cavity with imbedding distances d_H^E, d_+^E as in text. The center of the spherical cavity is O, the ellipsoidal foci are X; only fortuitously does the ionizable proton position lie at the left focus.

length of the ellipsoid is 4.4 Å. The d_H and d_+ distances correspond, respectively, to a normal carboxylic acid proton–hydroxylic solvent H-bond distance, and an ammonium N to average methyl hydrogen distance projected onto the ellipse major axis, plus 2.6 Å for a representative van der Waals distance to the cavity edge. The value of b is obtained in a similar manner from van der Waals repulsion distances for the aromatic ring hydrogens to solvent.[8]

Results and Discussion

It is apparent from examination of Table I that spherical-cavity KW theory predicts sizeable bulk effects, i.e., observable increases in ΔpK_a values for p-$CH_2NR_3^+$-substituted benzoic acid ionization with increased size of R, for any reasonable combination of cavity structure factors, in direct opposition to the experimental results in all solvents examined (H_2O to 75% ethanol), where no such effects can be detected. The predictions are in harmony with those of ref 2, but quantitatively not nearly (only about half) as large, for the reasons discussed in footnote c of Table I. Nevertheless, the differences remain sufficiently large to confirm earlier conclusions that significant disagreement exists between spherical-cavity-theory predictions and experimental measurements of bulk effects on reactivity (acidity). Moreover, if the most physically reasonable structure (imbedding) factors are used, this theory variant also predicts too large a substituent effect (of p-$CH_2NMe_3^+$ relative to p-CH_3 in all solvents), and too small solvent effects (e.g., 75% ethanol relative to H_2O).

Similar calculations carried out for ellipsoidal cavity models[11] evidence a number of differences, many of which are apparent from examination of Table II. The first and most important in the present context is that for any choices of parameters to represent changes in bulk of the substituent, in any of the solvents, *if there is little or no change in the lateral dimension of cavity* (as expressed in terms of b, the minor ellipsoid half-axis), *there is no bulk effect upon ΔpK_a predicted.* In fact, for constant b, the computed variations are even smaller than those observed experimentally. It should be noted that the range in variation of d_+ here as well as in the lower part of Table I correspond to the largest radial bulk effect assumed in ref 2. Figure 2 illustrates how bulk changes of this magnitude may be reflected in terms of cavity geometry.

Table I. ΔpK_a Values, Experimental and KW Spherical Cavity, for p-$CH_2NR_3^+$-Substituted Benzoic Acid Ionizations[a]

	R =		
solvent[b]	Me	Et	t-Bu
H_2O (78.5)	0.84	0.78	0.80
10%E (73.9)	0.91	0.87	0.85
50%E (53.4)	1.32	1.32	1.30
75%E (38.6)	1.52	1.53	1.57
	$d_H = 1, d_+ =$		
ϵ_s/ϵ_i	1.5	2.5	3.0
39[c]	0.81 (0.84)	1.08 (1.32)	1.19 (1.65)
20	1.09	1.37	1.49
	$d_H = 1.6, d_+ =$		
	4.2	5.2	6.9
39	1.96	2.18	2.49
20	2.24	2.47	2.79
	$d_+ =$		
	3.2	4.2	5.9
39	1.68	1.96	2.31

[a] Relative to p-toluic acid at 25 °C; all distances in angstroms. Structural parameters d as defined in Figure 1 and text, ρ = 8 Å. ϵ_i here and henceforth is assumed to be 2. [b] All experimental values from ref 2. E, ethanol, percentage by volume. Values in parentheses are ϵ_s values from: Åkerlöf, G. *J. Am. Chem. Soc.* **1932**, *54*, 4125. [c] The ΔpK_a values in this row vary increasingly with bulk from those reported in ref 2 (values in parentheses directly below) because individual-site formulae are used here. See eq 6 of ref 5 and note, for the factor preceding the sum term, that $r_{12}/b \neq 2x^{1/2}$ unless $r_1 = r_2$, an equality that is implied for this factor in the original KW theory derivation.

Table II. ΔpK_a Values from Ellipsoidal Cavity Models for p-$CH_2NR_3^+$-Substituted Benzoic Acid Ionizations[a, b]

	$d_+ =$		
ϵ_s/ϵ_i	4.2	5.2	6.9
39	0.89 (1.05)	0.88–1.03	0.85–1.25 (1.07–1.50)
27	1.03	1.03–1.17	1.00–1.39
20	1.19 (1.46)	1.19–1.33	1.16–1.56 (1.54–1.96)
	$d_+ =$		
	3.2		5.9
39	0.87 (1.00)		0.87–1.30 (1.07–1.52)
20	1.16 (1.39)		1.18–1.60 (1.52–1.97)

[a] Footnote a of Table I pertains. Where two entries appear hyphenated, the first is where b, the minor half-axis, is assumed invariant with change in bulk at 4.4 Å, the second is where it is varied proportionately to a (the major half-axis length, relative to R = Me, the first column model). The H-bond distance d_H = 1.6 Å is used in all cases. [b] Values given in parentheses are for the modified dielectric function labeled G in ref 5, presumed to incorporate mild saturation and electrostriction effects on solvent permittivity at and near the cavity boundary.

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(11) The ϵ_{eff} values are obtained from

$$\epsilon_i/\epsilon_{eff} = \left\{1 + (\xi_1 + \xi_2)\left[\frac{\epsilon_i}{\epsilon_s} - 1\right]\sum_{n=0}^{\infty}\frac{P_n(\xi_1)P_n(\xi_2)U_n}{1 - (\epsilon_i/\epsilon_s)C_n}\right\}$$

which is a generalization of eq 7 of ref 8, when the ionizable proton (site 1) and the substituent charge (site 2) are not symmetrically located on the ellipse major axis. All other symbols retain their original meaning (symbol ϵ replaces D). Further details of the derivation and use of such equations will appear elsewhere.

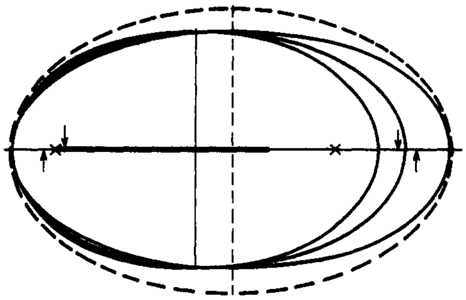

Figure 2. Illustration of how the ellipsoidal cavity changes with change in d_+ from 4.2 to 5.2 to 6.9 Å (see Table II) and no change in the lateral dimension (solid figures). Broken line is for proportional change in *a* and *b*. Movement of the focuses (originally X) for the 2.7 Å change in d_+ is indicated by arrows, pointing up for the solid, down for the broken-line figure.

For the more unlikely extreme where the lateral (*b*) and directly incremented (*a*) cavity dimensions are assumed to expand proportionally with bulk, effects approaching the size of those for the small spherical cavities are noted. This correspondence does not seem unreasonable from reconsideration of average molecule to cavity boundary distances in Figure 1, even though the ellipsoids of concern are rather eccentric (*e* from 0.77–0.84).

Much more likely upon end-group substitutions is that *b* expands only fractionally compared to *a* with bulk, i.e., $a\Delta b/b\Delta a = f$, and that *f* is $^1/_3$–$^1/_2$. In such a case, since it may be shown that ΔpK_a varies essentially linearly with this fraction, bulk effects of only 0.1–0.15 ΔpK_a unit are to be expected in all solvents, certainly now of a size small enough to be obscured by neglected effects and experimental uncertainties.

Further examination of Table II reveals that whereas a reasonable substituent effect for p-$CH_2NMe_3^+$ relative to p-CH_3 can only be obtained in the spherical model calculations by employing very shallow imbedding distances, here this effect is satisfactorily reproduced by employing the physically based distances discussed above. Obviously this effect is rather insensitive to d_+ variation, as the bulk effect results imply.[12]

Only in the matter of solvent-effect range does this body of results appear at all at variance with experiment. Here the change in ΔpK_a accompanying change from H_2O to 75% ethanol (ϵ_s/ϵ_i from 39 to 20) amounts to ~25–35% of the H_2O value, where the comparable experimental variation is ~95%. These predicted results are similar to those obtained from the spherical cavity models. It may be significant that results obtained upon reduced ionizable-proton to cavity-wall distance specification and with solvent boundary smoothing (~45%, see respectively footnote 12 and parenthesized entries of Table II) are in somewhat better agreement, but it seems inappropriate to attempt to refine this argument further at this time.

In short, it appears that bulk effects are only to be expected if interacting site distances to solvent are increased in all dimensions, i.e., are truly buried deeper within their cavities. Movement inward (relatively) in a spherical cavity, at least along a diameter, implies such burial, probably inappropriately for the present substrates. Structural considerations and various reactivity cross-comparisons suggest ellipsoidal cavities provide better physical representations of such acids in continuum solvents.[13] These generalizations, it should be recognized, may not hold in the event of strong specific interactions, which may have alternative directional characteristics, or if the shape of cavities become grossly distorted from ellipsoidal.

Registry No. $HO_2CC_6H_4$-p-$CH_2NEt_3^+$, 85371-51-3; $HO_2CC_6H_4$-p-$CH_2NMe_3^+$, 85371-50-2; $HO_2CC_6H_4$-p-$CH_2N(Bu$-$t)_3^+$, 85371-52-4.

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(12) Somewhat greater sensitivity to the imbedding distance of the ionizable proton is noted, decreasing to 0.72 and 1.03, respectively, for ϵ_s/ϵ_i of 39 and 20, when $d_H = 1$ Å and $d_+ = 3.2$ or 5.9 Å, (again with *b* unchanged).

(13) It may be useful, as a final detail, to dissect on a mathematical level how constancy of ΔpK_a, through constancy of ϵ_{eff}, may be maintained upon bulk variation. Increased bulk strongly decreases ξ_2 ($=\rho_+/0.5R$) by severely shortening ρ_+ while lengthening R (see arrows of Figure 2 and note that $\rho = \rho_+ + \rho_H$, $\rho_i = a - d_i$). ξ_1 ($=\rho_H/0.5R$), on the other hand, only changes slightly (decreases for *b* unchanged or increases for proportionally varied *b*). The overall effect of ξ decreasing therefore should be one of decreasing ϵ_{eff} in harmony with intuition (see footnote 11 and, e.g., Figures 1–4 of ref 8). Where *b* is unchanged or varies slowly with increase in bulk, however, λ is also found to decrease (e.g., from 1.30 to 1.18 for d_+ increased from 4.2 to 6.9 with $b = 4.4$). Decreasing λ is accompanied by increasing ϵ_{eff} (sharply in this region, as the figures of ref 8 again reveal). Apparently, the two effects are almost completely compensatory for the geometries of interest. This suggests (at least) two physically realizable tests of the theory. In the first, invariant frameworks characterized by larger λ values (more spherical, e.g., 2,3,5,6-substituted p-$CH_2NR_3^+$ benzoic acids) could be similarly examined to see if greater (observable) bulk effects pertain. Simultaneous increases in lateral and terminal bulk should provide even larger differences.

Inhibition of Ester Hydrolysis by a Lipid Vesicle Membrane

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The second-order rate constants for the imidazole- or hydroxide-mediated hydrolysis of [3-nitro-4-(palmitoyloxy)phenyl]trimethylammonium iodide (1), [11-(4-nitrocarbophenoxy)undecyl]trimethylammonium bromide (2), and [5-nitro-2-(palmitoyloxy)benzyl]trimethylammonium halide (3) were obtained in the absence and presence of phospholipid vesicles. The rate data were obtained under conditions where only bound ester contributed to the kinetics. In general, small retardations of the hydrolysis rates were effected by binding of the substrates to lipid bilayers with choline phosphate headgroups. The imidazole rates appear to be more sensitive to the depth within the bilayer of the reaction center. The relative rates also can be interpreted in terms of an intramolecular electrostatic acceleration of the hydroxide rate for 3 in aqueous solution, which is inhibited upon binding of this amphiphilic ester to the lipid bilayer membrane.

Lipid bimolecular layers are the backbone of biological membranes[2] and, as such, must organize a wide variety of biological reactions. Vesicles, formed by sonication of aqueous phospholipid dispersions, provide a convenient