Acidities of Cis-β-Substituted α,β-Unsaturated Carboxylic Acids. A View of the Ortho Effect[1]

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Abstract: A series of acids, 2-alkylcyclohexene-, 2-alkylcyclohexa-1,4-diene-1-, 3-alkylbicyclo[2.2.1]hept-2-ene-2-, and 3-alkylbicyclo[2.2.1]hepta-2,5-diene-2-carboxylic acids and *o*-alkylbenzoic acids, where the alkyl groups are methyl, ethyl, isopropyl, and *tert*-butyl, were prepared and their pK_a's in aqueous methanol were determined. The effect of structure and substituents on acidity is discussed; it is shown that *cis*-β-alkyl substituents in α,β-unsaturated carboxylic acids may produce either an increase *or* a decrease in acidity relative to the unsubstituted acids. An analysis of the factors producing these effects is outlined; the ortho effect is viewed simply as a special case of the overall pattern of structure–acidity relationships (including polar, steric, and other proximal factors) in cis-β-substituted α,β-unsaturated acids.

The effect of substituents on reactivity is a long-standing problem. A favorite method of studying the problem is the examination of structure–acidity relationships in carboxylic acids. Considerable progress and activity have occurred in correlating the effects of substituents distantly located relative to the reaction site, the carboxyl group, *i.e.*, the transmission of electronic effects.[2] On the other hand, very little progress or activity has been reported for systems in which the substituents are in close proximity to the carboxyl group. A number of factors in addition to the electronic one have been suggested as comprising what may be called the proximity effect. Unfortunately, these various factors are known only in qualitative terms so that at present, unlike the transmission of electronic effects from distant locations, there is no way of weighting the various factors and thereby obtaining a reliable composite result. Consequently, it is not possible to make reliable predictions of acidity for such systems, but conversely it is possible to explain any acidity influenced by a proximity effect by arbitrarily weighting the various factors comprising that effect.

One feature which may be a component of the proximity effect in some cases is intramolecular hydrogen bonding. For the case of 1,2-dicarboxylic acids, some progress in the unraveling of this factor has been reported.[3] Another factor in some α,β-unsaturated systems is "steric inhibition of resonance," and here also some progress has been reported.[4] The present work is an extension and combination of these two studies.

Experimental Section

Materials. The acids prepared in this work were obtained by Diels–Alder reactions using acetylenic acids;[5] physical constants of all intermediates in the Carpino procedure agreed with those previously reported. The isopropyl sequence has not been reported previously; 3-isopropyl-2-pyrazolin-5-one (73% yield) had mp 194–195.5° (recrystallized from 95% ethanol) (*Anal.* Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.18; H, 7.89; N, 22.44) and 4,4-dibromo-3-isopropyl-2-pyrazolin-5-one (99% yield) had mp 107.5–108° (*Anal.* Calcd for $C_6H_8Br_2N_2O$: C, 25.38; H, 2.84; Br, 56.28; N, 9.87. Found: C, 25.45; H, 2.94; Br, 55.07; N, 9.90). The alkylpropiolic acids were found to be deliquescent, and therefore all subsequent manipulations of these acids were conducted in a dry nitrogen atmosphere. 3-Alkylbicyclo[2.2.1]heptadiene-2-carboxylic acids were prepared by the procedure described by Jones, *et al.*,[6] for the preparation of 3-methylbicyclo[2.2.1]heptadiene-2-carboxylic acid. 2-Alkylcyclohexa-1,4-diene-1-carboxylic acids were prepared by a procedure patterned after that described by Jones, *et al.*,[6] for 2-methylcyclohexa-1,4-diene-1-carboxylic acid. 2-Alkylcyclohex-1-ene-1-carboxylic acids and 3-alkylbicyclo[2.2.1]hept-2-ene-2-carboxylic acids were prepared by selective half-reduction of the corresponding diene acids. The bicyclic acids were reduced using 5% palladium on charcoal and the cyclic acids were reduced with 5% platinum on charcoal, in ethyl acetate using a Brown[2] hydrogenator. Benzoic acid and *o*-toluic acid were obtained from Aldrich Chemical Co., and *o*-ethylbenzoic acid was obtained from Frinton Laboratories. *o*-Isopropylbenzoic acid and *o*-*tert*-butylbenzoic acid were prepared by a method patterned after several syntheses described by Reed, *et al.*,[7] using 2-pyrone.[8] A sample of bicyclo[2.2.1]hept-2-ene-2-carboxylic acid was kindly furnished by Dr. R. A. Finnegan.[9] Cyclohexene-1-carboxylic acid was obtained from Frinton Laboratories. Bicyclo[2.2.1]heptadiene-2-carboxylic acid was prepared by the method of Alder.[10] Cyclohexa-1,4-diene-1-carboxylic acid was prepared by sealing propynoic acid (4.0 g, 0.0714 mol), 1,3-butadiene (4.0 g, 0.0779 mol), and benzene (3 ml) in a Parr reaction bomb (No. 4711) and heating the system at 60–70° for 5 hr. A summary of the properties and method of purification for the acids used in this study is given in Table I.[11]

Titrations. A 50% by weight methanol–water mixture used in the titrations was prepared from carbon dioxide free distilled water and spectroquality methanol (Matheson Coleman and Bell). Sodium hydroxide in 50% by weight methanol–water titrant was prepared by diluting commercially prepared 0.1 *N* aqueous sodium hydroxide solution (Fischer Scientific Co., certified) with spectroquality methanol. The titrations were carried out using a Radiometer TTT 1C titrator, SBR 2C titragraph, and ABU 12 autoburet. The electrodes used were a Radiometer Type k 4312 calomel electrode and a Type G 202 B glass electrode. A Radiometer Type TT A 31 titration assembly was used in which a jacketed titration vessel attached to a thermoregulator and heat bank allowed the temperature to be held at 25.0 ± 0.1°. The pH meter was standardized against aqueous 0.05 *m* potassium hydrogen phthalate

(1) Based in part on the Ph.D. Thesis of E. E. Riecke, University of Missouri—Kansas City, 1971.
(2) A rather concise discussion is presented by C. L. Liotta and coworkers in *J. Amer. Chem. Soc.*, **94**, 4891 (1972); this discussion includes reference to many of the important papers in this area.
(3) L. L. McCoy, *J. Amer. Chem. Soc.*, **89**, 1673 (1967).
(4) E. A. McCoy and L. L. McCoy, *J. Org. Chem.*, **33**, 2354 (1968).
(5) L. A. Carpino, P. H. Terry, and S. D. Thatte, *J. Org. Chem.*, **31**, 2867 (1966).
(6) E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 4073 (1956).
(7) J. A. Reed, C. L. Schilling, Jr., R. F. Tarvin, T. H. Rettig, and J. K. Stille, *J. Org. Chem.*, **34**, 2188 (1969).
(8) H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. A. Sherwin, *J. Amer. Chem. Soc.*, **91**, 2330 (1969).
(9) R. A. Finnegan and R. S. McNees, *J. Org. Chem.*, **29**, 3234 (1964).
(10) K. Alder, G. Stein, S. Schneider, M. Leibmann, E. Roland, and G. Schulze, *Justus Liebigs Ann. Chem.*, **525**, 183 (1936).
(11) The ir, uv, and nmr spectra will be reported in a later paper.

Table I. Properties and Methods of Purification of β-Alkyl α,β-Unsaturated Acids[a]

Alkyl group	Mp, °C	Purification,[b] yield
	3-Alkylbicyclo[2.2.1]heptadiene-2-carboxylic Acids	
H	87 (93–94)[c]	A, 16
CH_3	90–91.5 (92)[d]	B, 25
C_2H_5	96–97.5	B, 28
i-C_3H_7	125–126.5	B, 46
t-C_4H_9	110–112	B, 30
	2-Alkylcyclohexa-1,4-diene-1-carboxylic Acids	
H	120–121 (122)[d]	A, 15
CH_3	126–128 (132)[d]	B, 16
C_2H_5	90–91	B, 45
i-C_3H_7	80–81.5	B, 32
t-C_4H_9		C[e]
	3-Alkylbicyclo[2.2.1]hept-2-ene-2-carboxylic Acids	
H	21.5–22.5 (21.5–22.5)[f]	D
CH_3	41–44 (41–44)[d]	C
C_2H_5		C
i-C_3H_7	122–124	E
t-C_4H_9	125–126.5	E
	2-Alkylcyclohex-1-ene-1-carboxylic Acid	
H	Bp 66° (0.1 mm) (131–132)[g]	F
CH_3	85–87 (87)[d]	B
C_2H_5	70.5–72	B
i-C_3H_7	103–104	B, C
	o-Alkylbenzoic Acids	
H	122.39	
CH_3	102–103.5 (107–108)[h]	A
C_2H_5	61.5–64.5 (65.6)[i]	A
i-C_3H_7	62.4–62.8 (59.4–59.9)[i]	B, 40
t-C_4H_9	70.2–70.5 (68.5)[i]	C

[a] Satisfactory analytical data were obtained. [b] Purification methods: A, recrystallized from water; B, recrystallized from methanol–water; C, gas–liquid chromatography on a small preparative scale; D, sublimation; E, sublimation followed by low-temperature recrystallization from pentane; F, distillation. [c] Reference 10. [d] Reference 6. [e] The crude product showed three peaks by gas chromatography; the first substance was identified as *o-tert*-butylbenzoic acid, the third was unidentified, and the second was used as the desired product. The analysis, neutralization equivalent, and ultraviolet spectra are consistent with the structure, but the nmr spectra leave the question of structural identity in doubt. [f] Reference 9. [g] R. C. Weast, Ed., "Handbook of Chemistry and Physics," 47th ed, The Chemical Rubber Co., Cleveland, Ohio, 1966, p C-274. [h] Footnote *g*, p C-194. [i] J. F. J. Dippy, S. C. R. Hughes, and J. W. Laxton, *J. Chem. Soc.*, 1470 (1954).

(pH 4.008 at 25°) and 0.008695 *m* potassium dihydrogen phosphate–0.03043 *m* disodium hydrogen phosphate (pH 7.413 at 25°).[12] Where titrations were to be carried out in methanol–water media, the electrodes were conditioned 1 hr in stock mixed solvent before titration.

Results

The data were treated by the method of Bates.[13] The titration technique and calculation method[14] were tested by titrating acetic acid (J. T. Baker Chemical Co., Baker Analyzed Reagent, 100.0% assay; Fischer Scientific Co., reagent ACS, 99.7% minimum) and gave agreement (within 0.01 pK_a unit) with the published pK_a value of 5.66.[15] The values for the acids of this study are shown in Table II.

(12) R. G. Bates, "Determination of pH," Wiley, New York, N. Y., 1964, Chapter 5.

(13) (a) Reference 12, Chapters 7 and 8; (b) K. C. Ong, R. A. Robinson, and R. G. Bates, *Anal. Chem.*, **36**, 1971 (1964).

(14) Calculations were carried out on a Wang 380 calculater system (Model 3802k keyboard and Model 362 E electronic package) using a program contained on a tape cartridge; see thesis of E. E. R. for details.

(15) M. Paabo, R. A. Robinson, and R. G. Bates, *J. Amer. Chem. Soc.*, 87, 415 (1965).

Discussion

The systems studied here are based on the same plan as that used in studying intramolecular hydrogen bonding in dicarboxylic acids.[3] By constructing cis-β-substituted acrylic acids within a rigid framework, it is possible, by varying the framework, to vary the distance between the β substituent and the carboxyl group in a controlled, well-defined way. The frameworks used are cyclohexene, 1,4-cyclohexadiene, benzene, bicyclo[2.2.1]heptadiene-2,5, and bicyclo[2.2.1]heptene-2. These systems were chosen for this initial study because they corresponded in spacing between substituent and carboxyl function to approximately the same range used in the diacid study, because they were relatively simple to make from a common set of precursors, the substituted acetylenic acids, through various Diels–Alder reactions, and because they included the ortho-substituted benzoic acids and therefore involved the well-known ortho effect.

It was intended that the acidities be determined in water, but for solubility reasons, a mixed organic–aqueous solvent was chosen. The choice of methanol–water was based on the possibility of obtaining meaningful thermodynamic values in this system;[15] for the present study, primarily the comparison of relative acidities, such thermodynamic values are not required, but it is believed that they will be of considerable value in future studies.

In discussing the acidities obtained, it is useful to have in mind those factors which might be components of the proximity effect and any other factors which might contribute to the relative acidities of the various series.

(1) The Electronic Factor. Relative to heteroatom functional groups, alkyl substituents normally produce only small electronic effects. Attached to saturated systems it has been suggested that no effect relative to hydrogen is produced while, when attached to unsaturated systems, the small effect produced arises from differences in hybridization of the alkyl carbon and the unsaturated carbon.[16] These differences result in a shift of electron density toward the unsaturated carbon. The effect of the resulting dipole, whether transmitted inductively or by a field effect, in the present systems might be expected to lead to a reduction in acidity; the angular dependence of the field effect as determined by the small changes in geometry of the acids should be negligible.[17]

(2) Steric Inhibition of Solvation. With increasing size of the β-alkyl substituent, an increasing exclusion of solvent should be noted. This should affect the stability of the anion to a greater extent than the stability of the undissociated acid, and this should lead to a decrease in acidity also.[18]

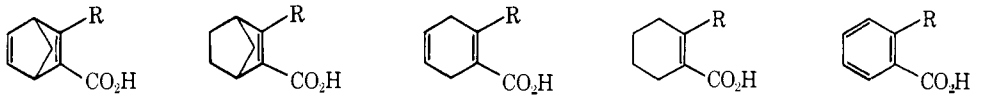
(3) Steric Inhibition of Resonance. This factor, a twisting of the carboxyl group out of the plane of the

(16) Two good and concise discussions of this feature (and appropriate references) are given by Stock: (a) L. M. Stock and H. D. Holtz, *J. Amer. Chem. Soc.*, **86**, 5188 (1964); (b) F. W. Baker, R. C. Parish, and L. M. Stock, *ibid.*, **89**, 5677 (1967).

(17) (a) C. L. Liotta, W. F. Fisher, and C. L. Harris, *Chem. Commun.*, 1312 (1971); (b) C. L. Liotta, W. F. Fisher, E. L. Slighton, and C. L. Harris, *J. Amer. Chem. Soc.*, **94**, 2129 (1972); (c) R. Golden and L. M. Stock, *ibid.*, **94**, 3080 (1972).

(18) (a) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 9; (b) A. G. Cook and G. W. Mason, *J. Org. Chem.*, 37, 3342 (1972).

Table II. pK_a Values[a] of β-Substituted α,β-Unsaturated Acids



I II III IV V

System	β substituent H	CH_3	C_2H_5	i-C_3H_7	t-C_4H_9
I	5.70	6.44*	6.50*	6.55*	5.71*
II	5.84	6.57	6.70	6.76	6.00
III	5.88	5.72	5.75	5.55	5.36
IV	6.12	5.96	5.94	5.80	
V	5.38	5.32	5.30	5.15	4.97

[a] All values are ±0.01 except those marked with an asterisk, which are ±0.02; values were determined in 50% water–methanol by weight at 25.0 ± 0.1°.

carbon–carbon double bond, the degree of twisting increasing with increasing size of the cis β substituent, normally leads to increased acidity.[4,19] Other effects such as intramolecular hydrogen bonding and a "proximity effect"[20] clearly do not apply to the systems studied here because of their alkyl substituents and their rigid frameworks. It should be noted that of the effects cited as contributing to the acidity, two result in decreases and one in increases. In addition, relative acidities between series may be affected by the "framework." By comparing differences between the substituted compounds and the parent systems, the "framework" factors should largely cancel and leave the relative effects due to substituents.

Application of these factors to the results listed in Table II and shown graphically in Figure 1 is difficult. There is no quantitative way of weighing the separate effects, combining them, and thereby obtaining a net effect. However, it is possible to find various patterns of changes.

Directly from Figure 1 it can be observed that the ortho effect is present in the aromatic acids; *i.e.*, the alkyl groups all produce an increase in acidity and the acidity increases with increasing size of the alkyl group. These changes essentially are paralleled by the cyclohexene and 1,4-cyclohexadiene series. Quite different changes are noted in the two bicyclic series. Here, decreases in acidity followed by an increase are noted for substituents of increasing size. Although the pK_a's of the cis-β-substituted acrylic acids were not determined in aqueous methanol, the values determined in aqueous solution[4] (Table III) are intermediate between these two extremes. If the various rigid skeletal systems are arranged in the order previously reported for the dicarboxylic acids, *i.e.*, increasing distance between β substituent and carboxyl function, and skeletal effects are eliminated or at least minimized by subtracting the parent pK_a value from that for the substituted compound, then a definite pattern of substituent effects emerges. For all of the alkyl substituents, the acidity increasing effect of the substituent decreases with increasing spacing; for methyl, ethyl, and isopropyl groups the result is to change from acid strengthening to acid weakening, while for *tert*-butyl the acid strengthening decreases essentially to zero (Figure 2). We predict that for the similar cyclobutene (and cyclopropene) systems all of the β-alkyl-substituted acids, including the *tert*-butyl case, would show decreased acidity relative to the unsubstituted acid.

These results might be likened to a three-dimensional contour map in which one horizontal dimension is the

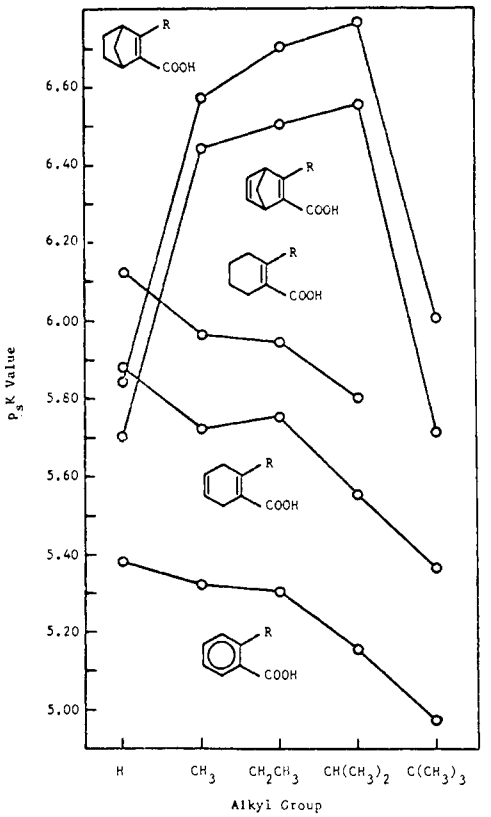


Figure 1. Effect of the change in the alkyl group on dissociation constants in 50% by weight methanol–water solvent at 25°.

Table III. pK_a of Some β-Substituted Acrylic Acids in Water at 25°[a]

Acid	pK_a Trans	Cis
$H_2C{=}CHCO_2H$	4.25	
$CH_3CH{=}CHCO_2H$	4.74	4.70
$CH_3CH_2CH{=}CHCO_2H$	4.74	4.70
$(CH_3)_2CHCH{=}CHCO_2H$	4.75	4.63
$(CH_3)_3CCH{=}CHCO_2H$	4.88	4.12

[a] Reference 4.

(19) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 744.
(20) N. Purdie and M. B. Tomson, *J. Amer. Chem. Soc.*, **95**, 48 (1973).

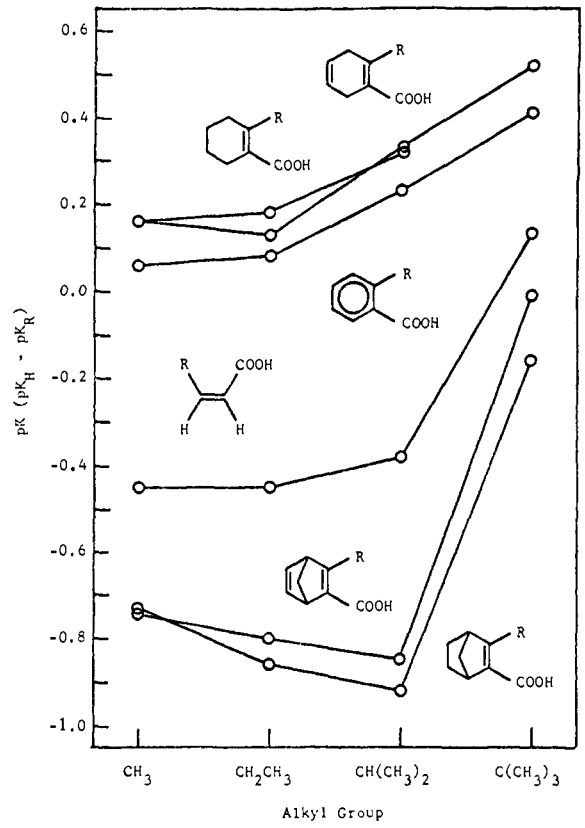


Figure 2. Effect of the change in the alkyl group on dissociation constants with respect to the parent acids in 50% by weight methanol–water solvent at 25°.

size of the substituent, another dimension is the space between the substituent and the reaction site (the carboxyl function), and the third (vertical) dimension is the acidity. This third dimension is a composite of all the acidity-influencing factors mentioned previously and possibly others as yet unknown. The question then arises as to whether or not we can analyze and distinguish the strata which together make up this composite. Examination leads to the following.

(1) The Electronic Effect. This electrostatic factor is best described by the model of Kirkwood and Westheimer or one of its several modifications.[21] These models generally can be described as the substituent and the reaction site being buried in a medium of low dielectric constant, the hydrocarbon portion of a molecule, and this cavity of low dielectric constant in turn being immersed in a medium of high dielectric constant, the solvent. These models have been reasonably successful in appropriate cases, but less successful or unsatisfactory in cases where the field effect may fall in part or primarily outside of the low dielectric cavity. In a rather general view, this latter will be the case for cis β-substituents and therefore for essentially all inductive or field effects contributing to the "proximity effect."[22] Until suitable modifications have been built into the Kirkwood–Westheimer model (or some new model or theory is devised), it would appear that direct calculation of this component from the molecular geometry will not be possible. Any resonance contribution that might be considered cannot account for the inversion of effect observed. This inability to calculate the electronic effects does not preclude obtaining various empirical correlations; however, data at this time do not appear to be sufficient to separate this specific factor.

(2) Solvation Factor. No quantitative theory of this factor seems to have been proposed, at least with respect to the effect of substituents on the exclusion, the ordering, or the disordering of solvent at the reaction site. Qualitatively, it is probable that this factor has decreasing effect as the substituent decreases in size and increases in distance from the carboxyl group. But it is not absolutely clear that such a decreasing effect would necessarily lead to a relative increase in acidity. Thus, although several examples of this factor showing decreasing acidity with increasing size of substituent are rationalized in terms of decreased solvation of the anion,[18] there seems to be little or no direct evidence to support this logical proposal, and indirectly there is some evidence[23] that casts doubt on its general applicability. In any case, the solvation factor seems to be the least quantitative and least amenable of the several affecting acidity.

(3) Steric Inhibition of Resonance. At first sight this might appear to be the most easily handled component. That is, from the geometry of the molecules and the various van der Waals radii of atoms and groups, it should be possible to calculate the volume occupied by a group and the overlap in space of these volumes. The steric inhibition of resonance then arises by a twisting of the carboxyl group out of the plane of the double bond so as to reduce the overlap of these volumes. However, there does not appear to be any way of balancing the loss in enthalpy arising from the change in conjugation against the gain in entropy for rotation of a substituent such as isopropyl; *i.e.*, is it better to restrict the rotation of the isopropyl group and retain maximum conjugation or is it better to allow the isopropyl group to rotate freely while twisting the carboxyl group? Even when this question can be answered, there would be difficulty in making appropriate calculations for the general case due to solvation effects. Thus, the effective volume of a substituent and of the carboxyl group (or other reactive center) may be influenced by solvation, and this will cast doubt on the validity of volumes calculated using the ordinary van der Waals radii. And finally, this solvation feature is intimately related to the steric inhibition of solvation previously cited.

Thus, theory is seriously deficient or totally absent in showing how to untangle the various components making up the observed acidities, and, unfortunately,

(21) A good discussion of this is given by E. J. King, "Acid-Base Equilibria," Macmillan, New York, N. Y., 1965, Chapter 7.

(22) In general, $\Delta pK \propto (\cos\beta)/\epsilon r^2$, where ΔpK is the difference in pK values arising from electrostatic effects for the substituted and unsubstituted acids, β is the angle between the direction of the dipole for the polar substituent and the line joining the midpoint of the dipole and the reaction site, in this case a point in the "center" of the carboxyl group (1.5 Å beyond the carboxyl carbon on the carbon–carbon axis), ϵ is the dielectric constant of the medium through which the effect is transmitted, and r is the distance between the dipole midpoint and the reaction site. For the systems of this study, β varies from about 81° for the bicyclic systems to about 90° for the cyclohexene and aromatic systems. It should be noted that the reliability of the relationship cited decreases as r decreases, but it is a reasonable first approximation in the present case where β approaches 90°. The small angular change cannot account for the inversion of effect noted in the present work (the values of cos β are all positive for angles less than 90°), and the closeness to 90° suggests a direct field effect will be very small or negligible (cos 90° = 0, cos 81° = 0.16).

(23) C. L. Liotta, A. Abidaud, and H. P. Hopkins, Jr., *J. Amer. Chem. Soc.*, 94, 8624 (1972).

the present work does not permit this untangling in empirical terms. In spite of this deficiency, another dimension, the distance between substituent and reaction center, the carboxyl group, is added in this work, and a surface map of acidities is beginning to take form.

The Ortho Effect. The ortho effect may be looked upon as simply one contour line of the "acidity surface," a contour corresponding to essentially constant distance between substituent and reaction site, but variable size of substituent. This contour, as for the surface generally, is a composite of a variety of factors which may be lumped together as a proximity effect. Charton[24] has listed these factors in three categories, polar, steric, and secondary bonding. The polar category consists of the usual inductive and resonance effects. The steric category consists of four types, steric hindrance to attack by reagent, steric inhibition of resonance, and steric control of reaction conformation. The secondary bonding category consists of such things as intramolecular hydrogen bonding and ion–dipole interactions. These features are assumed to be additive and expressed in a general equation

$$Q_X = \alpha_N\sigma_{I,X} + \beta_N\sigma_{R,X} + \alpha_P\sigma_{I,X} + \beta_P\sigma_{R,X} + \Psi\zeta_X + \nu\omega_X + h$$

or combining the normal (N) and proximal (P) inductive and resonance effects

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \Psi\zeta_X + \nu\omega_X + h$$

where $\Psi\zeta_X$ is the steric factor and $\nu\omega_X$ is the secondary bonding factor. It is suggested here that this model is inadequate; in the same way that the polar factor is not represented by a single term, the steric factor (and probably the secondary bonding factor) should not be represented by a single term.

The steric factor involves space-filling interactions. Until the substituent is large enough and occupies enough volume, it will have no steric effect. At size A (Figure 3), the substituent just enters the space of the solvent shell at the reaction site, and over some size increase, A to B, it effectively excludes some solvent molecule(s). Clearly, this will depend on the size and shape of the solvent molecules, the substituent, and the mode of solvation at the reaction site. Although preventing the solvent molecule(s) from occupying this volume, substituents at minimal size B will not themselves occupy the total volume excluded. So as the substituent size increases from B to C there will be relatively little additional influence on excluding solvent in the region between the substituent and the reaction site. In the same way that solvent is excluded, a reacting species may also be excluded, but because the direction of attack may be different than the line between the substituent and reaction site, the relative positions of A, B, and C may be different and the relative amount of interaction may be different. At C, the substituent will begin to contact the reaction site directly. Between C and D, then, it would be expected that either the substituent, the reaction site, or both would be twisted, bent, or otherwise deformed so as to minimize the volume-filling interactions; this would result in the steric inhibition of resonance contribution. In the case of twisting, when it has reached a maximum, 90°, the degree of interaction again would change, possibly to a lesser rate of change with increasing size of substituent as in the region from D to E. The factor of conformational control might be included within this region of direct contact, but the limits and degree of interaction would not coincide necessarily with those for the steric inhibition of resonance factor. From this description it should be obvious that a single steric parameter, ζ_X, cannot describe a substituent if two or more of these steric factors are operating simultaneously.

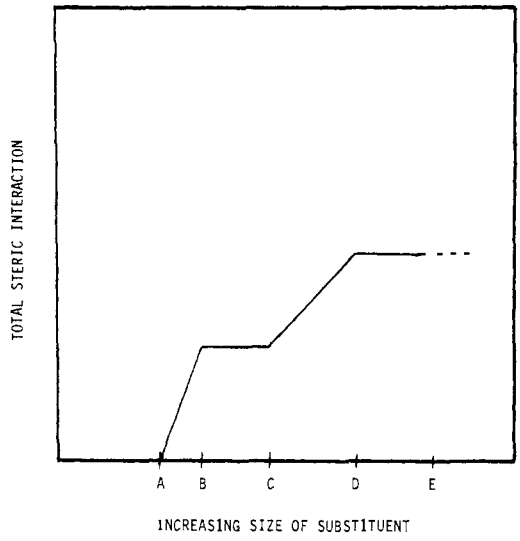


Figure 3. Steric interaction of cis β-substituents at a fixed distance from a reaction site.

Further, a single reaction parameter, Ψ, presumably describing the relative effect of substituents on a reaction, is inadequate. Thus, for example, inhibition of solvation usually decreases acidity while inhibition of resonance increases acidity in carboxylic acids. In a more general sense, it might be difficult to decide whether a specific steric factor would affect the starting material or the transition state (or product) to a greater extent, and consequently the sign of the reaction parameter, Ψ, for each steric component would be in doubt.

Applying those ideas to Taft's steric parameters,[25] the E_s values for aliphatic systems do not involve steric inhibition of resonance and probably do not involve steric control of conformation. The E_s values almost certainly do involve steric hindrance to solvation and probably some steric hindrance to reagent attack. Assuming these two factors do parallel each other, their effects can be combined and the resultant should correlate reasonably with their size as indicated by appropriate van der Waals radii and as shown by Charton.[24] For the E_s values for ortho substituents, both steric hindrance to solvation *and* steric inhibition of resonance will be involved. A direct steric interaction clearly is shown in the case of ortho-substituted benzoic acids; the carboxyl group is tilted relative to the benzene ring in direct proportion to the size of the ortho substituent.[24] This same sort of interaction certainly must be present in the closely related esters used to determine E_s. Assuming that in the esters, as in the acids, the effects of steric hindrance to solvation and steric inhibition of resonance operate in opposite directions, the net effect

(24) M. Charton, *Progr. Phys. Org. Chem.*, 8, 235 (1970).

(25) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

could be constant, not necessarily zero, or changing only very slowly with increasing size of the substituent. In this situation a correlation of E_s (ortho) with polar σ parameters only (omitting those substituents where $\nu\omega_X$, the secondary bonding factor, would contribute significantly) is reasonable, as shown by Charton.[24] It should be noted in such correlations that a constant is added (required) and this could include the "constant" steric contribution.

In the more general sense of reaction correlations for ortho-substituted benzene systems as tabulated by Charton,[24] in addition to the polar parameters, a constant, h, appears, possibly related to the parent unsubstituted structure. In many systems, however, the parent member, the hydrogen case, must be omitted to obtain satisfactory correlations. From the present analysis the hydrogen case simply occupies the region preceding A in Figure 3, and the constant h represents the net steric effect. The effect is essentially constant because it is in region B to C involving steric hindrance to solvation (phenol acidities, for example) or because steric hindrance to solvation, region A to B, and steric inhibition of resonance, region C to D, overlap and operate in opposite directions (acidities of carboxylic acids for example).

As can be seen in Figure 3, the steric interactions probably are not a simple linear relation with substituent size. When the conditions indicated above for a "constant" value are not met, then the steric factor becomes apparent and correlations involving only polar factors are no longer possible. Thus, certain substituents such as *tert*-butyl do not correlate with other substituents on the basis of a polar analysis only; it is suggested that, relative to other substituents, *tert*-butyl occupies a different region of Figure 3 and consequently the net effect from a steric standpoint is different.

It should be emphasized that Figure 3 is purely descriptive, that the curve and regions of Figure 3 would vary in any real sense with each system studied, and that the vertical axis of Figure 3 represents the total steric interaction and not a numerical net interaction. This and the previous discussion are simply to point out that unlike polar factors that die off uniformly with distance (inductive and field) or depend on specific atom–atom bonds (resonance), the steric effects are nonlinear, and they depend on geometry which is different for each system to which the substituent and reaction site are joined and on the geometry of the reaction site. Previous correlations involving aromatic systems have been reasonably successful because the geometry of the "core," the benzene ring, is constant and reasonably successful in aliphatic systems because only one steric factor, steric hindrance to solvation, or sometimes a second, steric hindrance to reagent approach, operating in the same way as the solvent factor and therefore largely additive, is involved. The present work points out the deficiency of a single steric parameter when the "core" system geometry changes; the polar factor would not change sign over the small changes in geometry of the systems studied, the secondary bonding characteristics of the substituents used should be negligible, and that leaves only the *net* steric factor for each substituent to change in value from plus to minus. It is not suggested that a proliferation of steric parameters take place, *i.e.*, a different set for each system. It is hoped that as a result of the work initiated and the ideas proposed here eventually techniques will be developed for calculating steric effects directly from the geometry of the reacting molecules and solvent molecules.