base-catalyzed reactions have appeared in the literature.[6,17-19] A particularly significant reaction in the present context is the protodetritiation of fluorene in MeOH-NaOMe recently reported from this laboratory.[20] The pseudo-first-order rate constants for this exchange reaction give curved correlations with H_M functions derived from the nitrogen and oxygen acids.

The correlation with the present H_M acidity function derived from the related hydrocarbon, DPI, is presented in Figure 3. Although this correlation is accurately linear over this range with a least-squares slope of 0.847 ± 0.006, over the whole range of $NaOCH_3$ concentrations the correlation mnst be nonlinear; that is, this line applies only at relatively high base concentrations ($H_M > 16$). At low $NaOCH_3$ concentrations, where the second-order rate constant is essentially constant, a line of unit slope is expected.

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Mechanism of Transmission of Nonconjugative Substituent Effects. IV. Analysis of the Dissociation Constants of 6-Substituted Spiro[3.3]heptane-2-carboxylic Acids[1,2]

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Abstract: The pK_a's of eight 6-substituted spiro[3.3]heptane-2-carboxylic acids in 50% (by weight) aqueous ethanol at 25° are presented. Excellent correlation is obtained between the experimental data and σ_I parameters, whereas only a fair correlation is obtained using the Dewar–Grisdale F parameters. The data are also analyzed by means of the Tanford modification of the Kirkwood–Westheimer cavity model. Excellent agreement between calculated and experimental results is obtained with the spherical cavity model as well as with Stock's modification of this electrostatic model. An analysis is presented which demonstrates that hydrogen and methyl substituents do not exhibit anomalous behavior when compared to more polar substituents by means of the cavity models. Analysis of the limiting models for the propagation of nonconjugative substituent effects (σ-inductive and field) suggests that the field model is more reliable in explaining the data.

The electrostatic approaches to quantitatively describing the effects of dipolar and charged substituents on the dissociation constants of organic acids are well known.[3-5] The most theoretically satisfying is the model of Kirkwood and Westheimer[6] which views the charges or dipoles as being embedded in a structureless spherical or ellipsoidal cavity of low dielectric constant immersed in a structureless solvent of high dielectric constant. Roberts and Moreland[7] have examined this model with a series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. Discrepancies were observed between theory and experiment and were of such a serious nature that Tanford[8] reexamined and modified the electrostatic model. He considered that the important parameter in evaluating interaction energies is the depth at which the dipole or charge is placed within the cavity. Siegel and Kormarmy[9] determined the pK_a value of a series of trans-4-substituted cyclohexane-1-carboxylic acids in several solvent systems and found that both models were qualitatively acceptable but still inadequate quantitatively. Stock and Holtz[10,11] have reexamined and extended the work of Roberts and Moreland. Nevertheless, even with the improved data, the discrepancy between theory and experiment still remained significant.

Dewar and Grisdale[12] have proposed a model for field effect based upon the ionization constants of meta-substituted benzoic acids. In this treatment, they criticize the point dipole model for relatively small molecules in which the length of the dipole is comparable to the distance separating it from the reaction center and contend that the important distance parameter is an r^{-1} term rather than r^{-2} as in the Kirkwood–Westheimer treatment. Stock,[10,11] however, has attempted to apply Dewar's field approach to the 4-sub-

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stituted bicyclo[2.2.2]octyl system with some serious deviations resulting.

Another approach to the mode of transmission of polar effects in nonconjugated systems is the σ-inductive model.[13-15] If one considers a substituent at a position S on a molecule, the polarization of the bond between the substituent and the atom to which it is attached can be transmitted to another position on the molecule, $S \pm n$, n bonds removed from the point at which the initial effect was exerted, by the successive polarization of the intervening σ bonds. The resultant effect, $\lambda_{S\pm n}$, will be equal to the initial effect, λ_S, multiplied by a constant factor per bond ($1/f < 1$) and summed over all pathways as illustrated by the following equation

$$\lambda_{S\pm n} = \lambda_S \sum_P \left(\frac{1}{f}^{S\pm n} \right)_p \qquad (1)$$

Attenuation factors (f) from 2 to 3 have been used in the correlation of organic Brønsted acids.[16-19]

The empirical parameter σ_I has been successfully used by a number of workers to correlate rate and equilibrium data.[20-22] What σ_I is actually measuring (the field or σ-inductive effect of a substituent) is the source of much controversy. That the field effect is an important mechanism for the transmission of polar effects is qualitatively shown by the observations of the angular dependence of substituent effects.[12,23-29] Indeed, to date, most studies indicate that the field model is qualitatively better than the σ-inductive model in predicting relative rates and relative equilibrium constants.[30,31]

Although a few series of rigid carboxylic acids free from resonance or steric interaction have been studied, 1,4-bicyclo[2.2.2]octanes,[7,10,32,33] 1,4-bicyclo[2.2.2]octenes,[11] 1,4-dibenzobicyclo[2.2.2]octadienes,[11] 1,4-bicyclo[2.2.1]heptanes,[30] 1,4-*trans*-cyclohexanes,[9] and 1,3-adamantanes,[34] information on other model systems is needed to help develop a quantitative treatment for evaluating substituent effects. We have thus synthesized a series of 6-substituted spiro[3.3]heptane-2-carboxylic acids[35] in order to compare the various empirical and theoretical approaches to substituent effects and to extend the analysis of the two limiting models (field and α-inductive).

Experimental Section

Materials. Distilled water was redistilled from alkaline permanganate with protection from carbon dioxide by a tube filled with Ascarite. Absolute ethanol was prepared by reacting stock 100% ethanol with magnesium turnings followed by distillation. The solvent used in the pK_a determinations, 50% by weight aqueous ethanol, was prepared by mixing equal weights of freshly purified water and absolute ethanol and stored in sealed brown bottles under an atmosphere of nitrogen.

Standard sodium hydroxide solution was prepared by diluting 1.5 ml of 6.66 N sodium hydroxide to 1 l. with 50% aqueous ethanol. The solution was standardized by titration with potassium acid phthalate and found to be 1.021×10^{-2} N. This was stored at 25° in sealed polyethylene bottles under an atmosphere of nitrogen.

Buffer solution for calibration of the pH meter was prepared by dissolving 0.0907 g of freshly sublimed benzoic acid in 100 ml of aqueous ethanol. The molarity of the acid was found to be 7.40×10^{-3} M by titration with the standard base. Benzoic acid-sodium benzoate buffer was then made by adding exactly one-half the volume of standard base required to neutralize 40 ml of the benzoic acid solution (39, 10). The buffer was stored in a capped bottle under a blanket of nitrogen.

Freshly recrystallized, distilled, or sublimed spiro acids were weighed into clean, dry 50-ml volumetric flasks and solutions were made up to the mark with solvent which had been stored at 25°. In each case these solutions were made up to be as close to 7.4×10^{-3} M as possible. The capped flasks were then stored in the constant temperature bath at 25° until they were titrated.

pK_a Determinations. The pK_a's of the various 6-substituted spiro[3.3]heptane-2-carboxylic acids were determined by potentiometric titration in 50% (by weight) aqueous ethanol using a Beckman Model 1019 pH meter equipped with glass and calomel electrodes.

The pH measurements were made in a 100-ml tall-form beaker which was clamped in the constant-temperature bath. The beaker was fitted with a rubber stopper through which were inserted the electrodes, a nitrogen inlet tube, an NBS thermometer, and the tip of the base dispensing buret. Stirring was accomplished by means of a Teflon encased stirring bar propelled by an air driven magnetic stirrer. Solvent saturated nitrogen was slowly admitted to the beaker throughout the measurements.

The pH meter was calibrated with the benzoic acid buffer to read 5.738, which is the reported thermodynamic pK_a of benzoic acid in 50% (by weight) aqueous ethanol.[10,36] The meter was checked with buffer between each set of measurements to ensure against drift. No significant adjustments were necessary throughout the measurements which took several hours.

The acid solution (40 ml) to be titrated was introduced to the beaker by volumetric pipet. The solution was stirred as standard base was added rapidly from the buret. The addition of base was stopped when enough had been added to come within 1 ml of the anticipated half-neutralized point of the acid. Stirring was continued until the temperature within the beaker had restablished itself at 25°. Stirring was then discontinued, and the pH of the solution and the volume of base added were recorded. This procedure was then repeated with base being added in increments between 0.1 and 0.2 ml until a point 1 ml beyond the anticipated half-neutralization point was reached. The equivalence points of the acid solutions were confirmed by titration. The data from about the half-neutralization point were used to calculate the pK_a of the acid by the Henderson-Hasselbach equation.[37] Deviations of pK_a for a single point were never more than 0.003 from the average while the average deviation in a single run was usually less than ±0.001. The pK_a's from the measurements of three independently prepared solutions were averaged to give the pK_a for each spiro acid and the average deviation.

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Corrections for liquid junction potentials and activity coefficients were made empirically by assuming that the carboxylate anions had the same intrinsic mobility and activity as the reference benzoate anion.[30,38–41] This assumption appears to be justified since the measurements were made at the same low ionic strength as the reference buffer (0.0025 ± 0.0001).

The dissociation constants of the 2,6-spiro[3.3]heptanedicarboxylic acid were determined by the method of Speakman.[42]

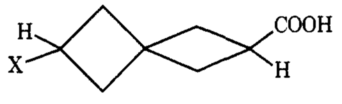
Calculations. The calculations to determine distances and angles were carried out using three-dimensional vector analysis and trigonometry. The bond lengths used in the calculations were 1.54 Å for C–C bonds and 1.09 Å for C–H bonds. The bond angles for external H–C–X were 112° while ring C–C–C angles were taken as 90.° The lengths of dipoles were considered to be standard C–X bond distances when X was a single atom. When X was a group of atoms, the dipole length was considered to be the maximum extension of the group as projected on the C–X bond axis. The dipole lengths used were C–H (1.09 Å), C–CN (2.62 Å), C–Br (1.94 Å), $C–CH_3$ (1.71 Å), and CO_2R (2.99 Å). The position of the ionizable hydrogen was fixed at 1.45 Å beyond the carboxyl carbon on the extension of the C–C bond in accordance with the suggestion of Kirkwood and Westheimer.[6]

Bond or group moments were assessed from data tabulated by Smyth[43] for the dipole moments of substituted methanes in benzene solution. It is suggested that these values be used as they present a better interpretation than values taken from gas-phase measurements.[43] It has been assumed that the bond moment of the C–H bond is 0.4 with hydrogen as the negative terminus.[6] Smyth devotes considerable discussion to this point and concludes that popular opinion supports 0.4 as the magnitude, but the controversy continues over the direction.

The effective dielectric (D_E) was calculated for both conformations by the spherical and ellipsoidal cavity models of Kirkwood and Westheimer[6] assuming an external dielectric of 49.5 and an internal dielectric of 2. The center of the dipole was placed 1.5 Å below the surface of the cavity, and the ionizable protons of the dicarboxylic acid were placed 1.0 Å below the surface of the cavity according to the suggestion of Tanford.[8] This procedure fixes the cavity dimensions so that the effective dielectric may be calculated from the tabulations of Westheimer, Jones, and Lad.[6]

Results and Discussion

The dissociation constants and the corresponding pK_a values of a series of 6-substituted spiro[3.3]heptane-2-carboxylic acids (I) in 50% (by weight) aqueous ethanol at 25° are summarized in Table I.



I

Table I. Dissociation Constants and Corresponding pK_a's of 6-Substituted Spiro[3.3]heptane-2-carboxylic Acids in 50% (by Weight) Aqueous Ethanol at 25°

Substituent	$K \times 10^{-6}$	pK_a
H	0.542	6.266 ± 0.015
CN	1.39	5.856 ± 0.018
Br	1.05	5.980 ± 0.015[b]
$CO_2C_2H_5$	0.867	6.062 ± 0.025
CH_3	0.478	6.321 ± 0.015
CO_2H[a]	0.802	6.096 ± 0.010
CO_2^-[a]	0.355	6.450 ± 0.015
$CoNH_2$[c]	0.777	6.110

[a] Statistically corrected. [b] Originally reported incorrectly as 5.931.[31] [c] One measurement.

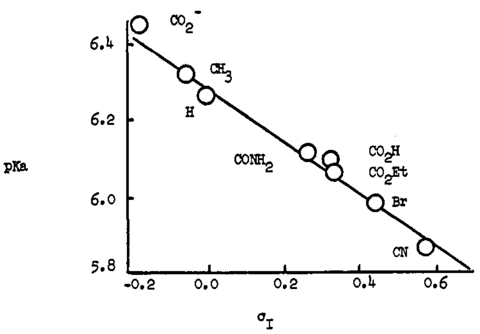


Figure 1. Correlation of pK_a with σ_I.

Empirical Analysis. It has been shown by Stock and his students[10,11] that the polar effects of substituents on the bicyclo[2.2.2]octane and bicyclo[2.2.2]octene systems are well correlated by σ_I.[20,21] In contrast, a somewhat unprecise relationship was found between these parameters and the pK_a's of the 4-substituted dibenzobicyclo[2.2.2]octadiene-1-carboxylic acids (hydrogen and methyl seriously deviating from the line).[11] The use of these parameters to describe the relative pK_a's of the spiro acids is shown in Figure 1. σ_I parameters based on chemical reactivities of substituted acetic acids were taken from Charton's extensive compilation.[22] The correlation equation is given as eq 2. The

$$\mathrm{p}K_a = -0.693\sigma_I + 6.288 \qquad (2)$$

high degree of correlation[41] ($r = 0.995$, $s = 0.205$, $n = 8$) provides additional evidence that σ_I is a good measure of nonconjugative substituent effects. In this case both hydrogen and methyl correlate extremely well.

The magnitude and direction of the polar effect of methyl has been the subject of much investigation.[44] In general, it appears that the effects are small and that their direction depends primarily on the hybridization of the carbon to which the methyl is attached. When bonded to sp^2 carbon, methyl acts as an electron donor as compared to hydrogen ($\sigma_{m\text{-}CH_3} = -0.07$). Stock has concluded that there is very little difference between methyl and hydrogen when attached to sp^3 carbon (σ_I varied from −0.02 to +0.02).[10,11] The spiro system presents an interesting case in that methyl is bound to carbon of hybridization intermediate between sp^2 and sp^3. Based upon analysis of eq 1, $\sigma_I^{CH_3} = -0.048$ indicating that in this saturated system the C_{sp^3}–C_{spiro} bond is polar in the direction of the spiro ring. This statement is predicated on the assumption that C_{sp^3}–H and C_{spiro}–H have identical bond moments in the same direction.

Application of the Dewar–Grisdale[12] approach to the spiro acids is shown in Figure 2. A fair correlation is produced ($r = 0.941$, $s = 0.550$, $n = 7$).[41] $\sigma_{2,6}$ parameters were generated from F parameters of meta-substituted benzoic acids where $\sigma_{2,6} = F/R_{2,6}$, $F = 1.73\sigma_m$, and $R_{2,6}$ is the distance from C-2 to C-6 in terms of

$$\mathrm{p}K_a = -1.33\sigma_{2,6} + 6.300 \qquad (3)$$

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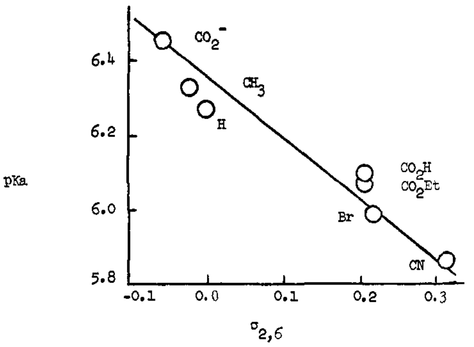


Figure 2. Correlation of pK_a with $\sigma_{2,6}$.

C–C bond lenths in benzene. That the observed deviations from linearity are not due to solvent effects is made clear by the fact that a plot of our data *vs.* the pK_a's of meta-substituted benzoic acids in 50% (by volume) aqueous ethanol at 25°[45,46] produced an even greater scatter (Figure 3). Closer inspection of Figure 2 reveals that several of the deviations appear to be in the same direction as the resonance contribution of the substituent. Stock and Holtz[10] have made a similar observation when attempting to correlate the pK_a's of substituted bicyclo[2.2.2]octanecarboxylic acids with *F* parameters. It would appear that the choice of a saturated system as model for field effect would be more successful since π-inductive and mesomeric effects seem to be operative in meta-substituted benzoic acids.[12,10,19,47,48]

Electrostatic Analysis. From the above discussion it may be concluded that the empirical approaches to quantitatively describing nonconjugative substituent effects are successful to varying degrees. The theoretical approaches based upon the electrostatic interaction of a substituent dipole or charge with the reaction center are examined next. To date, the most successful treatment is based upon the Kirkwood–Westheimer cavity model.[6,8] This approach has been extensively reviewed in several places.[49,50] The equation usually employed to calculate the ratio of dissociation constants of a substituted acid relative to the parent acid is

$$\log K_X/K_H = \frac{e\mu \cos\theta}{2.3kTR^2D_E} \qquad (4)$$

where μ is the bond or group moment of the substituent relative to the moment of the carbon–hydrogen bond, R is the distance between the center of dipole and the reaction center, θ is the angle between R and the sub-

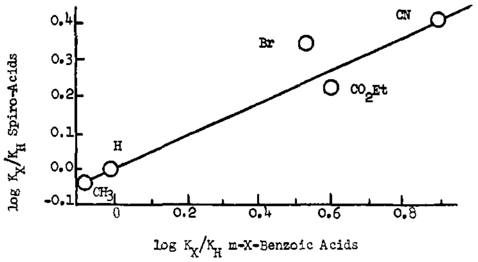
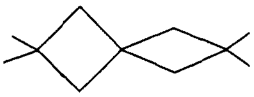
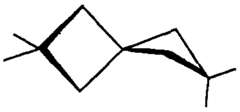


Figure 3. Correlation of log K_X/K_H spiro acids with log K_X/K_H *m*-X-benzoic acids.

stituent dipole, D_E is the "effective" dielectric constant, and e, k, and T have their usual meaning.

In order to examine the spiro acids by means of eq 4, a knowledge of the parameters R and θ is necessary. Since it has been shown by several workers that cyclobutane rings may be planar or puckered,[51] it was decided to carry out the calculations on what are considered to be two extreme conformational forms of the cyclobutane rings—one in which each ring is planar (Ia) and the other in which each ring is puckered with


Ia


Ib

a dihedral angle of 31° (Ib).

The log K_X/K_H ratios for the two conformational structures are compared by means of the Tanford modification of the Kirkwood–Westheimer (TMKW) spherical cavity model. The results are summarized in Tables II and III. Both extreme conformations give very much the same results. This is a case in which there is a partial compensation between R and θ as one proceeds from one conformation to the next (as the distance, R, decreases the angle, θ, increases).

Excellent agreement between the calculated log K_X/K_H ratios and the experimental values is found with the spherical cavity model for both the planar and the bent structure. The ellipsoidal cavity model, in both cases, results in log K_X/K_H values which are far below the experimental values found. This model appears to overestimate the value of D_E.

Table IV shows the calculations of log $K_1/4K_2$ for spiro[3.3]heptane-2,6-dicarboxylic acid by use of eq 1,

$$\log K_1/4K_2 = e^2/2.3kTRDe \qquad (5)$$

where all symbols have their usual meaning. It may be seen that the puckered ellipsoidal model gives a

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(45) The *F* values used for the H, CH_3, Br, $CO_2C_2H_5$, CN, COOH, and CO_2^- substituents are 0.00, −0.03, +0.21, +0.20, +0.31, +0.20, and −0.05, respectively, based on a C_2–C_6 distance of 4.40 Å.

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Table II. Parameters and Calculated Values for Log K_X/K_H of 6-X-Spiro[3.3]heptane-2-carboxylic Acids[a] at 25° by Eq 2

	Parameters			Tanford sphere		Tanford ellipse		Exptl
X	R, Å	μ_X, D	θ	De	Log K_X/K_H	De	Log K_X/K_H	Log K_X/K_H
H	6.82	0.40	56° 14′	4.80	0.00	9.88	0.00	
CN	7.27	3.90	50° 36′	5.02	0.42	10.19	0.21	0.41 ± 0.03
Br	7.07	2.20	52° 12′	4.90	0.23	10.15	0.11	0.28 ± 0.03
$CO_2C_2H_5$	7.41	2.26	48° 8′	5.21	0.22	11.08	0.10	0.20 ± 0.04
CH_3	7.00	0.00[b]	52° 58′	4.84	−0.05	9.96	−0.02	−0.06 ± 0.03
CO_2H	7.41	2.03	48° 8′	5.21	0.19	11.08	0.09	0.17 ± 0.03

[a] Planar cyclobutanes. [b] The bond moment for C_{spiro}–CH_3 has been arbitrarily set at 0.00 in comparison to C_{spiro}–H since it has been concluded that C_{spiro}–C_{methyl} has a nonzero moment in the direction of the spiro ring. $e = 4.80 \times 10^{-10}$ esu, $\mu = \mu_X - \mu_H \times 10^{-16}$ esu/cm, $k = 1.381$ ergs/,K° $T = 298$°K.

Table III. Parameters and Calculated Values for Log K_X/K_H of 6-X-Spiro[3.3]heptane-2-carboxylic Acids[a] at 25° by Eq 2

	Parameters			Tanford sphere		Tanford ellipse		Exptl
X	R, Å	μ, D	θ	De	Log K_X/K_H	De	Log K_X/K_H	Log K_X/K_H
H	7.29	0.40	30° 26′	5.08	0.00	10.19	0.00	
CN	7.97	3.90	26° 36′	5.61	0.45	12.38	0.20	0.41 ± 0.03
Br	7.66	2.20	28° 18′	5.43	0.25	11.39	0.12	0.28 ± 0.03
$CO_2C_2H_5$	8.14	2.26	26° 2′	5.75	0.22	12.60	0.11	0.20 ± 0.04
CH_3	7.56	0.00	28° 54′	5.33	−0.06	10.26	−0.03	−0.06 ± 0.03
CO_2H	8.14	2.03	26° 2′	5.75	0.19	12.60	0.10	0.17 ± 0.03

[a] Puckered cyclobutanes, 31° dihedral angle.

Table IV. Parameters and Calculated Values for Log $K_1/4K_2$ for Spiro[3.3]heptane-2,6-dicarboxylic Acid at 25°

			Log $K_1/4K_2$	
	R, Å	De	Calcd	Exptl
Planar sphere	8.46	37.58	0.76	0.35
Planar ellipse	8.46	58.54	0.49	0.35
Puckered sphere	9.51	42.37	0.61	0.35
Puckered ellipse	9.51	60.40	0.42	0.35

ratio much closer to the one experimentally determined than the spherical models. This result is difficult to explain in view of the fact that the spherical model gives by far the best results for the dipolar substituted spiro acids. Indeed, the spherical cavity model gives excellent results for the 1,4 diacids of the bicyclo-[2.2.2]octane,[10] bicyclo[2.2.2]octene,[11] and cubane[11] systems.

Stock and Holtz have proposed a modification of eq 4 which recognizes that the values of R, θ, and D_E of the parent acid are usually quite different from most dipolar substituted acids. Log K_X/K_H ratios should be more realistically calculated by

$$\log K_XK_H = \frac{e}{2.3kT}\left[\left(\frac{\mu \cos \theta}{R^2 D_E}\right)_X - \left(\frac{\mu \cos \theta}{R^2 D_E}\right)_H\right] \qquad (6)$$

The results using eq 6 are shown in Table V. The log K_X/K_H ratios are essentially the same as those obtained from the original formulation of the electrostatic equation.

Table V. Calculated Values of Log K_X/K_H for 6-X-Spiro[3.3]heptane-2-carboxylic Acids from Eq 3

	Log K_X/K_H	
X	Planar sphere	Puckered sphere
H	0.00	0.00
CN	0.41	0.43
Br	0.23	0.24
$CO_2C_2H_5$	0.22	0.21
CH_3	−0.05	−0.06
CO_2H	0.19	0.18

Application of the TMKW cavity model to the 1,4-bicyclo[2.2.2]octane[10] and 1,4-bicyclo[2.2.2]octene[11] systems has resulted in rather substantial deviations between experimental and calculated equilibrium constant ratios. From analysis based upon curvilinear relationships found in plots of μ cos θ/R^2 *vs.* ΔpK_a, Stock and his students have concluded that the discrepancies between theory and experiment result from hydrogen and alkyl-substituted carboxylic acids exhibiting anomalous behavior when compared to carboxylic acids substituted with more polar groups. Several speculative interpretations were put forth. The lyophobic character of the hydrogen and alkyl groups would allow the solvent continuum to begin closer to these substituents. In contrast to this, the more lyophilic substituents would incorporate more solvent within the cavity resulting in the solvent continuum beginning further away from the substituent. An alternate explanation, based upon the Dewar–Grisdale model,[12] suggests that the greater solvent interaction of the lyophilic substituents tends to decrease the magnitude of the exposed negative end of the dipole. The solvent influence on the lyophobic hydrogen and alkyl substituents would, in contrast, be much less. In support of these ideas it has been shown that the hydrogen and alkyl substituents of the dibenzobicyclo[2.2.2]-octadienyl system[11] do not show this anomalous behavior. This was attributed to steric inhibition of solvation due to the presence of the bulky benzene rings. In view of this, it is interesting to extend this analysis to the spiroheptane system. Figures 4 and 5 show a plot of μ cos θ/R^2 *vs.* log $(K_X/K_H)_{exptl}$ for the planar and bent conformation of the spiro acids. No curvilinear relationship is evident. Indeed, least-squares analysis indicate values for D_E of 4.83 and 5.44 in remarkable agreement with the average values of 4.91 and 5.49 as calculated by TMKW cavity model. This independent assessment of D_E suggests that the model may be more reliable than has been the general view.

σ-Inductive Model *vs.* Field Model. In order to explore the question of which model, field or σ-inductive, most adequately describes the transmission of noncon-

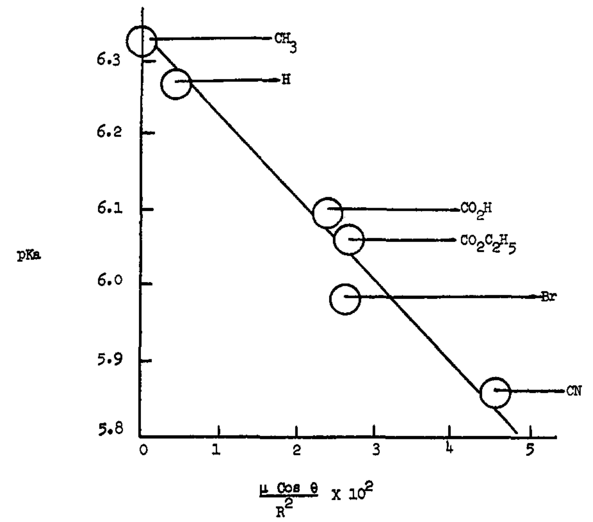


Figure 4. Correlation of pK_a with (μ cos θ)/R^2 for planar cyclobutanes.

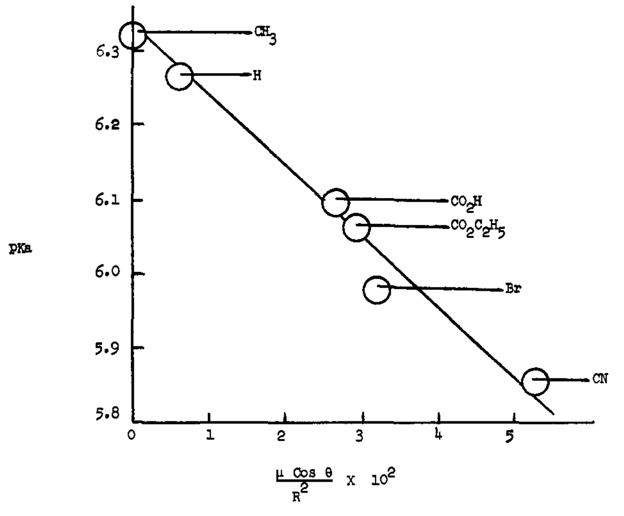


Figure 5. Correlations of pK_a with (μ cos θ)/R^2 for puckered cyclobutanes.

jugative substituent effects, a graphical comparison was made between the pK_a values of the 6-substituted spiro[3.3]heptane-2-carboxylic acids (I) and the pK_a values of the corresponding 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids (II) in 50% aqueous ethanol (by weight) at 25° (Figure 6). An excellent linear correlation was obtained with a slope equal to 2.12. It was desired to make a similar comparison between system I and the 4-substituted bicyclo[2.2.1]heptane-1-carboxylic acids (III).[30] Unfortunately, the pK_a values of III in 50% aqueous ethanol (by weight) have not been reported. Wilcox and Leung, however, have compared the relative acidities of systems II and III in pure water, 25% methanol-water, and 50% methanol-water and have obtained ρ values of 1.175, 1.183, and 1.195, respectively. A plot of ρ *vs.* $1/D$ produces a straight line, which when extrapolated to the $1/D$ value for 50% aqueous ethanol (by weight, D = 4.95) gives a ρ value of 1.210. The "experimental" slope in the comparison of I and III is then calculated to be 2.56. In order to evaluate the theoretical slopes from

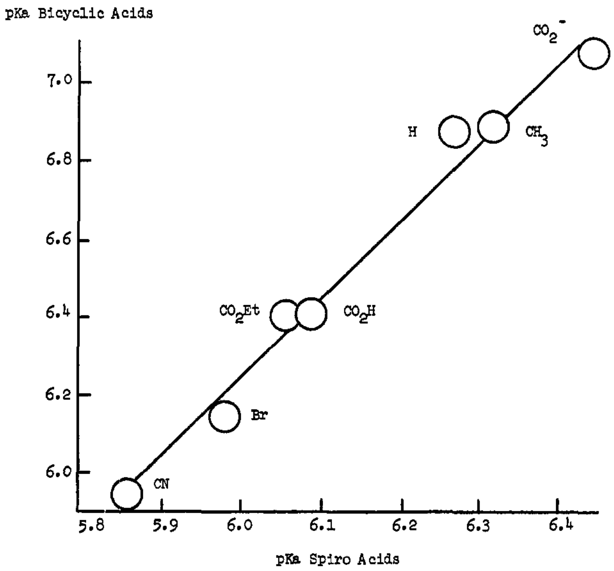
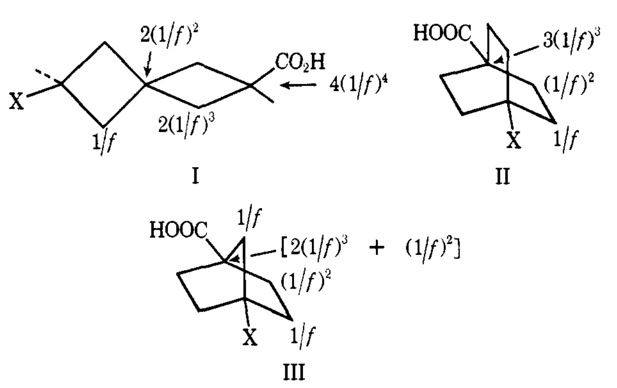


Figure 6. pK_a's of bicyclo[2.2.2]octane acids *vs.* pK_a's of spiro acids.

the inductive model, attenuation factors of 1/2.0 and 1/3.0 were used (see Chart I and eq 7 and 8).

Chart I



$$(\mathrm{II}):(\mathrm{I}) = 3(1/f)^3/4(1/f)^4 = 3f/4 \tag{7}$$

$$(\mathrm{III}):(\mathrm{I}) = [2(1/f)^3 + (1/f)^2]/4(1/f)^4 = [2f + f^2]/4 \tag{8}$$

The theoretical slopes based on the field model were evaluated by means of the TMKW spherical cavity model. The results are summarized in Table VI. It can be seen that the slopes predicted by the cavity model and the experimental slopes are very close, whereas the slopes predicted by the inductive model cover an extremely wide range, the experimental values falling

Table VI. Experimental and Theoretical ρ Values in the Comparison of Spiro[3.3]heptane (I), Bicyclo[2.2.2]octane (II), and Bicyclo[2.2.1]heptane Acids (III)

	II:I	III:I
Slope ρ (exptl)	2.12	2.56
Slope ρ (TMKW)	1.93	2.40
Slope ρ (inductive) f = 2-3	1.50-2.25	2.00-3.75
Slope μ (inductive) f = 2.7	2.02	3.17

within this range. Wilcox and Leung[30] have suggested that an attenuation factor of 1/2.7 is most reasonable. Using this value, the predicted inductive slope falls very close to both the experimental and field slopes in the comparison of systems I and II. This same attenuation factor, however, predicts a slope for systems I and III which is far from the field and experimental slopes. These results suggest that the cavity model is a more useful approach in predicting the relative magnitude of substituent effects.

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Carbon-13 Nmr Study of Aliphatic Amides and Oximes. Spin–Lattice Relaxation Times and Fast Internal Motions

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Abstract: ^{13}C Fourier transform nmr spectra and *partially relaxed Fourier transform* (PRFT) cmr spectra of aliphatic amides and oximes yield insight into intramolecular interactions in these molecules. *N,N*-Dimethylformamide, *N,N*-di-*n*-butylformamide, *N,N*-di-*n*-butylacetamide, acetone oxime, and methyl ethyl ketone oxime have been studied. Significant carbon steric compression shifts are reported for the four aliphatic carbons transoid to the formyl hydrogen and eclipsing the carbonyl oxygen in *N,N*-di-*n*-butylformamide (DBF). These steric shifts range from over 5 ppm for the α-CH_2 carbon to *ca.* 0.1 ppm for the δ-CH_3 carbon on the same chain. Carbon spin–lattice relaxation behavior in DBF indicates that the ends of both butyl chains have significantly increased motional freedom. PRFT studies also yield insight into intramolecular steric interactions. For example in methyl ethyl ketone oxime the 1-CH_3 carbons in the two isomers (syn and anti to the NOH group) have very different T_1 values (6.1 and 2.8 sec, respectively).

The ability of ^{13}C nmr to resolve small differences in molecular environment has been well documented in recent years. Chemical shifts arising from steric perturbations of carbon nuclei, known as *steric compression shifts*, have been utilized in studies of diverse organic compounds.[1,2] The experimental result of steric compression is an upfield shift for carbons experiencing the interaction. For example, in methyl cyclohexanes the upfield shift due to an axial CH_3 group at C_1 is over 5 ppm experienced by both the C_3 and C_5 ring carbons.[1] Evaluation of steric compression shifts is facilitated where conformations can be "locked" and where model compounds are available to allow determination of ^{13}C chemical shifts in the absence of steric compression. Amides and oximes are particularly suited and of particular interest for such studies.

In the present work we have examined the cmr (carbon magnetic resonance) spectra of *N,N*-dimethylformamide (DMF) and *N,N*-di-*n*-butylformamide (DBF), plus several other amides and oximes. All spectra were obtained by pulsed Fourier transform (FT) nmr methods. In several cases, the spin–lattice relaxation behavior of each carbon was investigated in order to gain insight into the fast, internal motions $\gtrsim 10^{11}$/sec) of the different aliphatic groups. No attempt was made to study rotation around the amide C–N bond.[3] At the temperatures of observation, rotation around that bond was slow enough to freeze out conformers and yield separate resonances for aliphatic peaks cisoid and transoid to the formyl hydrogen.

In amides having two different N substituents and in oximes with different derivatized carbonyl substituents, the two conformers or isomers are not of equal energy; the equilibrium populations can be very different. Using steric compression shifts to facilitate ^{13}C spectral assignments allows rapid determination of isomer ratios for many amides and oximes. It is necessary to have some knowledge of the carbon spin–lattice relaxation times (T_1) and nuclear Overhauser enhancements (NOE) in order to obtain quantitative or near quantitative results. The spin relaxation and NOE behavior of these compounds is also of interest because it probes molecular geometry and intramolecular interactions.

Experimental Section

^{13}C Nmr Spectra. All ^{13}C nmr spectra were recorded on a Varian XL-100-15 spectrometer equipped for both frequency sweep and pulsed Fourier transform (FT) operation. In all cases, the FT mode was utilized. Chemical shifts are reported in ppm downfield from the internal standard TMS. The accuracy of chemical shifts determined in 5000-Hz spectra is better than 0.1 ppm; for 1000 Hz spectra, the maximum error is <0.02 ppm. The system computer (Varian 620-i, 16K core) allowed acquisition of 8K data points, thus yielding 4K (4096) output data points in the transformed, phase corrected real spectrum (~1.3 Hz per data point in a 5000 Hz spectrum). ^{13}C spectra were obtained with complete proton decoupling utilizing the pseudorandom noise modulation mode of the Gyrocode decoupler. Off resonance, partial decoupling to differentiate nonprotonated carbons, CH, CH_2, and CH_3 carbons, was effected by offsetting the ^{1}H irradiation frequency 0.5–1.0 kHz and turning off the noise modulation. In both wide-

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