STUDIES IN THE MECHANISM OF TRANSMISSION OF NON-CONJUGATIVE SUBSTITUENT EFFECTS

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SUMMARY

Two 6-substituted spiro[3.3]heptane-2-carboxylic acids have been synthesized. The substituent groups are bromo and methyl. The pKa's of these compounds were measured by potentiometric titration in 50 percent (by weight) aqueous ethanol.

Excellent correlation was obtained between the pKa values and the empirical substituent parameter σ_I. The methyl substituent was found to be electron donating with respect to hydrogen. Application of the Tanford modification of the Kirkwood-Westheimer spherical cavity model produced excellent agreement between calculated and experimental values for ΔpKa.

CHAPTER I

INTRODUCTION

The effects of dipolar and charged substituents on the dissociation constants or organic acids have been approached both from electrostatic theory and empirically by the use of substitutent parameters. Nevertheless, the mode of transmission of these substituent effects across the molecule to the reaction center remains a complex conglomeration of many mechanisms, and attempts at separation of these effects have met with only partial success.

Recently, Dewar and Grisdale[1] have made a detailed analysis of the problem and have recognized five distinct modes of transmission of substituent effects:

(1) Field Effect: The bond between the substituent and the atom to which it is attached on the molecular framework produces a dipolar electric field, the effect of which can be transmitted through space to the reaction center.

(2) σ-Inductive Effect: The substituent can transmit its effect by the successive polarization of σ-bonds.

(3) π-Inductive Effect: The bond dipole between the substituent and the atom to which it is attached on the molecular framework can transmit its effect to the reaction center by the polarization of the intervening π-electron system.

(4) Mesomeric Effect: The substituent can transmit its effect by the polarization of the π-electron system by direct resonance interaction.

(5) Electromeric Effect: The substituent can transmit its effect by direct resonance interaction with the reaction center through the π-electron system.

It is obvious that the above can be divided into two categories—non-conjugative and conjugative effects. This work deals primarily with the former, and subsequent discussion will center mainly around field and σ-inductive effects.

A quantitative approach to the effects of charged substituents on ionic equilibria was pioneered by Bjerrum,[2] who used simple electrostatic theory to predict the ratio of the dissociation constants of symmetrical dibasic acids. Several years later, Eucken[3] extended the theory to include the effects of dipolar substituents. Both theories looked upon the charge as being embedded in a continuous medium, the dielectric of which was equal to the bulk dielectric (in this case, 80 for water). While the theories predicted good qualitative results, quantitatively much was left to be desired. The approach was far from realistic in that it ignored the presence of a structured molecular framework and its ability to transmit electrical effects. Smallwood,[4] on the other hand, suggested that the electrical effect is transmitted through the molecule instead of the solvent. He rationalized that since the molecular framework is a region of low dielectric, a value of unity should be used for the dielectric constant. When applied to acids containing dipolar substituents, his results were qualitatively good; however, when applied to charged substituents, his results were qualitatively poor.

In the Bjerrum model the molecular framework is ignored, while in the Smallwood approach the solvent is ignored. Both theories represent extreme points of view. Both extremes were taken into account by Kirkwood and Westheimer[5] in their proposal of a new electrostatic model. They viewed the charges or dipoles as being embedded in a structureless spherical or ellipsodial cavity of low dielectric surrounded by a structureless solvent or high dielectric. Because the molecular framework is not empty space, and because it contains a hydrocarbon skeleton which is polarizable, an internal dielectric of about 2 is ordinarily used to evaluate the overall effective dielectric, D_E. The quantitative expression for the effect of dipolar substituents is as follows:

$$\log \frac{K_x}{K_H} = \frac{e\mu \mathrm{Cos}\ \theta}{2{\cdot}3kTR^2D_E}$$

where e is the electronic charge, μ is the difference in group or bond moment between the substituent and hydrogen, R is the distance from the center of the dipole to the ionizable proton, θ is the angle R makes with the direction of the bond moment, D_E is the effective dielectric and kT has its usual meaning.

Roberts and Moreland[6] examined the electrostatic model of Kirkwood and Westheimer with a series of 4-substituted bicyclo[2.2.2]octanecarboxylic acids. Discrepancies were observed between theory and experiment and were of such a serious nature that Tanford[7] 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. For a charge, a depth of 1.0 Å was chosen and for a dipole, a depth of 1.5 Å was used. Siegel and Kormarmy[8] determined the pK_a values for a series of trans-4-substituted cyclohexanecarboxylic acids in several solvent systems and found that both models were qualitatively acceptable, but still inadequate quantitatively.

Stock and Holtz[9] have reexamined and extended the work of Roberts and Moreland on the bicyclo[2.2.2]octane system. They synthesized a series 4-substituted acids and determined their pK_a values in 50% aqueous ethanol, using cells without a liquid junction. The values they obtained were good to ± 0.03 pK_a units. Nevertheless, even with this improved data, the discrepancy between theory and experiment still remains significant.

Recently, Dewar and Grisdale[1] proposed an approach to substituent effects which recognizes the existence of both field and resonance phenomena within the same model. As a measure of field effect, F, the meta-substituted benzoic acids were used as standards and the following expression was proposed:

$$F = (\sigma_x)_m r_{1,3}$$

where $(\sigma_x)_m$ is the meta substituent parameter based on the ionization constants of meta-substituted benzoic acids and $r_{1,3}$ is the distance between the 1- and the 3- carbon atoms of benzene. In order to generate the field parameter for a substituent in any system, one must simply divide F by the distance between the carbon holding the substituent and the carbon holding the reaction center. In this treatment Dewar criticizes 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 contends that the important distance parameter is an r^{-1} term, rather than r^{-2} as in the Kirkwood Westheimer treatment.

Using this field parameter, plus a parameter which measures the combined π-inductive and mesomeric effects of a substituent, Dewar and Grisdale were able to generate σ-values for various substituents on the biphenyl, naphthalene and terphenyl[21] systems. Using these values within a Hammett-type equation, a good correlation between theory and experiment was obtained.

Stock,[9] however, attempted to apply Dewar's field approach to the 4-substituted bicyclo[2.2.2]octyl system with some serious deviations resulting. This probably stems from the inadequacy of the field model used by Dewar. The assumption that field effect is the only important mode of transmission for meta-substituted benzoic acids does not appear to be valid; π-inductive and mesomeric effects must also be operating to some degree. From a conceptual point of view, it would appear that the choice of a saturated system as model for field effect would be more advantageous. Also of a serious nature is the fact that the Dewar-Grisdale treatment does not take into account the orientation of the dipole with respect to the reaction center.[11]

Another apporach to the mode of transmission of polar effects in non-conjugated systems is the σ-inductive model as proposed by Branch and Calvin[12]. Consider 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 ($\varepsilon < 1$) and summed over all pathways as illustrated in the following equation:[21]

$$\lambda_{s \pm n} = \lambda_s \sum_p \left(\varepsilon^{s \pm n}\right)_p$$

Among the chief proponents of the σ-inductive model are Taft and McGowan. Taft[13] has recognized that the effect of a substituent is uniformly decreased as more and more methylene groups are interposed between it and the reaction center. This drop-off factor was found to vary from 2.3 to 3.3 per methylene group. Ritchie,[14] however, has pointed out an inconsistency in the Taft approach. From simple symmetry considerations, similar to those used by Hine[15] for the Hammett equation, he found that σ^*-values for alkyl groups are not consistent with those for other groups.

McGowan[16] has applied a fall-off factor of 2 for the correlation of the dissociation constants of organic Bronsted acids, and other workers such as Wepster[12] and Stevenson and Williamson[18] have estimated fall-off factors of from 2 to 3.

Taft[13] has long postulated that σ^*-values are direct functions of electronegativities. A method has been developed by Chang and Tai[19] for evaluating the inductive effect of a particular substituent on a certain chemical bond in the molecule from the electronegativities and the atomic radii of its constituent elements. The constant for the inductive effect of the group thus obtained is designated as the inductive index of the group. A fair correlation between calculated group electronegativities and Taft's σ-values has been obtained by Hinze, Whitehead and Jaffe.[20]

Dewar,[1,21] however, contends that the so-called inductive effect is nothing more than a field effect and that transmission of substituent effects by the successive polarization of σ-bonds is probably unimportant at positions separated from the substituent by more than one or two bonds. Ehrenson,[22] on the other hand, in his rather detailed review on structure-reactivity relationships, concludes that "Both inductive and direct field interactions as currently pictured are likely contributing factors in substituent effects upon reactivity." Peterson and his students[23] have recently proposed an alternate approach describing the transmission of non-conjugative substituent effects - the hyperconjugative model. This approach retains the electrostatic origin of inductive effect but emphasizes the importance of the pathway between the substituent and the reaction center.

An interesting approach to the understanding of transmission of polar effects has recently been made by Bowden.[24] Since the Hammett reaction constants (ρ-values) are measures of the susceptibility of a reaction to polar effects, Bowden has attempted to correlate these constants with the geometry of the molecular cavity and the nature of the surrounding medium. He felt that such a correlation would be valuable in assessing the relative importance of the various modes of transmission of polar effects.

As a measure of field effect, Bowden used the Kirkwood-Westheimer model and assumed a constant effective dielectric within a given reaction series. The factor $\mathrm{Cos}\theta/R^2$ was taken as a measure of the transmission ability of the hydrocarbon framework of a particular series of substituted carboxylic acids, where R is the distance between the center of the dipole and the reaction center, and θ is the angle between R and the dipole axis. Using the 4-substituted cyclohexanecarboxylic acids as the standard series for the aliphatic and alicyclic systems and the para-substituted benzoic acids as the standard series for the aromatic systems, the ratios of $\mathrm{Cos}\theta/R^2$ of the system in question to the standard were calculated. These ratios were then compared to the relative transmission ability of the systems as reflected by experimentally determined ρ/ρ_o values, where ρ and ρ_o are the reaction constants for the system in question and the standard, respectively.

As a measure of inductive effect, the Branch and Calvin approach was used. The inductive transmission factor, ϵ, has been estimated by several workers. Unfortunately the values vary over a wide range (0.1 to

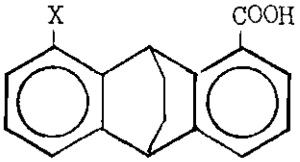
0.6) depending upon the types of atoms in the system. Based on empirical considerations, Bowden has assigned transmission factors to different classes of atoms [ϵ(Sp^3 carbon) = 0.48, ϵ(Sp^2 carbon) = 0.67, ϵ(aryl carbon) = 0.60]. Using the appropriate transmission factor and the same standard systems used in the field effect treatment, comparisons were made between the relative inductive transmitting ability and the ρ/ρ_0 values.

Bowden concludes that for systems involving conjugation the electrostatic model appears to give good agreement between theory and experiment. As for non-conjugative systems, fair correlation is obtained for both models.

In his rather detailed analysis, Bowden has pointed out the strong medium dependence of ρ for molecules substituted at great distances from the reaction center as compared to molecules substituted proximate to the reaction center, where ρ is essentially medium independent. Such an observation, if real, would necessitate the incorporation of electrostatic effects in any theoretical approach to the quantitative evaluation of substituent parameters.[25]

In order to determine the relative importance of the two limiting models (field and σ-inductive), Baker, Parish and Stock[26] have determined the dissociation constants of a series of bicyclo[2.2.2]oct-2-ene-1-carboxylic acids, dibenzo[2.2.2]octa-2,5-diene-1-carboxylic acids and cubane carboxylic acids. They conclude that the efficiency of propagation of the substituent effect is independent of the number of pathways between the substituent and the reaction center and independent of the hybridization of the intervening carbon-carbon bonds. Wilcox and Leung[27] have compared the ionization constants of 4-substituted bicyclo[2.2.2]heptane-1-carboxylic acids with those of the 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids in three solvent systems and have shown that the Kirkwood-Westheimer cavity model is far superior to the π-inductive model in explaining the relative efficiency of propagation of substituent effects.

Recently, Golden and Stock[28] have demonstrated a reversal in the normal substituent effect in 8-substituted ethano-bridged anthracene-1-carboxylic acids (I). The angular dependence of the substituent effects shown by these workers plus the complementary observations reported by Dewar and Grisdale,[1] Wells and Adcock,[11] and Adcock and Dewar[32] provide important evidence for the operation of field effects. Grubbs and Fitzgerald[29] have observed angular dependence of substituent effects in geometrically isomeric 11,12-dichloro-9,10-ethanoanthracenes. However, reversal of substituent effects was not seen as in the case of Golden and Stock.[28] Several rationalizations were offered which were based upon the operation of inductive effect, the inadequacy of the point dipole approximation and the influence of the effective dielectric on the two ends of the substituent dipole. Bowden and Parkin[30] have claimed



I

demonstration of reversal of substituent effects in 8-substituted naphthalene-1-carboxylic acids. Dewar,[31] however, contends that these observations are primarily due to stabilization of the unionized form of the acid because of direct hydrogen bonding between the substituent and the reaction center.

CHAPTER II

INSTRUMENTATION, EQUIPMENT AND SOLVENTS

Instruments and Equipment

Infrared spectra were obtained on a Perkin-Elmer 457 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded with a Varian A-60 spectrophotometer. Positions of nmr absorptions are reported downfield from the position of absorption of the protons on tetramethylsilane (TMS). The abreviations s, d, q and m refer to singlet, doublet, quartet and multiplet, respectively. Mass spectra were recorded on a Varian M-66 mass spectrometer. Measurements of pH were made using a Beckman Research pH meter, Model 1019. Solvents were removed by means of a Rinco rotating evaporator. Gas-liquid chromatography (glc) was conducted on an F and M Gas Chromatograph, Model 700, equiped with six-foot columns of SE-30 on chromosorb W. Column chromatorgraphy was performed in glass columns using silica gel. Constant temperature baths were controlled by a Sargent Thermometer.

Purification of Solvents

Ethanol

Stock 100 percent ethanol was refluxed with magnesium and distilled.

Water

Distilled water was redistilled from alkaline potassium permanganate with protection from carbon dioxide by an Ascarite tube.

CHAPTER III

EXPERIMENTAL

Preparation of 6-Bromo- and 6-Methylspiro[3.3]heptane-2-carboxylic Acids

The general outline for the preparation of 6-bromo- and 6-methylspiro[3.3]heptane-2-carboxylic acids is presented.

Pentaerythrityl Tetrabromide[32] (I)

A three-necked, three liter flask fitted with a powerful mechanical stirrer, thermometer, and dropping funnel was charged with 98 g (0.71 mole) pentaerythritol and 500 ml of dry pyridine. The mixture was cooled in an ice bath and 565 g (3.19 moles) of benzenesulfonyl chloride was added over a period of two hours with care being taken that the temperature did not rise above 35° C. The reaction mixture was stirred one hour and then added slowly to 600 ml of concentrated hydrochloric acid in 750 ml of water an two liters of methanol. The suspension was cooled by adding 500 grams of ice, filtered and washed with five liters of cold water and one liter of cold methanol. The solid was air dried and powdered. This was then added to one liter of diethylene glycol in a three liter, three-necked flask fitted with a mechanical stirrer. The mixture was heated in an oil bath to 160-170°C while 600 g (5.80 moles) of sodium bromide was added. The mixture was heated for 12 hours. After the reaction was cooled, two liters of ice water were added. The resulting white precipitate was filtered, washed with cold water, and air dried. The solid was recrystallized from acetone, yielding 188.3 g (68.4 percent) of I of m.p. 156-157.5°C.

Spiro[3.3]heptane-2,6-dicarboxylic Acid[33]

A five liter round bottom flask, fitted with a reflux condensor and calcium chloride drying tube, was charged with 2.5 liters of amyl alcohol and 57.5 g (2.5 moles) of sodium. When dissolution was complete, 400 g (2.5 moles) of diethyl malonate was added followed by 188.3 g (0.49 moles) of I. The mixture was heated and distilled until the vapor temperature reached 130°C to remove the ethanol formed by ester exchange. Amyl alcohol equal to the volume of the distillate was added and the mixture refluxed three days.

Most of the amyl alcohol was removed by distillation and water added so the remainder would be removed as the azeotrope. The layer which formed over the water was removed and the water extracted with ether. These layers were combined and the ther was evaporated *in vacuo*. The residue was saponified in 3.75 liters of ethanol with 450 g (7.5 moles) of potassium hydroxide at room temperature for 48 hours. The resulting salt was filtered, dissolved in water, treated with decolorizing charcoal and acidified with concentrated hydrochloric acid. The mixture was then extracted with ether for a 48 hour period.

The ether extract was dried over magnesium sulfate and removed *in vacuo*. The solid residue was heated to 200°C in an oil bath, until gas evolution ceased. The brown mass remaining was dissolved in one liter of boiling water and decolorized with charcoal. Diacid II, 24.6 g (27 percent), was recovered by concentration of water *in vacuo*. Recrystallization from ethyl acetate gave white crystals, m.p. 210-211.5°C; neutralization equivalent: calcd. 92.10, found 92.50; ν_{max}^{KBr} 3000, 1700, 1420, 1320, 1250 cm^{-1}.

Diethyl Spiro[3.3]heptane-2,6-dicarboxylate[33] (III)

Diacid II, 24.6 g (0.13 mole), was dissolved in 600 ml of absolute ethanol and 6.2 ml of concentrated sulfuric acid. After 24 hours of refluxing, the reaction mixture was poured into an equal volume of cold ten percent sodium bicarbonate solution. The solution was extracted several times with chloroform. The chloroform was dried over magnesium sulfate and evaporated in vacuo. Diester III, 28.0 g (87 percent), was obtained by distillation, b.p.$_{1.5}$ 95-96°C; ν_{max}^{neat} 2960, 1725, 1460, 1430, 1030 cm^{-1}; nmr ($DCCl_3$) τ: 5.90 (g,4), 7.10 (m,2), 7.75 (m,8), 8.76 (t,6).

6-Carbethoxyspiro[3.3]heptane-2-carboxylic Acid (IV)

Following a previously described procedure for converting diester to half-ester, 49.9 g (0.21 mole) III was refluxed 26 hours with 7.72 g (0.138 mole) of potassium hydroxide in 200 ml of absolute ethanol. The reaction mixture was poured into 500 ml of ice water and extracted with ether in three-200 ml portions to remove unreacted starting material. The water layer was acidified with hydrochloric acid to a pH of about two and extracted with ether in three-200 ml portions. The extract was dried over magnesium sulfate and the ther removed in vacuo. The residue was distilled yielding 17.5 g (39 percent) half-ester X; b.p.$_3$ 157-165°C and solid II. Neutralization equivalent: calcd. 212.25, found 212.63; Anal. calcd. for $C_{11}H_{16}O_4$: C, 62.24; H, 7.61. Found: C, 62.03; H, 7.93; ν_{max}^{neat} 3000, 2900, 2650, 2560, 1730 1700 cm^{-1}; nmr ($DCCl_3$) τ: -1.50 (s,1), 5.85 (q,2), 6.95 (m,2), 7.72 (m,8), 8.80 (t,3).

Ethyl-6-bromospiro[3.3]heptane-2-carboxylate[34] (V)

Mercuric oxide (red) (8.84 g, 0.04 mole) was added to 12.05 g (0.057 mole) of half-ester IV dissolved in 180 ml of bromotrichloromethane. The mixture was heated to 70-80°C with stirring and 8.86 g (0.054 mole) of bromine dissolved in 72 ml of bromotrichloromethane added from a dropping funnel. Upon completion of addition, the reaction was heated for one hour. A white salt precipitated on cooling to room temperature and was filtered off. The filtrate was washed with ten percent sodium bicarbonate to remove unreacted acid. Residual bromine was extracted with sodium bisulfite solution. The organic layer was dried over Drierite and the solvent removed *in vacuo*. Attempts at distillation resulted in pyrolysis. The bromo ester V was obtained in 39 percent yield by silica gel column chromatography using benzene as a solvent; ν_{max}^{neat} 2950, 1730, 1430, 1370, 1340 cm^{-1}; nmr (neat) τ: 5.90 (q,2), 7.45 (broad m,9), 8.85 (t,3).

6-Bromospiro[3.3]heptane-2-carboxylic Acid (VI)

Bromo ester V (0.92 g, 0.0037 mole) was added to 20 ml of 48 percent hydrobromic acid and stirred for ten hours at room temperature. The mixture was diluted with 25 ml of ice water and extracted with three-20 ml portions of chloroform. The chloroform extract was washed with three-20 ml portions of cold water and dried over magnesium sulfate. The chloroform was removed *in vacuo* leaving light tan crystals which were recrystallized from benzene-petroleum ether yielding 0.35 g (43 percent) bromo acid VI, m.p. 122-123°C; neutralization equivalent: calcd. 219.09, found 222.59.

2,6-Dihydroxymethylspiro[3.3]heptane[33] (VII)

To a stirred suspension of 11.0 g (0.29 mole) of lithium aluminum hydride in 500 ml of anhydrous diethyl ether was added dropwise 26 g (0.127 mole) of III in 100 ml of anhydrous ether. Stirring was continued two hours after which the suspension was cooled in an ice bath and 19 ml of water cautiously added dropwise. The resulting sludge was filtered and dissolved in 150 ml of 20 percent (volume) sulfuric acid. The pH of the solution was adjusted to 3.0 by the addition of sodium carbonate. The solution was extracted with ether overnight on a continuous extraction apparatus. The ether was dried over magnesium sulfate and evaporated *in vacuo*. The liquid residue was distilled on a spinning band column yielding 12.88 g VII (65 percent) b.p.$_{0.4}$ 115-117°.

2,6-Dihyroxymethylspiro[3.3]heptane, Monotosylate[33] VIII

To 20 ml of dry pyridine, cooled to 0°C, was added 13.58 g (0.087 mole) of VII. *Para*-toluenesulfonic acid, 16.58 g (0.087 mole) in 20 ml of dry pyridine was added over a period of two hours, the temperature being maintained at 4°. Upon completion of the addition, the reaction mixture was stored in the refrigerator overnight. The mixture was poured onto 100 ml of concentrated hydrochloric acid containing 100 g of crushed ice and extracted with carbon tetrachloride. The CCl_4 solution was dried over $MgSO_4$ and the solvent removed *in vacuo*. A yellow oil remained which partially solidified upon standing. The product was not purified further.

2-Hydroxymethyl-6-methylspiro[3.3]heptane[33] (IX)

To a stirred suspension of 5.1 g (0.13 mole) of lithium aluminum hydride in 300 ml of anhydrous tetrahydrofuran was added dropwise the mixture formed in the preparation of VIII dissolved in 100 ml of anhydrous tetrahydrofuran. Upon completion of addition, the reaction mixture was allowed to reflux 48 hours. The mixture was cooled and 10 ml of water cautiously added. The resulting sludge was filtered and dissolved in 150 ml of cold 20 percent (volume) sulfuric acid. The pH of the solution was adjusted to 3.0 by the addition of sodium carbonate. The solution was extracted with ether. The ether solution was dried over $MgSO_4$ and the solvent evaporated in vacuo. The product (IX) was isolated by distillation on a spinning band column yielding 2.85 g (23 percent); b.p.$_{0.1\ mm}$ 44-45°C; ν_{max}^{neat} 3440-3000 (broad); nmr (neat) 5.22τ (S,1H), 6.75τ (d, 2H, J=6 cps), 7.61-8.76τ (broad absorption, 10H), 9.14τ (d, 3H, J=6 cps).

6-Methylspiro[3.3]heptane-2-carboxylic Acid[38] (X)

Several attempts were made to oxidize the alcohol IX to the corresponding acid X.[35-38] The following procedure is the only successful method found.

To a solution of 10 g (0.0072 mole) of IX dissolved in 2.5 ml of water containing 2.5 ml of concentrated sulfuric acid was added 0.77 g (0.0024 mole) of sodium dichromate in 0.5 ml of water as quickly as possible without allowing the temperature to rise above 15°C. When the mixture had warmed to room temperature an equal volume of water was added and the organic phase extracted with ether. The ether was dried over magnesium sulfate and the solvated evporated in vacuo leaving an oily residue. The acid X was separated from the complex mixture by silica gel column chromatography using benzene as the elutant. Only 0.1 g of the acid, X, could be obtained completely pure; ν_{max}^{neat} 3170, 1700; nmr 7.8τ (q, J=8 cps, 1H), 8.15τ-9.2τ (broad absorption, 9H), 9.68τ (d, J=6 cps, 3H).

Determination of the pKa's of the 6-Substituted Spiro[3.3]heptane-2-carboxylic Acids

The pKa's of the various 6-substituted spiroheptanes were determined by potentiometric titration in 50 percent (weight) aqueous ethanol using a Beckman model 1019 pH meter with glass and calomel electrodes.

Solvent and Solutions

The solvent was prepared by mixing equal weights of freshly purified water and absolute ethanol. The solvent was 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 one liter with 50 percent 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° C 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 were made up to the mark with solvent which had been stored at 25° C. 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° C until they were titrated.

Apparatus and Titrations

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, a NBS thermometer and the tip of the base dispensing burrette. 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 pKa of benzoic acid in 50 percent (weight) aqueous ethanol. The meter was checked with buffer between each set of measurements to insure against drift. Significantly no adjustment was necessary throughout the measurements which took several hours.

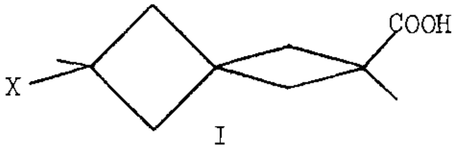
Forty milliliters of the acid solution to be titrated was introduced to the beaker by volumetric pipette. The solution was stirred as standard base; was added rapidly from the burrette. The addition of base was stopped when enough had been added to come within one ml of the aniticipated half-neutralization point of the acid. Stirring was continued until the temperature within the beaker had re-established itself at 25°C. Stirring was then discontinued and the pH of the solution and the volume of base added recorded. This procedure was then repeated with base being added in increments between 0.1 and 0.2 ml until a point one ml beyond the anticipated half-neutralization point was reached.

The equivalence point of the acid solutions were confirmed by titration. Base was added rapidly to a point about one ml short of the anticipated equivalence point. The pH and volume of base were recorded in increments of about 0.1 ml. The equivalence point was taken as the point where the slope of a pH vs volume plot is greatest. This may be calculated from $\Delta pH/\Delta$ ml data and the equivalence point is that point at which this value is a maximum.

CHAPTER IV

DISCUSSION OF RESULTS

In order to compare the various empirical and theoretical approaches to non-conjugative substituent effects and to extend the analysis of the 6-substituted spiro[3.3]heptane-2-carboxylic acids (I), the 6-methyl and 6-bromo spiro acids were synthesized. The dissociation constants in 50% (by weight) aqueous ethanol at 25° are summarized in Table 1.



I

Empirical Correlations

It has been shown by Stock and his students[9,26] 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.[13,29] In constrst, a somewhat unprecise relationship was found between these parameters and the pKa's of the 4-substituted dibenzobicyclo[2.2.2]octadiene-1-carboxylic acids —hydrogen and methyl seriously deviating from the line.[26] The use of these parameters to describe the relative pKa's of the spiro acids is shown

Table 1. The Dissociation Constants of 6-Substituted Spiro[3.3]heptane-2-carboxylic Acids, 25°C.

Substituent	$K \times 10^7$
H*	0.542
Br	1.047
CH_3	0.488

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*Prepared and measured by W. F. Fisher, private Communication

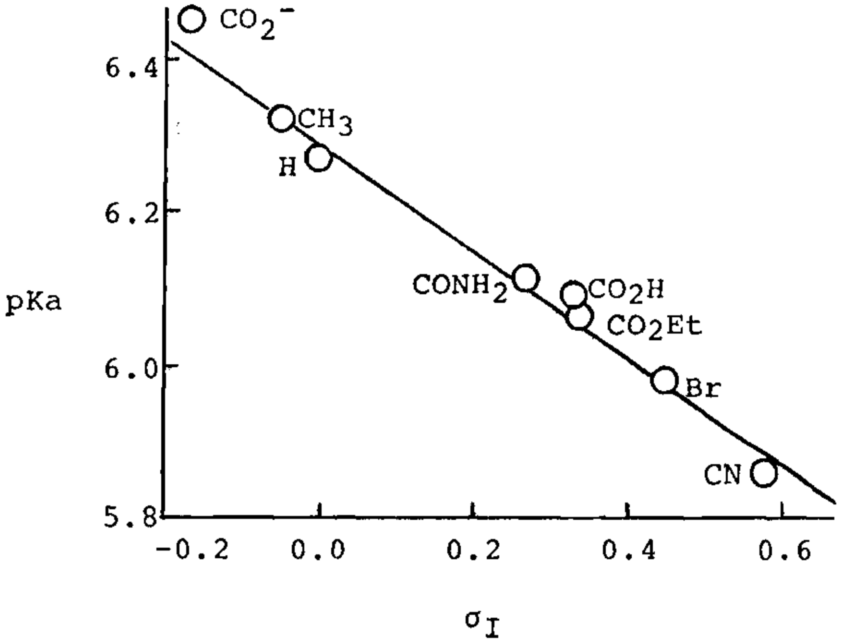


Figure 1. Correlation of pKa with σ_I

in Figure 1. σ_I parameters based on chemical reactivities of substituted acetic acids were taken from Charton's extensive compilation.[40] The correlation equation is given as follows:

$$pKa = -0.693\ \sigma_I + 6.288 \qquad (1)$$

The 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.[42] 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 ($\sigma_{m-CH_3} = -0.07$). 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).[9,26] 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 equation (1), $\sigma_I^{CH_3} = -0.048$ indicating that in this saturated system the $C_{Sp^3} - C_{spiro}$ bond is polar.

Only a fair correlation is obtained on application of the Dewar-Grisdalé approach to the spiro acids since π-inductive and mesomeric effects make up a small part of the total effect in their treatment.

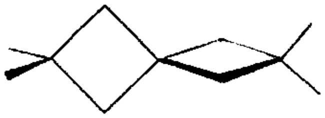
Field Effect

The electrostatic model of Kirkwood and Westheimer[5] is examined next. The equation usually employed to calculate the ratio of dissociation constants of a substituted acid relative to the parent acid is as follows:

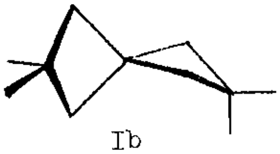
$$\log K_X/K_H = \frac{e\mu \mathrm{Cos}\ \theta}{2.3kTR^2D_E} \qquad (2)$$

where μ is the bond or group moment of the substituent ralative 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 substituent dipole, D_E is the "effective" dielectric constant and e, k and T have their usual significance.

In order to examine the spiro acids by means of equation 2, a knowledge of the parameters R and θ is necessary. It has been shown by several workers that cyclobutane rings may be planar or puckered. The <u>trans</u>-isomer of cyclobutane-1,3-dicarboxylic acid has been shown to have a planar cyclobutane ring in the solid state[43] while the <u>cis</u>-isomer has been shown to be puckered with a dihedral angle of 149°.[44] This angle is consistant with the values found for other cyclobutane compounds in the solid state.[45,46] As far as the conformation of the four-membered ring in solution is concerned, a dihedral angle of approximately 149° has been found for a variety of cyclobutane derivatives by means of dipole moment and NMR analyses.[47,48] The data is also in agreement with microwave spectroscopy studies.[49] It was dicided 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 a dihedral angle of 149° (Ib).



Ia



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 2 and 3. 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).

Tables 2 and 3 compare the calculated log K_X/K_H ratios with the experimental values. Excellent agreement is obtained for the ratios calculated from the spherical model but rather poor results are realized when the ellipsoidal model is used. The ellipsodial

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

	Parameters			Tanford Sphere		Tanford Ellipse		Exp.
Sub	R,Å	μ_X,D	θ°	D_E	log K_X/K_H	D_E	log K_X/K_H	log K_X/K_H
H	6.82	0.40	56° 14^{1}	4.80	0.00	9.88	0.00	0.00
Br	7.07	2.20	52° 12^{1}	4.90	0.23	10.15	0.11	0.28 ± 0.03
CH_3	7.00	0.00	52° 58^{1}	4.84	-0.05	9.96	-0.02	-0.06 ± 0.03

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[a] Planar cyclobutanes

$e = 4.80 \times 10^{-10}$ esμ, $\mu = \mu_X - \mu_H \times 10^{-18}$ esμ/cm, k = 1.381 erg/k°, T = 298°K

Table 3. Parameters and Calculated Values for Log K_X/K_H of 6-X-Spiro[3.3]-heptane-2-carboxylic Acids[a] at 25° by Equation 2.

Sub	Parameters			Tanford Sphere		Tanford Ellipse		Exp.
	R,Å	μ_X,D	θ°	D_E	log K_X/K_H	D_E	log K_X/K_H	log K_X/K_H
H	7.29	0.40	30° 26^1	5.08	0.00	10.19	0.00	0.00
Br	7.66	2.20	28° 18^1	5.43	0.25	11.39	0.12	0.28 ± 0.03
CH_3	7.56	0.00	28° 54^1	5.33	-0.06	10.26	-0.03	-0.06 ± -.03

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[a] Puckered cyclobutanes - 149° dihedral angle

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 over-estimate the value of D_E.

Stock and Holtz[9,26] have proposed a modification of equation 2 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 the following equation:

$$\log K_X/K_H = \frac{e}{2.3kT}\left[\left(\frac{\mu \text{Cos } \theta}{R^2 D_E}\right)_X - \left(\frac{\mu \text{Cos } \theta}{R^2 D_E}\right)_H\right] \qquad (3)$$

where each of the symbols has its usual significance. The results using equation 3 are shown in Table 4. The log K_X/K_H ratios are essentially the same as those obtained from the original formulation of the electrostatic equation (2).

Table 4. Calculated Values of Log K_XK_H for 6-X-Spiro-[3.3]heptane-2-carboxylic Acids from Equation 3.

Sub	Planar Sphere log K_X/K_H	Puckered Sphere log K_X/K_H
H	0.00	0.00
Br	0.23	0.24
CH_3	-0.05	-0.06

CHAPTER V

CONCLUSIONS

The use of the Tanford modification of the Kirkwood-Westheimer cavity model gave excellent agreement between calculated and experimental log K_X/K_H values. It is concluded that in the spiro[3.3]heptane series, this model adequately accounts for the transmission of non-conjugative substituent effects.

The methyl substituent on the spiro[3.3]heptane system is electron-donating with respect to the hydrogen substituent.

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