Transmission of Substituent Effects in Spiro[3.4]octane-2-carboxylic Acid Derivatives[1]

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Received December 29, 1975

The synthesis, separation, and characterization of *cis*- and *trans*-spiro[3.4]-6-octanone-2-carboxylic acids (**6a** and **6b**, respectively) is described. The pK_a's for these keto acids, for spiro[3.4]octane-2-carboxylic acid (**5**), spiro[3.4]-6-octene-2-carboxylic acid (**4**), and a cis–trans mixture of 6-methylenespiro[3.4]octane-2-carboxylic acid (**9**) have been determined. The experimentally determined ΔpK_a's are compared with values calculated using spherical and ellipsoidal cavities in the Tanford-modified Kirkwood–Westheimer expression. The base-catalyzed deuterium exchange of the spiro keto acids at C_5 and C_7 is also briefly discussed.

In an earlier publication[2] we suggested several geometric characteristics which should prove useful in attempts to evaluate the relative applicabilities of the Kirkwood–Westheimer electrostatic field model and the inductive model for polar substituent effects. In that report[2] the synthesis of a model spirooctane system was described. Subsequently we applied similar structural requirements to demonstrate the dependence of acidities and reactivities of carboxylic acids and esters on the angular orientation of remote dipoles.[3,4] The inductive model cannot accommodate such an angular dependence. The results were understandable in terms of the K and W field model, but were not quantitatively in accord. Numerous studies during the past 10 years have supported electrostatic field models in various modifications as more effective than inductive models.[5–8]

The initial objective of the present study was the preparation of the spiro[3.4]-6-octanone-2-carboxylic acids (**6a** and **6b**) (Scheme I). This system with a fairly rigid molecular framework facilitates reasonably accurate estimates of R and $\cos\theta$ employed in the K and W expression. These keto acids also possess a molecular cavity which approximates the shape of an ellipsoid of revolution more closely than other systems which had been studied at the time that this work was initiated.[9] Thus it was of interest to test whether the success of the K and W model in predicting ΔpK_a's for more "ellipsoid-shaped" systems was sensitive to choice of ellipsoidal or spherical cavity models. Studies of relative reactivities at the 5 position of geometrically isomeric spiro[3.4]octane-2-carboxylic acids were also envisioned. For example, comparisons between **6a** and **6b** or between **7a** and **7b** of rate-constant ratios k_5/k_7 for base-catalyzed deuterium exchange (at α methylene carbons) should provide information regarding charge–charge and charge–dipole effects on rate processes. These latter studies are yet in preliminary stages.

Results

Syntheses and Characterizations. The preparations of the various spiro[3.4]octane derivatives employed in this study are outlined in Scheme I.

Catalytic hydrogenation of the olefinic acid **4**[10] provided the parent saturated acid previously reported by Buchta.[11] Oxymercuration–demercuration of **3** followed by dichromate oxidation and decarboxylation afforded a mixture of the isomeric keto acids **6a** and **6b**. The intermediates **3a** and **3b** were used directly without complete characterization because of purification difficulties. The keto acids **6a** and **6b** were separated chromatographically. The cis isomer **6a** melts at 81–83.5 °C; the trans isomer **6b** melts at 85.5–87.5 °C. Geometric assignments were made on the basis of the dipole moments of the corresponding methyl esters.[12] The dipole moment of **7a** is 3.40 D, that for the trans isomer **7b** is 2.82. The order of

Scheme I

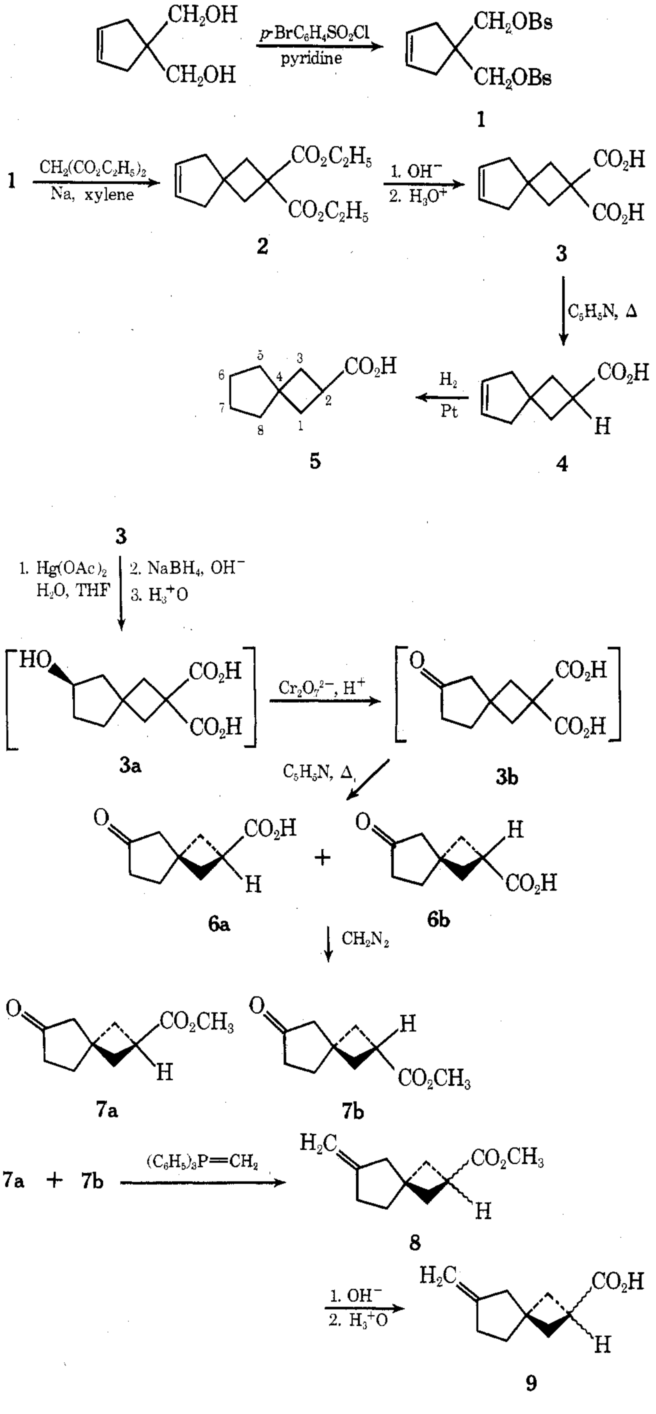


Table I. Thermodynamic pK_a's for Spiro[3.4]octane-2-carboxylic Acid and Related Acids in Water at 25 °C

Compd	pK_a[a]	Std dev[b]
4	4.754	(0.008)
5	4.856	(0.003)
6a	4.585	(0.004)
6b	4.567	(0.003)
9	4.747	(0.005)
$C_6H_5CO_2H$	4.192[c]	(0.004)

[a] Each pK_a is considered accurate within ±0.025. [b] The standard deviation for the 18 points of a two-run set is shown in parentheses. See the Experimental Section for further discussion. [c] Average of four separate determinations performed at various times during the period of the other measurements.

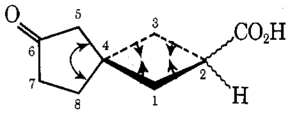
elutions (trans before cis) for **6a** and **6b** (liquid chromatography) and for **7a** and **7b** (GLC) usually expected is also in accord with the geometric assignments. That the carbonyl is located at the 6 position and not the 5 position was demonstrated by the exchange of four protons (followed by NMR) when the keto acid is dissolved in D_2O containing NaOD at room temperature. The dominant mass spectral fragmentation paths for both the keto acids and the keto esters appear to involve elimination of acrylic acid or methyl acrylate from the molecular ion as evidenced by a prominent peak at *m/e* 96.

In order to assess the extent to which rehybridization ($sp^3 \rightarrow sp^2$) at C_6 is responsible for the increased acidity of **6a** and **6b** over **5** (Table I), a mixture of the keto esters was converted to the 6-methylene esters by the Wittig reagent. Hydrolysis to the mixture of 6-methylene acids **9** provided the requisite model compounds.

Acid Dissociation Constants. The thermodynamic pK_a's were determined in water at 25 °C as outlined in the Experimental Section. They are listed in Table I. Although the pK_a's for **6a** and **6b** are nearly identical, the possibility of epimerization at C_2 during the pK_a determinations was excluded. This was done by reisolating the acids (following simulated pK_a measurements) with unchanged geometry which was demonstrated by conversions to methyl esters and examination of the separate esters on GLC.

Discussion

The introduction of a carbonyl group at C_6 increases the acidity of **6a** and **6b** over **5** by about 0.28 pK_a units. However, not all of this modest acid enhancement can be attributed to an electrostatic effect of the carbon–oxygen dipole. As seen in Table I, a carbon–carbon double bond at C_6 results in a pK_a lowering of 0.10 when compared with the saturated parent acid **5**. This increase in acidity is the same whether the carbon–carbon double bond is endocyclic or exocyclic. It is unlikely that these double bonds at such a remote position (ϵ to the CO_2H carbon) exert their influence via successive polarizations of intervening σ bonds. Dewar, for example, has concluded that the σ-inductive effect may be unimportant at positions separated from a substituent by more than one or two bonds.[14] Nonetheless, it would be reassuring to find that straight-chain olefinic acids bearing the carbon–carbon double bond at remote positions possessed the same pK_a as the saturated analogue. However, data bearing on this question are surprisingly few and sometimes conflicting, and a precise indication of the probable error is rarely found. Furthermore, acidity data for a series of unsaturated acids obtained by one group must usually be compared with the acidity of saturated analogues determined by different workers.[15] An alternate source of the acidity enhancement of **4** and **9** over **5** (and a portion of the increase in acidity of **6a** and **6b** over **5**) could be a conformational transmission effect similar to that discovered by Barton and co-workers.[16] These effects presumably arise from conformational distortions which are relayed to the reaction site where rehybridization is usually occurring. The transmission is believed to be effected by small flexings of valency angles and changes of atomic coordinates. As applied to **6a** or **6b**, this would suggest that the introduction of the carbonyl group at C_6 would result in a slight increase in the $C_5C_4C_8$ bond angle compared with **5**. The effect of this would be a small contraction of $\angle C_1C_4C_3$ and $\angle C_1C_2C_3$. Such a deformation of the four-membered ring would increase the s character in external bonds at C_2 and thus enhance the acidity.[17] In support of this hypothesis is the observation that the $C_2C_3C_4$ bond angle in cyclopentanone[18] (105.1°) is slightly expanded [with $\angle C_1C_2C_3$ contracted (102.2°)] compared with the average CCC bond angle (103.3°) for puckered cyclopentane.[19] A similar conformational transmission could be expected with an exomethylene group at C_6 of the spirane system (compounds **9**) or internal unsaturation at C_6 (compound **4**).[20] Although these interatomic angle deformations are small, they may reflect only a portion of interorbital angle changes. It would also seem reasonable that in systems wherein substantial rehybridization is absent at the reacting site, rigid molecular frameworks would provide the best opportunity to observe conformational transmission effects. For in these cases the alterations of valency angles at a remote site would be directly linked to the reaction site by concomitant changes in hybridization of methylene groups incapable of rotational accommodation.[22]



The data in Table I and the discussion above suggest that as little as 0.18 pK unit of the acid-strengthening effect of the carbonyl group at C_6 may be attributable to a charge–dipole interaction. Thus it is against approximately this value that the applicability of the various modifications of the K and W model is measured. The experimental and calculated[23] values for log K_X/K_H are listed in Table II along with molecular parameters and effective dielectric constants.

These calculations show that the ellipsoidal cavity model provides the better agreement with experiment. It should be recalled that the portion of the experimental ΔpK's attributable to interactions directly addressed by the K and W expressions may be close to 0.18. It is interesting that the nearly identical ΔpK values calculated for the two geometric isomers may be the consequence of a more favorable cos θ value for **6b** almost perfectly compensated by a shorter distance, R, and a lower effective dielectric constant for **6a**. For those advocates of the inductive model (who remain unconvinced of the dependency of reactivity on the angular orientation of substituent dipoles) these data may buttress their skepticism.

The study of base-catalyzed deuterium exchange α to the cyclopentanone carbonyl in **6a** and **6b** has not yet been completed. However, several preliminary observations provide structural insight. The high-field portion of the ^1H NMR spectrum of the trans acid **6b** (in H_2O) is shown in Figure 1. Spectra of the sodium salt of **6b** in water and in NaOD–D_2O determined at room temperature at 18, 78, and 208 min are also shown in Figure 1. The three two-proton singlets at 2.13, 2.27, and 2.39 ppm in **6b** show that the methylenes at C_7 and C_8 are not coupled. The remaining multiplet partially obscured by these singlets is produced by the cyclobutane methylenes coupled to the C_2 proton whose multiplet is centered at 3.1 ppm. When **6b** is converted to its sodium salt (titrimetrically using aqueous NaOH) and then dissolved in water, a methylene singlet attributed to C_5 H_2 becomes a

Table II. Experimental and Calculated[23] Values of ΔpK for 6a and 6b and K–W Parameters

		Sphere		Ellipsoid		Exptl
Compd	R, Å; cos θ	D_E	ΔpK	D_E	ΔpK	ΔpK
6a	6.94; 0.688	4.92	0.442	9.64	0.226	0.271
6b	7.68; 0.989	5.32	0.479	11.65	0.219	0.289

multiplet presumably via long-range coupling with the cyclobutane methylenes. This leaves two singlets at 2.17 (C_8 H_2) and 2.39 ppm (C_7 H_2). It is seen that the two-proton singlet at 2.39 ppm is completely removed by exchange after 18 min. Most of the second set of exchangeable methylene protons have also been replaced by deuterium at this point. However, further exchange is clearly observable during the following 3-h period. During this time, the complex multiplet between 1.7 and 2.1 ppm slowly diminishes (approximately 90% of the second methylene set exchanged) and evolves into an approximate doublet (J = 8 Hz). Excluding the C_8 H_2 singlet, the remainder of the spectrum then closely approximates the $A_2A_2'X$ system observed for cyclopropylamine in benzene which has been analyzed by Hutton and Schaefer.[28] These spectra confirm the structure of **6b** and are in accord with expectation that the C_7 methylene protons should exchange more rapidly than the C_5 methylene protons. Both steric and electrostatic effects contribute to this order. Similar preliminary observations have been made with **6a.** A quantitative study comparing the exchange behavior of the two isomers and directed toward a separation of the steric and electrostatic effects is in progress.

Experimental Section[29]

1,1-Dimethylol-3-cyclopentene Di-*p*-bromobenzenesulfonate (1). The dibrosylate was prepared as previously described for the ditosylate.[2] Reaction of 89.2 g (0.696 mol) of 1,1-dimethylol-3-cyclopentene[2] in 1 l. of dry pyridine with 400 g (1.565 mol) of *p*-bromobenzenesulfonyl chloride afforded the crude dibrosylate. This was recrystallized from a 50/50 by volume mixture of benzene/petroleum ether (bp 60–90 °C) affording 288 g (73%) of the dibrosylate, mp 143–146 °C.

The dibrosylate (1) from a similar preparation was recrystallized a second time from methanol, affording an analytical sample, mp 146–147 °C.

Anal. Calcd for $C_{19}H_{18}O_6Br_2S_2$: C, 40.32; H, 3.18; Br, 28.75; S, 11.31. Found: C, 40.53; H, 3.34; Br, 28.70; S, 11.27.

The ^1H NMR spectrum of 1 in $CDCl_3$ shows a narrow multiplet at δ 7.72 (8, aromatic) and three singlets at δ 5.54 (2, vinyl), 3.95 (4, $-CH_2OB_s$), and 2.18 (4, allyl).

Diethyl spiro[3.4]-6-octene-2,2-dicarboxylate (2) was prepared in 75% yield (based on unrecovered dibrosylate) by the cycloalkylation of diethylmalonate by the dibrosylate 1 as previously reported[2] using the corresponding ditosylate.

Spiro[3.4]-6-octene-2,2-dicarboxylic acid (3), mp 165–169 °C, was prepared in 86% yield by the hydrolysis of the diester 2 as previously described.[2]

Spiro[3.4]octane-2-carboxylic acid[30] (5) was prepared by the platinum-catalyzed hydrogenation of 4[2] in ethanol at atmospheric pressure. The sample was analytically pure and the NMR spectrum (CCl_4) showed no residual olefinic hydrogen. The saturated acid obtained in this way in 91% yield was a waxy solid, mp 31–32 °C (lit.[30] mp 39 °C).

***cis*- and *trans*-Spiro[3.4]-6-octanone-2-carboxylic Acid (6a and 6b).** To a suspension of 35.8 g (0.112 mol) of mercuric acetate in 95 ml of water plus 95 ml of tetrahydrofuran was added 19.9 g (0.101 mol) of the olefinic diacid 3 dissolved in 380 ml of water. The mixture was stirred for 55 h. Then 111 ml of 3.0 N sodium hydroxide was added, followed by a solution of 2.13 g of sodium borohydride and 1.12 g of sodium hydroxide in 190 ml of water. The resulting black precipitate was filtered. The filtrate was acidified with 6 N hydrochloric acid to a pH of approximately 6. This aqueous phase was then subjected to continuous ether extraction for 24 h. The ether extract was dried and concentrated affording 14.3 g (65%) of 6-hydroxyspiro[3.4]octane-2,2-dicarboxylic acid (**3a**) which was used in the next step without further purification.

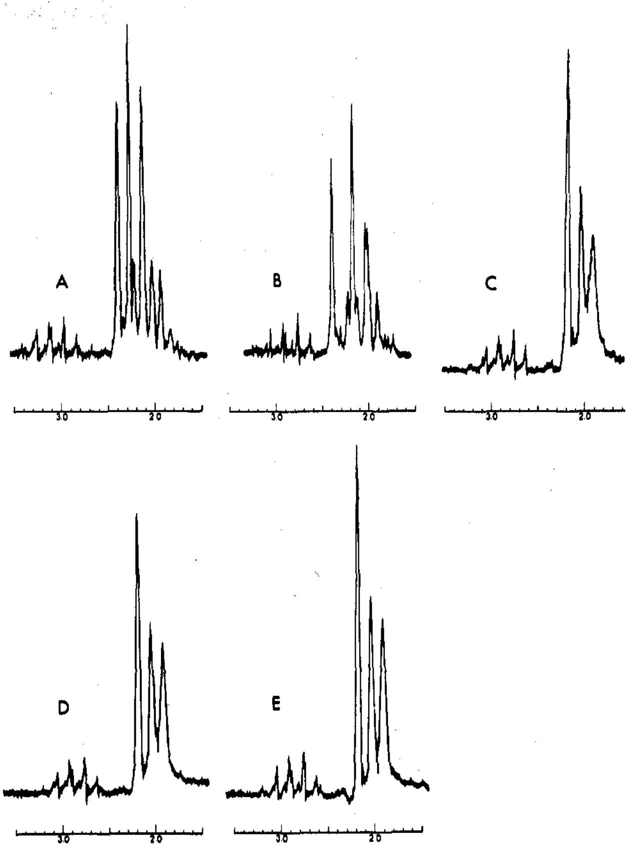


Figure 1. ^1H NMR spectra of (A) **6b** in H_2O, (B) sodium salt of **6b** in H_2O, (C) sodium salt (40 mg) in 0.6 N NaOD–D_2O after 19 min, (D) after 78 min, and (E) after 208 min at 35 °C.

To a stirred solution of 7.56 g (0.0353 mol) of the hydroxy diacid **3a** in 140 ml of ether was added a solution prepared from 5.95 g (0.0585 mol) of sodium dichromate dihydrate and 7 ml of 96% sulfuric acid diluted with water to 175 ml. During the addition, which required 10 min, the temperature was maintained at 25 °C. After 55 h, the ether layer was separated and the aqueous layer extracted with six 150-ml portions of ether. The combined ether extract was dried and concentrated to give 6.5 g (86%) of the crude spiro[3.4]-6-octanone-2,2-dicarboxylic acid (**3b**). Similar oxidations of hydroxy diacid **3a** yielded an additional 24 g of the keto diacid. The infrared spectrum of **3b** (KBr disk) shows three bands in the carbonyl region at 1680, 1710, and 1740 cm^{-1} and a broad absorption centered at 3200 cm^{-1} (acid O–H). These products were subjected to decarboxylation without further purification.

A solution of 5.8 g (0.028 mol) of the above keto diacid **3b** in 37 ml of pyridine was boiled under reflux for 6 h. The resulting mixture was cooled, acidified with 84 ml of 6 N hydrochloric acid, and subjected to continuous extraction with ether for 24 h. The ether extract was dried and concentrated to give 4.0 g of a yellow oil. A second decarboxylation of 10.9 g of **3b** afforded 7.2 g of yellow oil.

The isomeric keto acids **6a** and **6b** were separated chromatographically using a 7 × 75 cm column packed with a silicic acid–Celite mixture. The mixture was prepared from 500 g of 100 mesh silicic acid (Mallinckrodt), 100 g of Celite, 51 ml of water, and 270 ml of methanol. Using columns of this size and crude keto acid mixtures (2–3 g) the separations were effected. An initial chromatograph was followed by second chromatographs on intermediate fractions of the partially purified isomers. The trans isomer was eluted with a 45/30/1 (v/v/v) mixture of hexane, ether, and acetic acid, respectively. The cis isomer was eluted with a 45/45/1 (v/v/v) mixture of hexane, ether, and acetic acid, respectively. From a total of 8.02 g of the original unresolved crude mixture of keto acids was obtained 1.97 g of the trans keto acid **6b** as an oily semisolid. GLC (5 ft × 0.12 in. FFAP) analysis of the methyl ester (prepared from diazomethane) revealed its isomeric purity to be approximately 88%. Two recrystallizations from ether afforded 0.905 g of **6b,** mp 85.5–87.5 °C, containing less than 2% of the cis isomer. From the same 8.02 g of unresolved sample was similarly obtained 1.95 g of the cis keto acid **6a** as an oily semisolid. Its isomeric purity was also approximately 88%. Two recrystallizations of this material from ether gave 0.814 g of **6a,** mp 81–83.5 °C, containing less than 2% of the trans isomer. The mixture melting point of pure **6a** added to **6b** was 45–57 °C.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found for **6b:** C, 64.29; H, 7.08. Found for **6a:** C, 64.50; H, 7.23.

The infrared spectra (saturated in CCl_4) of **6a** and **6b** show bands at 1704 (CO_2H carbonyl) and 1744 cm^{-1} (ketone C=O) and a broad absorption envelope in the region 2500–3400 cm^{-1} attributable to a combination of O–H and C–H stretching vibrations. Subtle differences mainly in intensities were observable in the fingerprint region.

The ^1H NMR spectrum of the trans keto acid **6b** ($CDCl_3$) shows the following: δ 10.37 (s, 1, CO_2H), 2.8–3.4 (m, 1, $J \sim 8$ Hz, C_2 H), and 1.7–2.5 (m, 10, ring CH_2). The ^1H NMR spectrum of the cis isomer **6a** under the same conditions ($CDCl_3$) shows the following: δ 9.60 (s, 1, CO_2H), 2.8–3.5 (m, 1, $J \sim 8$ Hz, C_2 H), and 1.7–2.6 (m, 10, ring CH_2). The mass spectra for **6a** and **6b** are very similar. In addition to other lower molecular weight fragments, the trans isomer **6b** shows at 15 eV the following peaks: *m/e* (rel intensity) 168 M^+ (100), 150 $M^+ - H_2O$ (36), 140 M^+ − CO (12), 123 $M^+ - CO_2H$ (10), 96 $M^+ - CH_2{=}CHCO_2H$ (64). The corresponding intensities for these same peaks in the mass spectrum of the cis isomer **6a** at approximately the same ionization voltage are 100, 18, 8, 4, and 28, respectively.

Methyl *trans*-Spiro[3.4]-6-octanone-2-carboxylate (7b). A 0.432-g (2.57 mmol) sample of pure trans keto acid **6b** in 10 ml of methanol was converted to the methyl ester using ethereal diazomethane. After removing the ether, the residual oil was distilled under reduced pressure using a micro-Hickman still. The ester distilled at 0.025 mmHg at a pot temperature of 55–70 °C. The ester (a colorless oil) [0.385 g (82%)] contained less than 2% of the cis isomer as determined by GLC using a 5 ft × 0.25 in. DEGS on Chromosorb W column.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.69. Found: C, 66.02; H, 7.47.

The spectral features are as follows: ir (CCl_4) 1740 cm^{-1} (ester and ketone C=O); NMR ($CDCl_3$) δ 3.70 (s, 3, CO_2CH_3), 2.80–3.45 (m, 1, C_2 H), 1.8–2.7 (m, 10, ring methylene protons); MS (15 eV) *m/e* (rel intensity) 182 M^+ (38), 123 $M^+ - CO_2CH_3$ (17), 96 $M^+ - CH_2{=}CHCO_2CH_3$ (100).

Methyl *cis*-Spiro[3.4]-6-octanone-2-carboxylate (7a). Using the same procedure as employed for the trans isomer, 0.421 g (2.50 mmol) of the cis keto acid **6a** was esterified. Distillation [pot temperature 55–70 °C (0.025 mm)] of the product yielded 0.378 g (83%) of **7a** as a colorless oil. GLC analysis (as above) showed it to contain less than 2% of the trans isomer.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.69. Found: C, 65.86; H, 7.75.

The spectral features are very similar to those of the trans isomer and are as follows: ir (CCl_4) 1740 cm^{-1} (ester and ketone C=O); NMR ($CDCl_3$) δ 3.68 (s, 3, CO_2CH_3), 2.87–3.50 (m, 1, C_2 H), 1.8–2.7 (m, 10, ring methylene protons); MS (15 eV) *m/e* (rel intensity) 182 M^+ (35), 123 $M^+ - CO_2CH_3$ (10), 96 $M^+ - CH_2{=}CHCO_2CH_3$ (100).

Methyl *cis*- and *trans*-6-Methylenespiro[3.4]octane-2-carboxylates (8). Freshly distilled dimethyl sulfoxide (5.00 ml) was treated with sodium hydride (0.281 g of ca. 57% NaH in mineral oil) which had been washed repeatedly with pentane under nitrogen. The total base content was determined by titration. Methyltriphenylphosphonium bromide (1.09 g, 2.79 mmol) was dissolved in 4 ml of warm Me_2SO and added to 2 ml (2.66 mequiv) of the Me_2SO–carbanion solution. This reaction mixture was stirred at room temperature for 20 min. To this Wittig reagent was added 0.461 g (2.52 mmol) of a ca. 50/50 mixture of the keto esters **7a** and **7b**. An additional 1 ml of Me_2SO was added. The light-orange solution was stirred at room temperature for 2 h and poured into 25 ml of water. This was acidified with 0.1 N HCl and continuously extracted with pentane for 24 h. The extract was dried and concentrated to a yellow oil (0.480 g). The mixture of esters was isolated from this reaction mixture by preparative GLC using a 5 ft × 0.25 in. DEGS on Chromosorb W column at 160 °C. In addition to 0.065 g of unreacted starting esters was collected 0.231 g (59% based on unrecovered starting keto esters) of the two methylene esters as a ca. 50/50 mixture. These isomers were not appreciably separable with a variety of columns. Partial resolution was achieved with the DEGS and FFAP columns, but it was not sufficient for preparative scale separation.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.30; H, 8.81.

The spectral features of the mixed esters **8** are as follows: ir (neat) 3070 (olefinic C–H), 1730 (ester C=O), 1660 (>C=CH_2), and 875 cm^{-1} (gem-disubstituted alkene C–H bend); NMR ($CDCl_3$) δ 4.77 (narrow m, 2, >C=CH_2), 3.61 (s, 3, CO_2CH_3), 2.50–3.16 (m, 1, C_2 H), and 1.50–2.50 (m, 10, ring methylene protons); MS (12 eV) *m/e* (rel intensity) 180 M^+ (33), 121 $M^+ - CO_2CH_3$ (35), 94 $M^+ - CH_2{=}CHCO_2CH_3$ (100).

***cis*- and *trans*-6-Methylenespiro[3.4]octane-2-carboxylic Acids (9).** A 0.151-g (0.840 mmol) sample of the methylene esters **8** was hydrolyzed in 0.423 ml of 1.99 N aqueous NaOH at 80 °C for 3 h. The cooled basic reaction mixture was then continuously extracted with ether for 12 h. The aqueous phase was acidified and continuously extracted with ether for 12 h. This extract was dried and concentrated affording 0.133 g (95%) of the methylene acids **9** as an oil. GLC analyses of this acid mixture (and a small portion reconverted to the methyl esters with diazomethane) showed it to contain only a mixture of the geometric isomers.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.62; H, 8.60.

The spectral features of the mixed methylene spiro acids **9** are as follows: ir (neat) 3070 (olefinic C–H), 2500–3600 (broad envelope, C–H and acid O–H), 1700 (CO_2H carbonyl), 1660 (>C=CH_2), and 875 cm^{-1} (gem-disubstituted alkene C–H bend); NMR (CCl_4) δ 11.6 (s, 1, CO_2H), 4.80 (narrow m, 2, >C=CH_2), 2.6–3.3 (m, 1, C_2 H), and 1.50–2.50 (m, 10, ring methylene protons); MS (15 eV) *m/e* (rel intensity) 166 M^+ (63), 121 $M^+ - CO_2H$ (77), 94 $M^+ - CH_2{=}CHCO_2H$ (100).

Measurements of pK_a's. These measurements were performed in water at 25 °C. The values were determined potentiometrically with the aid of a Beckman Research pH meter. The electrodes (glass, Beckman Model 39000 or 41263, and calomel, Beckman Model 39071 or 39402) were standardized using an aqueous potassium hydrogen phthalate buffer (0.0500 M) and an aqueous phosphate buffer (0.02500 M KH_2PO_4 and 0.02500 M Na_2PO_4). Titrations were carried out using approximately 0.01 N NaOH. Distilled or deionized water was redistilled and stored under nitrogen prior to preparation of stock solutions. Titrations were conducted under nitrogen in a water-jacketed cell maintained at 25.0 °C.

A modified version of the method described by Albert and Serjeant[31] was used to calculate the pK_a values from the experimental data. The method involves a preliminary determination of the concentration of the titrating base. Next a value for the pK_a was calculated for each of the nine points in the midrange of the titration by use of the equation $pK_a = pH + \log [HA]/[A^-]$. The activities of the species were calculated using appropriate activity coefficients. A correction (0.025 pH units) was made for the liquid junction potential error.[32] The pK_a values reported are the average values for 18 points of a two-run set and are considered to be accurate to 0.025 pK units (the approximate uncertainty in the liquid potential correction). The pK_a of benzoic acid was determined at various times during the course of this study. The largest difference between average values for sets of two runs was 0.013 and the average deviation was 0.004, which can be taken as a measure of the precision.

Test for Possible Equilibration of 6a and 6b during pK_a Measurements. Because of the near identity in pK_a values for spiro keto acids **6a** and **6b**, the possibility of epimerization at C_2 was investigated. Samples of **6a** and **6b** were separately subjected to conditions of the pK_a determinations. The basic solutions were acidified, extracted with ether, and dried. The recovered acids were then converted to their methyl esters by diazomethane and examined by GLC (5 ft × 0.25 in. FFAP on Chromosorb W at 180 °C). No detectable (<2%) epimerization had occurred.

Registry No.—**1,** 59015-16-6; **3,** 14377-07-2; **3a,** 59015-17-7; **3b,** 59015-18-8; **4,** 14377-08-3; **5,** 18386-63-5; **6a,** 59015-19-9; **6b,** 59015-20-2; **7a,** 59015-21-3; **7b,** 59015-22-4; *cis*-**8,** 59015-23-5; *trans*-**8,** 59015-24-6; *cis*-**9,** 59015-25-7; *trans*-**9,** 59015-26-8.

References and Notes

(1) Abstracted in part from the Ph.D. Thesis of Curtis Lee McLendon, University of California, San Diego, and San Diego State University, 1974.

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(7) C. F. Wilcox and C. Leung, *J. Am. Chem. Soc.*, **90,** 336 (1968).

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(9) Subsequent to our report[2] on the synthesis of our parent system Liotta and co-workers[6] described the syntheses and pK_a measurements of 6-substituted spiro[3.3]heptane-2-carboxylic acids which also approximate an ellipsoid of revolution.

(10) R. D. Miller and M. Schneider [*Tetrahedron Lett.*, 1557 (1975)] have recently employed this olefinic acid as a starting point for their synthesis of spiro[3.4]octa-1,5,7-triene.

(11) E. Buchta and K. Geibel, *Justus Liebigs. Ann. Chem.*, **648**, 36 (1961).

(12) Dielectric constants of solutions were measured using a Dipolmeter Type DM 01 (Wissenschaftlich-Technische Werkstätten GmbH, Weilheim,-Germany). The Guggenheim method[13] was employed for obtaining dipole moments.

(13) E. A. Guggenheim, *Trans. Faraday Soc.*, **74**, 2193 (1952).

(14) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3548 (1962).

(15) (a) See G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961, for a compendium of acid-dissociation constants and a discussion of measurement methods. (b) A reviewer has suggested that an estimate of the magnitude of an inductive effect of our carbonyl at C-6 might be made on the basis of data from appropriate 6-keto acids or from analogous chloro acids. Such data do not appear to be available, and were they available their ΔpK magnitudes would not suffice to establish the better model accounting for the transmission of the substituent's effect. The question regarding the source of the unexpected acid-strengthening effect of the carbon–carbon double bond at the 6 position may be resolved by pK_a comparisons of **4**, **5**, and *trans*-spiro[3.4]-5-octene-2-carboxylic acid (see note 22).

(16) See D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960), for evidence that a remote carbon–carbon double bond can influence rates of base-catalyzed condensations of benzaldehyde with steroidal ketones.

(17) The relationship between electronegativity and s character has been documented by H. A. Bent, *Chem. Rev.*, **61**, 275 (1961), and by J. Hinze and H. H. Jaffé, *J. Am. Chem. Soc.*, **84**, 540 (1962), among others. A wealth of data are available which demonstrate the effects of bond-angle deformation on acidities (presumably through s-character alterations). See, for example, K. B. Wiberg and B. R. Lowry, *ibid.*, **85**, 3188 (1963); F. W. Baker, R. C. Parish, and L. M. Stock, *ibid.*, **89**, 5677 (1967); A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *ibid.*, **91**, 529 (1969); A. G. Cook and G. W. Mason, *J. Org. Chem.*, **37**, 3342 (1972); A. Streitwieser, Jr., P. H. Owens, R. A. Wolf, and J. E. Williams, Jr., *J. Am. Chem. Soc.*, **96**, 5448 (1974), and references cited therein.

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(20) The $C_3C_4C_5$ bond angle of cyclopentene is reported to be 104.0°; that for $C_2C_3C_4$ is 103.0°.[21]

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(22) A planned test for conformational transmission in these spirane systems is the determination of the pK_a's of 5-methylenespiro[3.4]octane-2-carboxylic acid or spiro[3.4]-5-octene-2-carboxylic acid. In these derivatives the bond-angle deformations conformationally transmitted to C_2 should decrease the s character of its external orbitals. ^{13}C–H coupling constants at C_2 may also reveal these effects.

(23) Because of uncertainties in the conformations of the five-membered ring and to greatly simplify calculations estimating R and $\cos\theta$, the cyclopentane ring was assumed to be planar. Consequently a 108° bond angle was employed for the five-membered ring. Calculations were performed with the cyclobutane ring either planar or bent with a dihedral angle of 152.6°[24] (moving the carboxyl group into a more equatorial position). The difference in ΔpK_a's (≤ 0.01) obtained using these two geometries were insignificant and thus only the "planar model" results are given. Other bond angles and lengths used[24-26] were 1.55 Å for the C–C bonds of the five-membered ring, 90° and 1.55 Å for the C–C–C bond angles and C–C bond lengths, respectively, for the cyclobutane, 109° for the H–C_2–CO_2H bond angle, and 1.50 Å for the C–CO_2H bond. The ketone C=O bond was assigned a length of 1.24 Å and the position of the carboxyl proton located at 1.45 Å beyond the carboxyl carbon on the extension of the C–C bond. The C=O dipole was assigned a group moment of 3.0 D from Smyth's data[27] for cyclopentanone.

The effective dielectric constants (D_E) and ΔpK's were calculated from the Kirkwood–Westheimer equations using alternately a sphere and an ellipsoid to approximate the molecular cavity. Tanford's modification was employed locating the point dipoles and charges 1.5 and 1.0 Å, respectively, below the surface of the cavity. A value of 78.5 was used for the external (solvent) dielectric constant and a value of 2.0 for the internal dielectric constant.

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(29) Melting points were determined on a Fisher-Johns or a Hoover apparatus and are corrected. Infrared spectra were obtained on a Perkin-Elmer Model 621 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Model A-60 spectrometer. Gas–liquid chromatographic analyses and preparative-scale separations were conducted with a Varian Model 90-P or Model A-700 chromatograph. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E spectrometer. Calculations were performed with the aid of IBM Model 1130 and Model 360/45 computers. Analyses were performed by M-H-W Laboratories.

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(32) The method of A. L. Bacarella, E. Grunwald, H. P. Marshall, and E. L. Purlee [*J. Org. Chem.*, **20**, 747 (1955)] was employed.

Carbon Acids. 10. Resonance Saturation of Substituent Effects in the Fluorene Series

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Equilibrium acidities for 14 2-substituted fluorenes were found to vary over a range of 6.1 pK units in dimethyl sulfoxide solution. A rather poor Hammett plot was obtained with σ_m ($\rho = 7.5 \pm 0.53$, $r = 0.969$). Groups capable of strong electron acceptor resonance interactions (CN, PhCO) or strong electron donor resonance interactions (MeO, F) deviated most from the line, indicating that the 2 position in the fluorene ring has considerable "para character", as well as "meta character". The effect of substituting a second CN, Et_2NSO_2, or Br atom into an equivalent position on the fluorene nucleus (the 7 position) was substantially less than additive (by 0.5–0.8 pK units). This is attributed to a resonance saturation effect. Similar resonance saturation effects were observed for $PhSO_2$, Ph, and p-MeC_6H_4S groups in 2,9-disubstituted fluorenes, but no saturation of the effects of MeO or PhS was observed in 2,7-disubstituted fluorenes. The conclusion is drawn that, in the absence of steric effects, saturation effects result from changes in electron distribution in the anion caused by resonance delocalization, and that polar saturation effects are of little or no importance.

Three distinct mechanisms for "saturation" of the electronic effects of substituents, namely, polar, resonance, and steric, were visualized in 1941 by Branch and Calvin in their classical book on theoretical organic chemistry.[1] In discussing acidities of acids without resonance, including aliphatic carboxylic acids, they remark that "there should be a tendency for polar effects of groups to increase less rapidly than the calculated values when the sum of the inductive constants of the component parts becomes very great (a saturation effect)". In addition, they suggested that two π-electron-donor groups in para positions on a benzene ring should destabilize the system by what they termed "cross-conjugation", and that the effects of the two π donors should be nonadditive.[1] (Additional evidence for a "saturation" effect of this kind was provided later.[2]) Finally, Branch and Calvin recognized that ortho groups could interfere with quinoidal resonance giving rise to steric inhibition of resonance, which causes a damping or "saturation" of substituent effects.

Experiments in the ensuing years have provided abundant examples of attenuation ("saturation") of electronic effects