column, a fraction composed of 90% XIV and 10% of an unidentified ketone was collected. The ketone was removed from XIV by "dry column" chromatography[47] on an alumina column with $CHCl_3$ as the eluent.

The *p*-nitrobenzoate of XIV melted at 113–114°. *Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60: N, 4.23. Found: C, 68.53; H, 7.66; N, 4.15.

6-*t*-Butylspiro[2.5]octan-4-one (XXVIII). To 90 ml of pyridine cooled in an ice bath was carefully added 8 g of CrO_3; a yellow complex formed. To this mixture a solution of 8 g of XIV and 10 ml of pyridine was added. The reaction was stirred for a day at room temperature and then poured into 800 ml of water. The aqueous solution was extracted with ether. The ether extracts were washed with dilute HCl, dilute $NaHCO_3$ solution, and finally with water. The extracts were dried, and the ether was distilled. Distillation of the residue yielded 4 g (50%) of XXVIII, bp 57–57.5° (0.1 mm).

***cis*-6-*t*-Butylspiro[2.5]octan-4-ol** (XV). XXVIII (2.8 g) was reduced by 0.4 g of $LiAlH_4$ to yield 2 g (72%) of XV,[48] bp 77–77.5° (0.5 mm), mp 49–50°

The *p*-nitrobenzoate melted at 101–103°. *Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.83; H, 7.41; N, 4.27.

Determination of Configuration of XV and XIV. A distinction between structures XV and XIV was made on the basis of the band shapes and the chemical shifts of the *CH*O– pmr absorption. As compared with equatorial protons, axial protons produce broader pmr bands.[49] The C-4 proton in XV appears as a quartet with a width of 18 cps[50] whereas the C-4 proton in XIV appears as an asymmetrical singlet with a width of 13 cps.[50] Therefore, the C-4 proton in XV is axial and that of XIV is equatorial. The C-4 proton in XIV occurs at a lower δ (2.97 ppm) due to the shielding anisotropy of the spiro cyclopropane ring[51] than the δ (3.63 ppm) of the C-4 proton in XV. $\Delta\nu(H_a{-}H_e)$ is approximately +42 cps.[52] Additional support for the configurational assignment of XV was provided by the stereochemical result for the $LiAlH_4$ reduction of a ketone analogous to XXVIII; 4-*t*-butyl-2,2-dimethylcyclohexanone when treated with $LiAlH_4$ produced an epimeric mixture containing 95% of the *trans* isomer of 4-*t*-butyl-2,2-dimethylcyclohexanol (XVII).[54]

Acknowledgments. We wish to thank the Whitehall Foundation who provided funds for the instrument upon which the spectral determinations were made. Computer time was provided by the Princeton University Computer Center, supported in part by National Science Foundation, Grant GP-579. This research was supported, in part, by the National Institutes of Health, Grant No. A107766, and the Petroleum Research Fund, administered by the American Chemical Society.

(47) See B. Loev and K. M. Snader, *Chem. Ind.* (London), 15 (1965), for a description of the method.

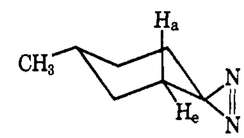
(48) The isomeric alcohol XIV was not detected by gas chromatography.

(49) N. C. Franklin and H. Feltkamp, *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965), and references cited therein. Following these authors the band widths are measured at one-fourth height.

(50) A trace of acid was added to the CCl_4 solution to remove coupling with the hydroxylic proton.

(51) The magnetic anisotropy of the cyclopropane ring is discussed in D. J. Patel, M. E. N. Howden, and J. D. Roberts, *J. Am. Chem. Soc.*, **85**, 3218 (1963).

(52) In a somewhat analogous system (XXIX), $\Delta\nu$ (H_a–H_e) was found to be +76 cps at 31° in CCl_4.[53]



XXIX

(53) J. J. Uebel and J. C. Martin, *ibid.*, **86**, 4618 (1964).

(54) J.-C. Richer, *J. Org. Chem.*, 30, 324 (1965).

Transmission of Substituent Effects. Dominance of Field Effects[1]

C. F. Wilcox and C. Leung

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York. *Received July 31, 1967*

Abstract: The dissociation constants of bicyclo[2.2.2]octane- and bicyclo[2.2.1]heptane-1-carboxylic acids substituted in the 4 position by $N(CH_3)_3$, CN, Br, CO_2CH_3, CO_2H, H, and CO_2^- groups have been measured. The results are in excellent agreement with expectations from a field effect model and in poor agreement with the classical inductive model. It is concluded from these results and other considerations that the purely inductive component of the total substituent effect is minor.

An old problem of organic chemistry is the interpretation of the electronic details of the processes by which substituents influence reactivity. From Ostwald's early investigations[2] of acidities of substituted carboxylic acids has developed several models to account for the varying acidity. Microscopic models based on simplified treatments of the electrostatic situation were initiated by Bjerrum[3] with his analysis of dissociation constants of dicarboxylic acids. He equated the statistically corrected ΔpK of a diacid to the simple Coulomb potential of one ionizable proton in the field of the other (eq 1). The effective dielectric

$$\Delta pK \text{ (statistically corrected)} = \frac{q_i q_j}{r_{ij} D_{\text{eff}}} \qquad (1)$$

q_i = charge of proton 1

q_j = charge of proton 2

r_{ij} = distance between proton 1 and 2

(1) Based in part on the Ph.D. dissertation to be submitted to the Cornell Graduate School, July 1967. This material was presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) W. Ostwald, *J. Prakt. Chem.*, **31**, 300 (1885); *Z. Physik. Chem.*, **3**, 170, 241, 369 (1889).

(3) N. Bjerrum, *ibid.*, **106**, 219 (1923).

constant, D_{eff}, was equated to the dielectric constant of the solvent, D_{sol}. Eucken[4] extended the Bjerrum approach to include dipolar substituents (eq 2) but

$$\Delta pK\,(\text{dipolar substituent}) = \frac{q_i \mu_j \cos \theta_{ij}}{r_{ij}^{\,2} D_{eff}} \qquad D_{sol} > D_{eff} > 2 \quad (2)$$

μ_j = dipole moment of substituent
θ_{ij} = angle between the dipole axis and line joining the center of dipole and proton

noted that unlike the situation with charged substituents the effective dielectric constant was clearly intermediate between that of the solvent and the hydrocarbon portion of the acid. Eucken discussed D_{eff} in terms of the fractions of lines of force passing through the chain and the solvent.[5,6] Eucken did not solve the problem but instead reversed it and used the experimental data and assumed geometry to calculate the effective dielectric constant.

Kirkwood and Westheimer[7] were the first to attempt to calculate the effective dielectric constant from the chain and solvent dielectric constants. In spite of the structural simplifications introduced for necessary mathematical simplification, their cavity model has been extraordinarily successful and useful. The refinement and extension of this model has been described.[8,9]

An alternate treatment of substituent effects is through empirical relationships (extrathermodynamic models[10]) founded on the idea of successive electron displacements transmitted down the chain. Beginning with Derick[11] and his "rule of thirds" (eq 3), it has

$$\frac{pK_A - pK_{ref}}{pK_B - pK_{ref}} = \frac{1}{3B - A} \quad (3)$$

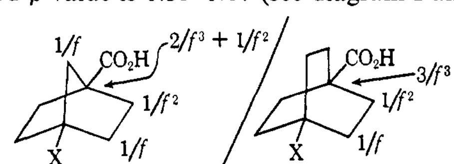
been observed that changes in pK's of acids can be correlated with the number of carbon atoms interposed between the substituent and the carbonyl group.[9] This approach with its focus on the inductive effect (I effect) was extended and refined by Branch and Calvin, who found the average empirical constant to be nearer 2.7.[12,13]

Several attempts to determine experimentally the relative importance of a direct or field effect and the inductive effect have appeared.[14] The first, by Roberts and Moreland,[15] was with the 4-X-bicyclo[2.2.2]octane-1-carboxylic acids; they concluded that at least half of the substituent effect could be ascribed to the direct effect. In spite of this and later studies by other workers,[9,16] no unambiguous division of relative importance of the two effects has appeared. General difficulties involved in this distinction are that (1) many of the molecules are flexible and hence have an uncertain average geometry, (2) frequently the molecules have different environments around the reaction site giving rise to an unknown reactivity difference, (3) the molecules compared may have different numbers of chains with possible ambiguities in the estimate of the inductive effect, (4) the quality of fit between the predictions of the cavity model and experiment is not sufficiently good to justify a semiempirical distinction, and (5) for most molecules the two effects operate in the same direction.

Two general methods for making a qualitative demonstration of the major importance of the direct effect have been proposed. One involves "inverted" molecules in which the dipole is held in an atypical configuration such that the two effects work against one another.[16,17] The other involves "horseshoe" molecules[18] in which the substituent and reaction site are held near to each other for maximum direct effect by a backbone with so many atoms that the inductive effect becomes negligible. Ehrenson[9] has suggested that because of conceivable special solvent interactions the "horseshoe" approach would be ambiguous for all but impracticably large molecules.

One way around these difficulties is to compare pairs of identically substituted molecules in which the direct effects are as similar as possible but the inductive effects are different. This approach transfers the burden of distinction from the difficult-to-analyze field effect model onto the simple inductive model (eq 3).

The bicyclo[2.2.2]octanes and bicyclo[2.2.1]heptanes constitute excellent parallel systems. The inductive model, using a constant fall-off factor, f, with account of all three chains yields a substituent effect ratio, ρ, of $(2 + f)/3$. With a range of f values of 2.0–3.0[19] the predicted ρ value is 1.33–1.67 (see diagram I and eq 4).



I

$$\text{ratio} = \rho = [(2/f^3) + (1/f^2)]/(3/f^3) = \frac{2 + f}{3} \quad (4)$$

f = fall-off factor per carbon

(4) A. Eucken, *Angew. Chem.*, **45**, 203 (1932).

(5) Closely related considerations had been presented earlier by Ingold with his I (inductive) and D (direct) effects [C. K. Ingold, *J. Chem. Soc.*, 417 (1928)] although this was apparently unknown to Eucken.

(6) H. M. Smallwood, *J. Am. Chem. Soc.*, **54**, 3048 (1932), used an electrostatic model in which the effective dielectric constant was that of a vacuum.

(7) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506, 513 (1938).

(8) C. Tanford and J. G. Kirkwood, *J. Am. Chem. Soc.*, **79**, 5333, 5340 (1957); C. Tanford, *ibid.*, **79**, 5348 (1957).

(9) For a recent review of this and related models, see S. Ehrenson, *Progr. Phys. Org. Chem.*, 2, 195 (1964); C. D. Ritchie and W. F. Sager, *ibid.*, 2, 323 (1964).

(10) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

(11) C. G. Derick, *J. Am. Chem. Soc.*, **33**, 1152, 1162, 1167, 1181 (1911).

(12) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1941.

(13) For a review of various fall-off factors, see J. C. McGowan, *J. Appl. Chem.*, 10, 312 (1960).

(14) Ehrenson[9] has pointed out that the Kirkwood–Westheimer model includes both a direct and an inductive effect. The latter is simulated by polarization of the central (low dielectric constant) cavity which is taken as a crude analog of the molecular framework.

(15) J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.*, **75**, 2167 (1953).

(16) R. Golden and L. M. Stock, *ibid.*, **88**, 5928 (1966). After this paper had been prepared, Professor Stock kindly drew our attention to some recent unpublished work of his group which demonstrates nicely the inadequacy of the inductive model and the general good fit obtained with the Kirkwood–Westheimer cavity model.

(17) J. D. Roberts and R. Carboni, *ibid.*, 77, 5554 (1955).

(18) This term was introduced by Roberts and Carboni[17] in connection with what we call "inverted" molecules; however, it seems more apt for the bent molecules. In this sense a horseshoe molecule might or might not be inverted. For example, with substituents behaving like simple charges the state of inversion is not defined.

(19) This range includes the low transmission factor of 0.5 proposed by McGowan;[13] however, this is based largely on aromatic systems with their complicating resonance effects (*i.e.*, anisotropic polarizabilities) and on charged substituents that have inherently lower fall-off factors.

The most realistic value for ρ from this model is believed to be $(2 + 2.7)/3 = 1.57$. The value of ρ is independent of the substituent.

The value of ρ expected from a cavity model depends on the choice of substituents. The value of ρ calculated with a spherical cavity[7,8] for CN, Br, CO_2CH_3, and CO_2H substituents using reasonable geometries[20-22] was 1.20 ± 0.02. In these calculations the depth of the substituent and ionizable proton below the cavity surface was adjusted by matching the calculated and experimental aqueous ΔpK's of the bicyclooctane compounds. These same substituent depths were used for calculating the corresponding bicycloheptane molecules. In a similar fashion the positively charged $N(CH_3)_3$ substituent gave a calculated ρ of 1.20. Similar calculations with solvent dielectric constants corresponding to 25% methanol–water and 50% methanol–water gave ρ values differing by less than 0.01 even though substantial changes (*ca.* 0.4A) of the cavity radii were involved.[23] The parameters for the aqueous solvents are summarized in Table I. It is also true that ρ was essentially independent of the value of D_{int} selected for the inner cavity.

Table I. Parameters for Cavity Calculations in Water

Substituent	μ,[a] D.	Bicyclooctane R,[b] A	Bicyclooctane d,[c] A	Bicycloheptane R,[b] A
$N(CH_3)_3^+$	...	7.06	1.2	6.49
CN	4.0	7.56	1.2	6.98
Br	2.0	6.49	1.3	5.98
CO_2CH_3	1.8	7.65	1.7	7.07
CO_2H	1.68	7.65	1.8	7.07

[a] Dipole moment of substituent.[22] [b] Distance between ionizable proton and substituent charge or dipole. [c] Cavity depth from matching bicyclooctane data.

In summary, the simple inductive model predicts a linear relation between the acid ΔpK's of two series with a ratio of about 1.57. The field effect model predicts an essentially linear relation but with a lower ratio of about 1.20. The experimental problem is to measure the acidities with sufficient precision to make this distinction.

Experimental Section

The preparation of the 4-substituted bicycloheptane and bicyclooctane acids and their purification has been described elsewhere.[24,25] The pK's were measured potentiometrically using cells with liquid junction potentials in water, 25% v/v methanol–water and 50% v/v methanol–water, all at $25.00 \pm 0.01°$. Liquid junction potential corrections were made empirically[26] assuming that all carboxylate anions of the monoanions have the same intrinsic mobility as that of the benzoate anion. For the diacid the mobilities were related to those of succinic acid. The apparatus was calibrated by the determination of the pK of benzoic acid.

In the reduction of the pH data to pK values, corrections were made for liquid junction potential dependence on concentration, ionic strength dependence of the relative activity coefficients of the charged species, the change in volume of the solution during titration, and the ionization of the solvent.[27]

The dissociation constants of the dicarboxylic acids were calculated from the data by means of the Speakman method.[28] With both the mono- and diacids the data were analyzed using nonlinear least-squares[29,30] programs.[31]

Apparatus. The sample cell was a flat-bottomed Teflon-stoppered cylindrical glass beaker (2.5×4.0 cm) equipped with a water jacket. The jacket was maintained at constant temperature with a Haake circulator ($25.00 \pm 0.01°$). The Teflon stopper was filled with a glass electrode (Radiometer Model G 202C), calomel electrode (Radiometer Model K 4312), and a Y-tube for insertion of a capillary delivery tube and a nitrogen gas inlet tube. The sample was stirred magnetically by a glass-enclosed micromagnetic stirring rod (from a section of a paper clip).

The pH of the cell was measured with a Radiometer 7TTI titrator equipped with a Radiometer PHA630T scale expander. The titration buret was a Micro-Metric Instrument Co. SB-2 Syringe Micro Buret fitted with a 1.00-ml S2YP syringe, graduated in 1-μl divisions. The syringe was attached to a Teflon three-way stopcock with one arm leading to a reservoir of base and the other arm to the cell by means of a Teflon microtubing fitted at the delivery end with a capillary glass tubing. The capillary was bent in a spiral 0.4 cm above its tip and the tip was partially constricted (*ca.* half-closed). When positioned in the cell, the tip was 0.5 cm below the surface of the solution.

Calibration and Measurement. The microsyringe was calibrated for delivery with water and found to be constant within the reading error provided that the delivery rate and surrounding temperature remained constant (within a couple of degrees).

Suitable pairs of electrodes were selected carefully to give stable and reproducible pH readings for any given solution. Electrodes were kept immersed in the particular solvent for at least 2 days before any measurement was made. The calomel electrode was filled with freshly prepared solvent, identical with that in the cell, that had been saturated with potassium chloride.

A very slow stream of solvent-saturated carbon dioxide–free nitrogen was passed over the cell contents throughout the measurement. The cell and contents were temperature equilibrated for 10 min before the measuring process began. Before and after each titration the pH of secondary reference buffers were determined. A run that gave buffer readings differing by more than 0.005 pH unit was rejected. In general, the before and after readings were either much smaller or much greater than this.

The solution of an acid was transferred to the cell by means of a calibrated 5-ml syringe under a blanket of solvent-saturated carbon dioxide free nitrogen. The pH readings at seven stages of neutralization between 25 and 75% neutralization were recorded as were pH readings in the neighborhood of complete neutralization. The latter were used to verify the acid concentration of the original solution. After each increment of base was added the solution was stirred for 45 sec followed by a waiting period of 1 min before the meter was read. All electric current in the vicinity of the meter was shut off during the reading.

The thermodynamic dissociation constants of acetic acid, pivalic acid, and succinic acid measured by the present techniques are recorded in Table II along with the corresponding literature values. The deviations recorded are standard deviations for several measurements.

Results and Discussion

The dissociation constants of the two sets of acids are recorded in Table III. The standard deviation within a single run is 0.004 pK unit or less. Additional errors may be introduced from the estimation of the liquid

(20) The internuclear distances and geometry of the bicycloheptane nucleus was taken from the structure of 1,4-dichlorobicycloheptane: S. H. Bauer, J. Chiang, C. F. Wilcox, and M. F. Wilcox, unpublished work.

(21) "Tables of Interatomic Distances and Configuration in Molecules and Ions," Supplement 1956–1959, Special Publication No. 18, The Chemical Society, London, 1965.

(22) C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1958.

(23) With a constant depth using the Tanford assignment[8] the calculated ρ was 1.18 ± 0.01.

(24) C. F. Wilcox and J. S. McIntyre, *J. Org. Chem.*, 30, 777 (1965).

(25) Unpublished work of C. Leung. The methods used closely paralleled the earlier preparations.[24]

(26) A. L. Bacavealla, E. Grunwald, H. P. Marshall, and E. L. Purlee, *J. Org. Chem.*, 20, 747 (1955).

(27) The ionization constant of all three solvents was taken as that of water at 25°, 10^{-14}.

(28) J. C. Speakman, *J. Chem. Soc.*, 855 (1940).

(29) W. E. Deming, "Statistical Adjustment of Data," John Wiley and Sons, Inc., New York, N. Y., 1943.

(30) W. E. Wentworth, *J. Chem. Educ.*, 42, 96, 162 (1965).

(31) Undocumented listings of these progams (Fortran II, CDC 1604) are available.

Table II. Thermodynamic Acid Dissociation Constants in Water at 25°

Acid	Measured	Literature[a]
Benzoic	4.199; 0.004	4.199
Acetic	4.757; 0.004	4.756
Pivalic	5.032; 0.002	5.031
Succinic	4.206; 0.003	4.206
	5.639; 0.004	5.636

[a] G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth and Co., Ltd., London, 1961.

Table III. Experimental pK Values for 4-Substituted Bicyclo[2.2.1]heptane-1-carboxylic Acids and 4-Substituted Bicyclo[2.2.2]octane-1-carboxylic Acids at 25°, with Liquid Junction Potential Corrections

	Solvent		
4-Substituent	Water pK[a]	25% vol. methanol–water pK[a]	50% vol. methanol–water pK[a]
	Bicycloheptane		
$N(CH_3)_3$	3.716; 0.003[b]	4.113; 0.001[b]	4.553; 0.004[b]
CN	4.227; 0.004	4.663; 0.004	5.230; 0.003
Br	4.356; 0.004	4.816; 0.004	5.393; 0.004
$COOCH_3$	4.494; 0.004	4.964; 0.003	5.570; 0.004
COOH	4.197; 0.002	4.670; 0.002	5.295; 0.002
H	4.876; 0.003	5.391; 0.002	6.039; 0.004
COO^-	5.284; 0.003	5.851; 0.004	6.563; 0.004
	Bicyclooctane		
$N(CH_3)_3$	4.083; 0.003	4.517; 0.003	5.007; 0.003
CN	4.545; 0.003	5.008; 0.003	5.581; 0.002
Br	4.619; 0.003	5.103; 0.004	5.690; 0.003
$COOCH_3$	4.764; 0.004	5.257; 0.004	5.867; 0.004
COOH	4.468; 0.002	4.960; 0.002	5.578; 0.002
H	5.084; 0.003	5.612; 0.004	6.261; 0.003
COO^-	5.457; 0.004	6.027; 0.003	6.728; 0.003

[a] Thermodynamic pK's. [b] Standard deviations.

junction potential corrections and other sources. While the magnitude of these possible errors is unknown, the excellent agreement of the pK's of the reference acids (Table II) with the literature values suggests that the uncertainty in individual aqueous pK's is, conservatively, less than 0.02. The errors in ΔpK's are presumably still smaller because of additional cancellation of any systematic errors. In other solvents adequate reference data are unavailable to assess the errors in the pK's; however, the similarity of the standard deviations of individual acids with the corresponding deviations in water indicates no major deterioration in precision. It does not seem unreasonable to suggest that the uncertainty in the ΔpK's in all three solvents is about 0.01 pK unit.

It is worth noting from the data in Table III that the bicyclooctanemonocarboxylic acid has an aqueous pK of 5.084, nearly the same as the structurally similar pivalic acid, pK = 5.032. The bicycloheptanemonocarboxylic acid with a pK of 4.876 is a significantly stronger acid. The 0.21 pK unit difference is consistent with a larger amount of s character in the bicycloheptane C_1 and C_4 orbitals contributing to the bond to the carboxyl groups. The increased s character relative to the unrestrained bicyclooctane and pivalic acids is expected for the bicycloheptane nucleus.[32,33]

(32) C. F. Wilcox, J. G. Zajacek, and M. F. Wilcox, *J. Org. Chem.*, **30**, 2621 (1965).

The ΔpK values are recorded in Table IV. It is interesting that the ΔpK's of the CO_2CH_3 and CO_2H substituted acids are so similar for both series in the three solvents. While there is no *a priori* reason for an identity, the close similarity provides additional confidence in the separation of dicarboxylic acid dissociation constants into K_1 and K_2.

Table IV. Experimental Log (K_X/K_H) Values for 4-Substituted Bicyclo[2.2.1]heptane-1-carboxylic Acids and 4-Substituted Bicyclo[2.2.2]octane-1-carboxylic Acids in Water and Aqueous Methanol at 25°

	Solvent		
4-Substituent	Water	25% vol. methanol–water	50% vol. methanol–water
	Bicycloheptane		
$N(CH_3)_3$	1.160	1.278	1.486
CN	0.649	0.728	0.809
Br	0.520	0.575	0.646
$COOCH_3$	0.382	0.427	0.469
COOH[a]	0.378	0.420	0.443
H	0.0	0.0	0.0
COO^- [b]	−0.107	−0.159	−0.223
	Bicyclooctane		
$N(CH_3)_3$	1.001	1.095	1.254
CN	0.539	0.604	0.680
Br	0.465	0.509	0.571
$COOCH_3$	0.320	0.355	0.394
COOH[a]	0.315	0.351	0.382
H	0.0	0.0	0.0
COO^- [b]	−0.072	−0.114	−0.166

[a] Statistically corrected by subtraction of log 2 from the observed ΔpK. [b] Statistically corrected by addition of log 2 to the observed ΔpK.

Plots of the ΔpK's of the bicycloheptane acids *vs.* the ΔpK's of the bicyclooctane acids are recorded in Figure 1. The bicycloheptane data in 25% methanol–water have been incremented by 0.60 pK unit and those in 50% methanol–water by 1.20 pK units since without these the lines would be essentially superposed. The least-squares fit of these lines to a linear relationship[34] gives the parameters recorded in Table V. Since it might be argued that the extreme $N(CH_3)_3^+$ substituted acids distort the slopes, Table V also records the slopes obtained by consideration of the dipolar groups alone. The results do not differ in a statistically significant way.

$$\Delta pK(2.2.1) = \rho \Delta pK(2.2.2) + I \quad (5)$$

A striking feature of the data in Table V is the close correspondence of the observed slopes in the expectations based on the cavity model. They agree within the uncertainty of either. By contrast the observed slopes are about 20 standard deviations removed from the expectations based on an inductive model. Even if the extreme fall-off factor of 2 is used the observed slopes differ by more than seven standard deviations. It is difficult to avoid the conclusion that the purely

(33) P. T. Lansbury and L. D. Sidler, *Tetrahedron Letters*, **11**, 691 (1965).

(34) Errors in both the abscissa and ordinate were considered using the "Least-Squares Cubic" of D. York, *Can. J. Phys.*, **44**, 1079 (1966). We are grateful to Professor York for making a documented printout of his IBM 7094 program available. Although it was pointed out by Deming[29] and others (see the York reference), it is not sufficiently appreciated that the usual least-squares fit of data involving error in both variables is strictly correct only in the limit of small deviations.

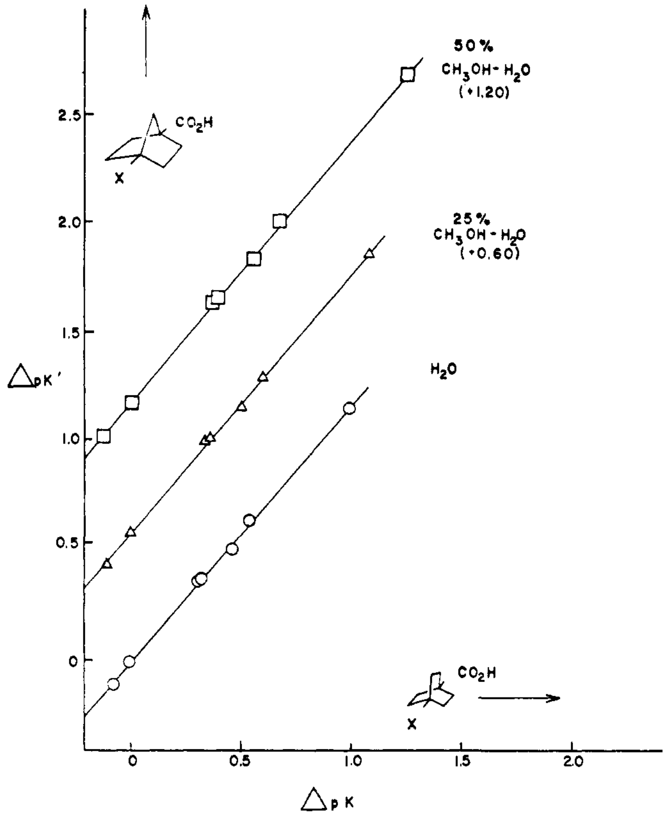


Figure 1. Relationship of substituent effects in the bicyclooctane and bicycloheptane systems. Note arbitrary displacement of the data for clarity.

inductive model does not represent the facts and that the cavity model with its component of direct effect does. These results thus establish the essential role of a direct effect in accounting for transmission of substituent effects on acidity and, by the nonspecific nature of these molecules, the essential role of a direct effect on substituent effect transmission in general.

Table V. Parameter for Linear Relation of ΔpK's of Bicycloheptane Acids to Bicyclooctane Acids

Solvent	Water	25% vol. methanol–water	50% vol. methanol–water
Slope, ρ	1.175	1.183	1.195
σ_ρ	0.021	0.018	0.013
Intercept, I	−0.005	−0.006	−0.013
σ_I	0.010	0.010	0.008
Predicted slope (inductive model)	1.57[a]	1.57[a]	1.57[a]
Predicted slope (cavity model)	1.20[a] ± 0.02	1.20[a] ± 0.02	1.20[a] ± 0.02
Slope,[a] ρ (dipolar group only)	1.175	1.181	1.172

[a] See text.

In order to avoid possible confusion it is desirable to stress what the present results do *not* demonstrate. It can be suggested that there are inductive models alternate to the simple one implied in diagram I and eq 4. For example, one might propose that the transmission of electrical effects through the alkyl chains in close proximity would show electrostatic saturation effects and that an increased value of f, the fall-off faction per carbon, should be employed. For the 4-substituted bicyclo[2.2.2]octane acids compared to the correspondingly substituted acetic acids an apparent value of $f \approx 2.3$ is obtained. For the same comparison of the bicyclo[2.2.1]heptane acids one obtains $f \approx 2.5$. The calculations are outlined for the cyano-substituted (data from Table IV and Table II, footnote *a*) acids in water.

bicyclooctane

$$\frac{1}{(3/f^3)} = \frac{2.29}{0.54}$$

$$f = 2.3$$

bicycloheptane

$$\frac{1}{(2/f^3) + (1/f^2)} = \frac{2.29}{0.65}$$

$$f = 2.5$$

Both values are at the *lower* range of fall-off factors found for single chain systems[12] and do not show any marked saturation effect. Alternately it might be proposed that differences in hybridization of the bicyclic systems would alter the polarizabilities of the atoms and their connecting bonds. To a first approximation any diminished polarizability of the bonds external to the ring at C_1 and C_4 of the heptane series due to increased s character of the external C_1 and C_4 orbitals is accompanied by a corresponding increase in ρ character and polarizability of the internal ring bonds attached to C_1 and C_4. The polarizability of the ring bonds attached to C_7 in the bicycloheptane series should if anything be slightly larger than the bridge bonds of the [2.2.2] series. Thus the over-all effect of f expected from hybridization changes is that the octane series should be normal and the heptane series should show a smaller value. This is not observed.

Despite these contradictions it is possible that a model based on altered hybridization and saturation effects combined with additional considerations could be developed to account for the present ΔpK *vs.* $\Delta pK'$ slopes. All that can be said is that the simplest and traditional inductive model does not work.[35,36]

The next stage in the problem is to assess the relative importance of the direct and inductive effects.[37] The analysis turns out to be more subtle than it might appear and will be reserved for a separate publication. Several crude but suggestive arguments can be advanced that deny the major importance of the inductive[37] component. One such argument depends on the

(35) The present discussion has not considered or compared quantum mechanical models of σ systems.[36] These differ from their classical approximations by the possibility of having alternating substituent effects analogous to the well-known alternation of substituent effects in aromatic systems. Although rapid strides are being made in this area the uncertainties in parameterization do not yet allow certain limits to be placed on the magnitude of the alternation.

(36) These include M. J. S. Dewar and G. Klopman, *J. Am. Chem. Soc.*, **89**, 3089 (1967); H. Hamano, *Bull. Chem. Soc. Japan*, **37**, 1574 (1964); R. Hoffman, *J. Chem. Phys.*, **39**, 1397 (1963), and J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967). Models of a semiclassical nature include those of N. C. Baird and M. A. Whitehead, *Theoret. Chim. Acta*, **2**, 259 (1964); C. Sandorfy, *Can. J. Chem.*, **33**, 1337 (1955), and R. P. Smith and E. M. Mortensen, *J. Am. Chem. Soc.*, **78**, 3932 (1956), based on a bond by bond or atom by atom equalization of electronegativity.

(37) By inductive effect here is meant that part of the total effect transmitted exclusively by successive polarization of intervening atoms. This definition would count as part of the direct effect any ΔpK contribution arising from the electrostatic field of a polarized atom not adjacent to the carboxyl group regardless of the source of the polarization. This classification coincides with the accepted picture of an inductive effect; it may extend the usual concept of the direct effect by assigning to it the class "not inductive." It might be useful to reserve the term direct effect for that part of the substituent effect that would occur under vacuum and call "polarization effect" that part that was *neither* direct *nor* inductive.

results of extrapolating the ΔpK data for individual substituents to infinite dielectric constant on a $1/D$ plot. Although the extrapolation is long, the linearity is excellent and the intercept is statistically significant to about 20% of its value. For the ten sets of ΔpK's (the CO_2-substituted acids are not considered) the intercept amounted to only *ca.* 20–40% of the ΔpK in 50% methanol–water and less in pure water. If it is argued that an infinite dielectric constant in the solvent corresponds to a situation in which all lines of force pass through the low dielectric constant interior then this sets an upper limit of *ca.* 40% to the inductive effect. It might be argued further that this grossly overestimates the inductive component since the low dielectric constant interior simulates both the bonds and their interstites. The latter should properly be included in the direct effect.

A second, indirect argument against the inductive effect being the major mechanism for substituent interaction is the result obtained when the low dielectric cavity is given a dielectric constant equal to that of a vacuum. The calculated ρ's do not vary by more than about 1% from the previous calculations.[38] This model provides no cavity material for simulating successive polarization and still gives excellent agreement with the experimental results.

A final qualitative argument for the minor role of the inductive mechanism is the very similar dipole moments observed for the monochlorobicycloheptanes[32] and reference monochlorides.[39] If the fall-off factor were as small as 2.7, the expected dipole moments of the bicyclic chlorides would be nearer 2.6–2.8 D.[40] than the observed range of 2.05–2.15 D. A fall-off factor of 10–20 would produce a dipole moment increment of only about 0.1–0.2 D.[40] and might be consistent with the observed dipole data. Such a high value for the fall-off factor would give a negligible substituent effect in the bicyclic systems being studied.

Thus far, emphasis has been placed on the agreement between experiment and the Kirkwood–Westheimer cavity model for the three solvents. It should be stressed that this agreement exists only between ratios of ΔpK's and that the predictions of individual ΔpK's in one solvent with parameters derived from measurements in another solvent are unsatisfactory. The ΔpK's for the bromo and cyano acids calculated using the Tanford depth assignment[8] when compared with the experiment gives slopes against $1/D$ that differ by a factor of 10. In practice, the discrepancies are not too severe because of the generally restricted range of $1/D$ considered. Neither of the limiting models, inductive or cavity, satisfactorily predicts individual ΔpK's in arbitrary solvents; however, the present work shows that the Kirkwood–Westheimer cavity model can correctly account for the ratio of ΔpK's in the same solvent. It lends hope that with suitable modifications the cavity model would be useful for individual ΔpK's.[41]

Acknowledgments. We are grateful to the National Science Foundation for their support of this research.

(38) The individual ΔpK's do change drastically, however. It is the ratio that is independent. This and related matters will be analyzed in a subsequent publication now in preparation.

(39) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Co., San Francisco, Calif., 1963.

(40) It perhaps should be emphasized that these bicyclic molecules are relatively rigid and unlike open chain systems do not present the complication of averaging over conformations. The latter has been involved [*e.g.*, R. P. Smith and E. M. Mortensen, *J. Am. Chem. Soc.*, **78**, 3932 (1956)] to account for the small dependence of dipole moment of *n*-alkyl halides on chain length.

(41) In a formal way the poor agreement of the cavity model in predicting ΔpK's while correctly predicting ratios of ΔpK's can be accounted for if the experimental slope, the dominant term in the linear relation of ΔpK to $1/D$, were essentially proportional to the theoretical values for $D = \infty$ with the proportionality constant being independent of substituent. It is possible that just this relationship could arise if the point dipole approximation were abandoned while simultaneously using smaller charge and dipole depths. Another possible way to achieve this proportionality is to invoke oriented solvent around the carboxyl group. With the plausible assumption of an additive relationship of $\Delta\Delta F$ (oriented solvent) to $\Delta\Delta F$ (electrostatic), one could account for the cancellation of the oriented solvent term in the calculation of the solvent dependence of the substituent effects of the two acid series. It is planned to test these two variations of the cavity model in the near future.