

## ELECTROSTATIC EFFECTS ON IONIZATION EQUILIBRIA. 3-SUBSTITUTED BICYCLO[2,2,2]OCTANE-1-CARBOXYLIC ACIDS

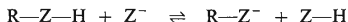
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Nine 3-substituted (*I-IX*) and one 2-substituted (*XI*) bicyclo[2,2,2]octane-1-carboxylic acids were prepared as model compounds for verification of the electrostatic theory of substituent effects. On the one hand they are regular-shaped and suitable for calculations, on the other hand they allow to evaluate the role of the angle  $\Theta$  of the substituent dipole. The apparent pK values in 50% ethanol and 80% methyl cellosolve were correlated with  $\sigma_1$  constants ( $\sigma_1$  1.18 and 1.42, respectively) and compared with theoretical predictions based on the spherical and ellipsoidal cavity models. The agreement is very good with the new Ehrenson model but still satisfactory with some others not matching exactly the actual molecule shape. The substituent effects are reasonably correlated with the substituent dipoles and with the geometrical parameters but exceptions are notable. Comparison with the previous results implies that the theory reproduces fairly the substituent effects in carboxylic acids of a given molecular size and not too unsymmetrical shape; the cavity model is, however, sufficiently flexible to compensate partly even for some non-electrostatic effects neglected by the basic theory.

In this series of papers<sup>1-3</sup> we are dealing with electrostatic effects on conformational and ionization equilibria in the intention to test the individual assumptions and approximations of the theory. In the case of an isodesmic ionization reaction



with a dipolar substituent R, the electrostatic effect on the equilibrium constant (denoted as  $K/K^0$ ) is expressed by the equation<sup>4,5</sup>

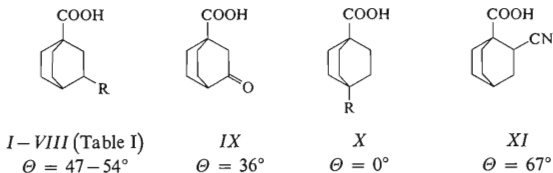
$$\log (K/K^0) = \frac{e\mu \cos \Theta}{2.303kT r^2 \epsilon_{\text{ef}}} \quad (1)$$

The equation assumes among other things that an inhomogeneous system consisting of the molecule and the surrounding solvent can be described by an average, "effective" dielectric constant  $\epsilon_{\text{ef}}$ . This in turn is computed using a cavity model<sup>5-8</sup> which

represents the molecule as a simple geometrical cavity of low dielectric constant  $\epsilon_1$ , encompassed by a medium of high dielectric constant  $\epsilon_c$ .

Another important feature of Eq. (1) is the angle  $\theta$  between the substituent dipole  $\mu$  and the vector  $r$  connecting it with the ionizable proton (taken from H to R). Since this angle is not involved in other theoretical treatments of substituent effects, most attention has been focused on it. For example, pairs of isomers were prepared<sup>3,9-13</sup> differing mainly in the angle  $\theta$ , and their different dissociation constants were considered to prove the essential correctness of Eq. (1). Such an oversimplified reasoning neglects possible difference in  $\epsilon_{ef}$ ; on the other hand, if these are accounted for, the results are dependent on the imperfections of the cavity model. On two particular examples of isomeric 1-oxoindane-4(6)-carboxylic<sup>3</sup> and *c(t)*-8a-cyano-*trans*-decahydronaphthalene-*r*-2-carboxylic<sup>14</sup> acids we have shown that the actual effects do not follow the changes of  $\theta$ , even if allowance is made for unequal  $\epsilon_{ef}$ . The most probable explanation would be that other effects are operating in addition to the electrostatic forces. However, before reaching this conclusion one must deal with the objection that any simple cavity model can be inadequate for strongly unsymmetrical molecules; in particular the angles  $\theta$  larger than  $90^\circ$  require unusual molecules of a horse-shoe shape<sup>13</sup> for which an effective dielectric constant can be hardly even defined<sup>3</sup>.

For these reasons we searched for molecules of a more regular shape, corresponding more closely to a spherical or ellipsoidal cavity, but with the angle  $\theta$  different from zero. In this communication we report the results on racemic 3-substituted bicyclo[2,2,2]octane-1-carboxylic acids *I*–*IX* which satisfy these conditions. The dependence on  $\theta$  may be followed by comparing with the 4-substituted isomer *X* investigated previously<sup>8,15-19</sup> and with 2-cyano derivative *XI*; from the substituents available to us only the CN groups is both rigid and sterically not pretentious.



The molecules *I*–*IX* can be reasonably approximated by a sphere or a little eccentric ellipsoid. However, the spherical model in use<sup>5</sup> requires the substituent dipole and the ionizable proton to be situated on a diameter, in the case of an ellipsoidal model<sup>6,8</sup> on its main axis. Therefore, we applied – in addition to these

classical models — still a new one<sup>20</sup> assuming a spherical cavity with the substituent dipole, centre of the sphere, and the ionizable proton in one plane. This model matches satisfactorily the shape of our molecules but not the direction of the dipole. In fact, two discrete values are attributed to this direction during the calculation: one for the cavity model, the other, more realistic, in calculating  $\theta$ . Our results reveal that the imperfections of the cavity models are not decisive since the most telling results were drawn from the dependence on the substituent and on the geometrical parameters  $r$  and  $\theta$ , irrespective of the value of  $\epsilon_{\text{eff}}$ .

## EXPERIMENTAL AND RESULTS

### Materials

Melting points were determined on a Kofler block and are uncorrected. Analytical samples were dried over phosphorus pentoxide at 25°C/10 Pa. The identity of compounds was checked by melting point determination, by thin-layer (TLC) and gas-liquid (GLC) chromatographies, by microanalyses and by IR, <sup>1</sup>H-NMR and mass spectra. The IR spectra were taken on a Zeiss UR-20 instrument; wavenumbers are given in cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectra were measured on a Varian HA-100 spectrometer at the frequency 100 Mz with tetramethylsilane as internal standard and are given in the  $\delta$ -scale. The mass spectra were recorded on a AEI MS-907 spectrometer.

*Bicyclo[2,2,2]octene-1-carboxylic acid* (XII) was prepared from ethyl 1,3-cyclohexadiene-carboxylate<sup>21,22</sup> by the Diels-Alder reaction with maleic anhydride and subsequent catalytic hydrogenation<sup>22</sup>, oxidative decarboxylation<sup>22-25</sup> and alkaline hydrolysis of the ethyl ester; the overall yield was 28%, m.p. 118°C (aqueous acetone), literature<sup>24</sup> reports 117.5–118.5°C. <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.07–2.18 (m, 8 H, CH<sub>2</sub>), 2.43–2.77 (m, 1 H, H<sub>4</sub>), 6.17–6.60 (m, 2 H, CH=CH), 11.22 (bs, 1 H,  $W_{1/2} = 12$  Hz, OH).

*Bicyclo[2,2,2]octane-1-carboxylic acid* (I) was prepared from XII by catalytic hydrogenation with platinum oxide catalyst in dioxan at room temperature and atmospheric pressure; yield 79%, m.p. 142°C (aqueous acetone), literature<sup>22</sup> reports 140.5–142°C. <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.62 (bs, 13 H,  $W_{1/2} = 7$  Hz, CH<sub>2</sub>, H<sub>4</sub>), 11.37 (bs, 1 H,  $W_{1/2} = 7$  Hz, OH).

### 3-Chlorobicyclo[2,2,2]octane-1-carboxylic Acid (II)

The solution of XII (1.0 g, 6.57 mmol) and anhydrous zinc chloride (0.1 g) in the mixture of glacial acetic acid (9.5 ml) and acetic anhydride (0.5 ml) was cooled to 0°C and saturated with gaseous hydrogen chloride. The mixture was allowed to stand at room temperature for 9 days, then poured on 80 g ice, the product taken up in dichloromethane and purified *via* sodium salt and finally by chromatography on a silica gel column (120 g). Elution with pentane-ether (5 : 1) afforded 36% of II; m.p. 118°C (pentane-ether). <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.32–2.61 (m, 11 H, CH<sub>2</sub>, H<sub>4</sub>), 4.05–4.39 (m, 1 H, H<sub>3</sub>). For C<sub>9</sub>H<sub>13</sub>ClO<sub>2</sub> (188.6) calculated: 57.30% C, 6.94% H, 18.79% Cl; found: 57.08% C, 6.65% H, 18.61% Cl.

### 3-Bromobicyclo[2,2,2]octane-1-carboxylic Acid (III)

The solution of XII (6.0 g, 39.4 mmol) in glacial acetic acid (30 ml) was cooled to 0°C and saturated with gaseous hydrogen bromide. The mixture was allowed to stand at room temperature for

12 h, poured into 300 ml water, the product was collected, washed with water; yield 69%, m.p. 144–5°C (hexane–cyclohexane), literature<sup>24</sup> reports 144–144.5°C for the sample prepared from the ethyl ester of *XII*. <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.42–2.80 (m, 11 H, CH<sub>2</sub>, H4), 4.17–4.55 (m, 1 H, H3), 11.15 (bs, 1 H, *W*1/2 = 7 Hz, OH).

### 3-Iodobicyclo[2,2,2]octane-1-carboxylic Acid (*IV*)

The mixture of *XII* (1.8 g, 10 mmol) and potassium iodide (5 g, 30 mmol) was added to 95% phosphoric acid (17 g) under stirring. The pasty mixture was heated at 80°C for 4 h and poured into 60 ml water. The product was taken up in ether, washed with 10% aqueous sodium thiosulphate and with saturated aqueous sodium chloride. The crude evaporate was recrystallized from pentane–ether and washed with pentane; yield 33%, m.p. 142°C. <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.43–2.43 (m, 10 H, CH<sub>2</sub>), 2.53–2.75 (m, 1 H, H4), 4.40–4.56 (m, 1 H, H3), 11.39 (bs, 1 H, *W*1/2 = 11 Hz, OH). For C<sub>9</sub>H<sub>13</sub>IO<sub>2</sub> (280.1) calculated: 38.59% C, 4.68% H, 45.31% I; found: 38.62% C, 4.70% H, 45.91% I.

### 3-Hydroxybicyclo[2,2,2]octane-1-carboxylic Acid (*V*)

was prepared<sup>24</sup> from the corresponding bromo acid *III*; yield 66%, m.p. 154°C (benzene–ethyl acetate), literature<sup>24</sup> reports 153–154°C. <sup>1</sup>H-NMR spectrum (acetone-d<sub>6</sub>): 1.27–2.32 (m, 11 H, CH<sub>2</sub>, H4), 3.53–3.68 (m, 1 H, H3).

### Methyl 3-Hydroxybicyclo[2,2,2]octane-1-carboxylate

The solution of the hydroxy acid *V* (7.5 g, 44.1 mmol) in methanol (25 ml) was treated with diazomethane in ether, the product evaporated and distilled at 94–95°C/6.6 Pa; yield 94% (GLC). <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.33–2.45 (m, 11 H, CH<sub>2</sub>, H4), 3.53–3.80 (m, 1 H, H3), 3.62 (s, 3 H, CH<sub>3</sub>). For C<sub>10</sub>H<sub>16</sub>O<sub>3</sub> (184.2) calculated: 65.19% C, 8.75% H; found: 65.22% C, 8.49% H.

### 3-Methoxybicyclo[2,2,2]octane-1-carboxylic Acid (*VI*)

The solution of the methyl ester of *V* (0.5 g, 2.94 mmol) and of methyl iodide (15.9 g, 112 mmol) in dimethylformamide (3.5 ml) was treated with dry silver oxide (4.1 g) at 0°C and the mixture was allowed to stand at room temperature for 48 h with occasional stirring. The solid was filtered off, washed with pentane, the filtrate was diluted with water (50 ml), extracted with pentane and the organic layer was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (500 g). Elution with benzene–ethyl acetate (6:1) afforded 87% of the methyl ester of *VI* which was hydrolyzed with sodium hydroxide to *VI* (60%), m.p. 59–61°C (pentane). <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.40–2.58 (m, 11 H, CH<sub>2</sub>, H4), 3.08–3.35 (m, 1 H, H3), 3.27 (s, 3 H, CH<sub>3</sub>). For C<sub>10</sub>H<sub>16</sub>O<sub>3</sub> (184.2) calculated: 65.19% C, 8.75% H; found: 65.27% C, 8.74% H.

### Ethyl 2-Cyanobicyclo[2,2,2]octane-1-carboxylate

A mixture of ethyl 1,3-cyclohexadienecarboxylate<sup>21,22</sup> (20 g, 0.13 mol), acrylonitrile (28.2 g, 0.53 mol), and hydroquinol (0.35 g) was heated in a sealed tube at 170°C for 9 h. After cooling 30 ml benzene was added, the precipitate was filtered off, the organic layer evaporated and distilled *in vacuo* to yield the mixture of four ethyl esters of *endo* and *exo* 2- and 3-cyanobicyclo[2,2,2]-oct-5-ene-1-carboxylic acids; b.p. 90–110°C/10 Pa 19.6 g (73%). This mixture was hydrogenated

on 5% palladium/calcium carbonate catalyst (6 g) in ethanol (250 ml) at room temperature and atmospheric pressure. Evaporation and distillation at 100–110°C/6 Pa afforded in 95% yield a product containing 22% of the 3-cyano derivative and 78% of the 2-cyano derivative (GLC). The mixture crystallized in the course of one week, the solid was separated and crystallized four times from pentane-ether, yield 47%; m.p. 51°C. <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.26 (t, 3 H, *J* = 7 Hz, CH<sub>3</sub>), 1.44–2.24 (m, 11 H, CH<sub>2</sub>, H4), 3.00–3.22 (m, 1 H, H2), 4.17 (q, 2 H, *J* = 7 Hz, OCH<sub>2</sub>). IR spectrum (CCl<sub>4</sub>): 2241 (C≡N). For C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub> (202.3) calculated: 69.53% C, 8.27% H, 6.76% N; found: 69.77% C, 8.25% H, 6.79% N.

#### Ethyl 3-Cyanobicyclo[2,2,2]octane-1-carboxylate

The mother liquor from the preceding experiment (3.7 g) containing 70% of 3-cyano derivative (GLC) was chromatographed on a silica gel column (400 g). Elution with pentane-ether (5 : 1) afforded 2.8 g of the product, b.p. 100–102°C/6 Pa. <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.23 (t, 3 H, *J* = 7 Hz, CH<sub>3</sub>), 1.50–2.34 (m, 11 H, CH<sub>2</sub>, H4), 2.64–2.94 (m, 1 H, H3), 4.10 (q, 2 H, *J* = 7 Hz, OCH<sub>2</sub>). IR spectrum (CCl<sub>4</sub>): 2241 (C≡N). For C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub> (202.3) calculated: 69.53% C, 8.27% H, 6.76% N; found: 69.94% C, 8.20% H, 6.91% N.

#### 2-Cyanobicyclo[2,2,2]octane-1-carboxylic Acid (XI)

was prepared from its ethyl ester by refluxing with 1% ethanolic sodium hydroxide 4 h, yield 81%, m.p. 113°C (pentane-ether). <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.43–2.24 (m, 11 H, CH<sub>2</sub>, H4), 2.96–3.21 (m, 1 H, H2), 10.72 (bs, 1 H, *W*<sub>1/2</sub> = 6.5 Hz, OH). For C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub> (179.2) calculated: 67.02% C, 7.31% H, 7.82% N; found: 67.09% C, 7.20% H, 8.23% N.

#### 3-Cyanobicyclo[2,2,2]octane-1-carboxylic Acid (VII)

was prepared from its ethyl ester in the same manner as in the preceding experiment; yield 74%, m.p. 124°C (pentane-ether). <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.50–2.37 (m, 11 H, CH<sub>2</sub>, H<sub>4</sub>), 2.69–2.93 (m, 1 H, H3), 10.63 (bs, 1 H, *W*<sub>1/2</sub> = 11 Hz, OH). Mass spectrum: 179 (M<sup>+</sup>), 161 (M–H<sub>2</sub>O), 126 (M–CH<sub>2</sub>CHCN). For C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub> (179.2) calculated: 67.02% C, 7.31% H, 7.82% N; found: 66.60% C, 7.26% H, 8.03% N.

#### 3-Oxobicyclo[2,2,2]octane-1-carboxylic Acid (IX)

was prepared<sup>24</sup> from *V* by oxidation with Jones' reagent; yield 36%, m.p. 131–133°C (hexane-ethyl acetate; literature<sup>24</sup> reports 85–93°C for a crude product). <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>): 1.72–2.60 (m, 10 H, CH<sub>2</sub>), 2.70–2.97 (m, 1 H, H4), 10.33 (bs, 1 H, *W*<sub>1/2</sub> = 4.5 Hz, OH). IR spectrum (CHCl<sub>3</sub>): 2990 v br (OH), 2964, 2880 (CH<sub>2</sub>), 2670 v br (OH, dimer), 1707 and 1720 sh (C=O), 1460 (δCH<sub>2</sub>), 1418, 1299 (C–O and δO–H dimer), 939 (δOH dimer). For C<sub>9</sub>H<sub>12</sub>O<sub>3</sub> (168.2) calculated: 64.27% C, 7.19% H; found: 64.69% C, 7.21% H.

#### Bicyclo[2,2,2]octane-1,3-dicarboxylic Acid (VIII)

was prepared from *VII* by acid hydrolysis in 80% sulphuric acid, yield 45%, m.p. 205°C (pentane-acetone); literature<sup>26</sup> reports 206–208°C for the sample prepared from its diethyl ester. <sup>1</sup>H-NMR spectrum (hexadeutero-2-propanone): 1.50–2.30 (m, 11 H, CH<sub>2</sub>, H4), 2.50–2.76 (m, 1 H, H3). IR spectrum (KBr): 2650 (OH, dimer), 1709 and 1696 sh (C=O). Mass spectrum: 180 (M–H<sub>2</sub>O).

## Physical Measurements

The apparent dissociation constants of the acids *I-IX*, *XI* were determined by potentiometric titration in 50% (vol.) ethanol and 80% (weight) 2-methoxyethanol (methyl cellosolve) as described previously<sup>3</sup>. The results are assembled in Table I.

The IR absorption spectra in the 3400–3700 cm<sup>-1</sup> region were registered on a Perkin-Elmer 621 spectrometer with 4.0 cm Infrasil cells in 0.001M tetrachloromethane solution at 39°C, calibration with NH<sub>3</sub> and H<sub>2</sub>O vapour. The O—H stretching frequencies are listed in Table I.

## CALCULATIONS

The relative dissociation constants of acids *II-VII*, *IX-XI* predicted by the electrostatic theory were calculated from Eq. (1) introducing the difference  $\mu_X - \mu_H$  for  $\mu$ . Standard bond moments<sup>27</sup> were used (in 10<sup>-30</sup> Cm): C—H 1.0, C—Cl 5.67, C—Br 5.67, C—I 5.23, C≡N 12.0, C=O 8.33. The group moments OH and OCH<sub>3</sub> were obtained from bond moments H—O 5.0, C—O 2.47 and from bond angles C—O—H 105°C, C—O—C 113°; the resulting vector differences  $\mu_X - \mu_H$  were 5.33 (at 114° to the C—O bond) for OH and 3.83 (at 124°) for OCH<sub>3</sub>.

The geometrical parameters *r* and  $\theta$  were calculated assuming the C<sub>3h</sub> symmetry of the bicyclooctane skeleton. Standard bond lengths<sup>28</sup> were used, combined with the more recent values from electron diffraction<sup>29,30</sup> (in pm): C<sub>(1)</sub>—C<sub>(2)</sub> and C<sub>(3)</sub>—C<sub>(4)</sub> 153.8, C<sub>(2)</sub>—C<sub>(3)</sub> 155.2, C<sub>(1)</sub>—C(O) 152, C—Cl 176.7, C—Br 193.8, C—I 220.7, C—CN 146, C≡N 116, C—O 143, C=O 122; in the case of compound *IX* the C<sub>(2)</sub>—C(O) and C<sub>(4)</sub>—C(O) bonds are shortened to 153 pm. The bond angles used were C—C—C 109.7°, C—C—X 109.5°; in the case of compound *IX* C<sub>2</sub>—C<sub>1</sub>—C(O) 110°, C<sub>(1)</sub>—C<sub>(2)</sub>—C<sub>(3)</sub> 109°, C<sub>(2)</sub>—C<sub>(3)</sub>—C<sub>(4)</sub> 113°, C<sub>(2)</sub>—C<sub>(3)</sub>—O 123°. The ionizable proton of the carboxyl group was localized<sup>5</sup> at the distance of 145 pm from C(O) in the direction of the prolonged bond C<sub>(1)</sub>—C(O). The point dipoles of the OH and OCH<sub>3</sub> substituents were placed on oxygen and two limiting conformations were considered. The calculated values of *r* and  $\theta$  are listed in Tables II and III.

The cavity models of Kirkwood and Westheimer, spherical<sup>5</sup> and ellipsoidal<sup>6</sup> were used in the Tanford modification<sup>31</sup>, *i.e.* with the proton and the substituent dipole localized in the depth *d* = 150 pm under the cavity surface. The modified ellipsoidal model<sup>8</sup> was used with the proton in the depth of 160 pm and the dipole 260 pm. The new spherical model<sup>20</sup> was applied with the same dipole moments as above and with  $\epsilon_{er}$  read off the tables kindly made available to us by Professor Ehrenson; the results should be considered as preliminary. The internal dielectric constant  $\epsilon_i$  was taken as 2 in any case. The values of  $\epsilon_{er}$  and log(*K/K*<sup>0</sup>) resulting according to the individual models are collected in Table II for 50% (vol.) ethanol (the external dielectric constant <sup>32</sup>  $\epsilon_e$  = 53.8) and in Table III for 80% (weight) methyl cellosolve ( $\epsilon_e$  = 33.0, ref.<sup>33</sup>).

## DISCUSSION

The experimental results in Table I reveal first of all that the dependence on solvent is not decisive for the conclusions to be achieved. As expected, all the acids are weaker in 80% methyl cellosolve than in 50% ethanol by *c.* one pK unit, while the substituent effects (Tables II and III) are mostly *c.* 10% stronger. Such a general pattern for these two solvent systems is well documented in the case of substituted benzoic acids (*e.g.*<sup>34</sup>) and can be seen more generally from the tables of pK values<sup>35</sup>; it accords roughly with the difference in dielectric constants, although preferential

solvation may play an important role in mixed solvents. The forthcoming discussion applies equally to either solvent system.

Irrespective of their interpretation, the substituent effects in  $I-IX$  can be accounted for by the inductive constants<sup>36</sup>  $\rho_1$ . The correlations are not very good, the correlation coefficients for the two solvents are  $r = 0.953$  and  $0.974$ , the slopes  $\rho_1 = 1.35$  and  $1.54$ , respectively (8 points). The constant for the oxo substituent replacing two hydrogen atoms ( $\sigma_1 = 0.66$ ) was derived from  $pK$ 's of *trans*-4-substituted cyclohexane-1-carboxylic acids<sup>37</sup> ( $\rho_1 = 1.066$ ) and is somewhat uncertain, but dropping this substituent does not improve the fit. Comparison with 4-substituted bicyclo[2,2,2]octane-1-carboxylic acids<sup>15-19</sup> can be made either through the  $\rho_1$  constants, or, probably more reliably, by a direct plot of  $pK$ -values. It reveals that the substituent effects are transmitted more effectively to the 4-position in the ratio of 1:12. For the 2-position the ratio can be estimated from one derivative only *XI* to be 1.45. These results are clearly at variance with the theory of  $\sigma$ -inductive effect<sup>38</sup> transmitted through bonds, which predicts the ratio for 2-, 3-, and 4-derivatives to be between 2.55 : 1 : 0.81 and 1.67 : 1 : 0.97, according to the value given to the transmission coefficient  $\varepsilon$  (0.33 to 0.46) — in any case a stronger effect in 3- than in 4-position. Note, however, that the usual form of this theory assumes not only a regular fall-off with each intervening bond but also an additive action of several transmission ways<sup>15</sup>; the latter simplification is particularly open to criticism<sup>39</sup>.

TABLE I

Apparent Dissociation Constants of 3-Substituted Bicyclo[2,2,2]octane-1-carboxylic Acids (25°C)

| Compound    | X                | 50% (v) EtOH<br>$pK_a$ | 80% (w) MCS<br>$pK_a$ | $\nu(\text{OH})^d$<br>$\text{cm}^{-1}$ |
|-------------|------------------|------------------------|-----------------------|--|
| <i>I</i>    | H                | 6.83 <sup>b</sup>      | 7.81                  | 3 536                                  |
| <i>II</i>   | Cl               | 6.33                   | 7.25                  | 3 533                                  |
| <i>III</i>  | Br               | 6.29                   | 7.19                  | 3 532                                  |
| <i>IV</i>   | I                | 6.49                   | 7.39                  | 3 533                                  |
| <i>V</i>    | OH               | 6.47                   | 7.63                  | 3 535 (3 625) <sup>c</sup>             |
| <i>VI</i>   | OCH <sub>3</sub> | 6.48                   | 7.59                  | 3 535                                  |
| <i>VII</i>  | CN               | 6.05                   | 7.01                  | 3 530                                  |
| <i>VIII</i> | COOH             | <sup>d</sup>           | <sup>d</sup>          | 3 534.5                                |
| <i>IX</i>   | =O               | 5.85                   | 6.83                  | 3 531                                  |
| <i>X</i>    | 4-CN             | 5.90 <sup>e</sup>      | —                     | —                                      |
| <i>XI</i>   | 2-CN             | 5.70                   | 6.61                  | 3 528                                  |

<sup>a</sup> O—H stretching frequency in tetrachloromethane solution; <sup>b</sup> ref.<sup>15</sup> gives 6.74, ref.<sup>17,19</sup> 6.87 and 6.95, respectively, in 50% (weight) ethanol; <sup>c</sup> the stretching frequency of the CHOH group; <sup>d</sup> the two dissociation steps were not separable; <sup>e</sup> ref.<sup>15</sup>.

The O—H stretching frequencies (Table I) are not very sensitive to substitution as compared with the experimental inaccuracy; nevertheless they vary quite regularly with  $\sigma_1$ . As anticipated, the proportionality constant  $\rho_1$  is negative, its value  $c. -10 \text{ cm}^{-1}$  is comparable with  $\rho$  for *meta*- and *para*-substituted benzoic acids<sup>40</sup> ( $-11.7 \text{ cm}^{-1}$ ).

TABLE II  
Calculated Relative Dissociation Constants of Substituted Bicyclo[2,2,2]octane-1-carboxylic Acids (50% ethanol, 25°C)

| Compound<br>Substituent<br>X    | $r, \text{pm}$<br>$\theta^0$ | Sphere <sup>a</sup><br>$\log(K/K^0)$<br>$\epsilon_{cf}^e$ | Ellipsoid <sup>b</sup><br>$\log(K/K^0)$<br>$\epsilon_{cf}^e$ | Ellipsoid <sup>c</sup><br>$\log(K/K^0)$<br>$\epsilon_{cf}^e$ | Sphere <sup>d</sup><br>$\log(K/K^0)$<br>$\epsilon_{cf}^e$ | Experiment<br>$\log(K/K^0)$<br>$\epsilon_{cf}^{e,f}$ |
|---------------------------------|------------------------------|---|--|--|---|--|
| <i>II</i>                       | 572                          | 0.43  | 0.26   | 0.42   | 0.46  | 0.50   |
| 3-Cl                            | 54.1                         | (4.20)  | (6.89)   | (4.30)   | (3.94)  | (3.63)   |
| <i>III</i>                      | 575                          | 0.42  | 0.26   | 0.41   | 0.44  | 0.54   |
| 3-Br                            | 54.5                         | (4.22)  | (6.94)   | (4.34)   | (4.03)  | (3.29)   |
| <i>IV</i>                       | 583                          | 0.39  | 0.23   | 0.37   | 0.40  | 0.34   |
| 3-I                             | 53.4                         | (4.26)  | (7.09)   | (4.44)   | (4.18)  | (4.88)   |
| <i>V</i>                        | 621                          | 0.43  | 0.24   | 0.38   | 0.47  | 0.36   |
| 3-OH <sup>g</sup>               | 25                           | (4.45)  | (7.84)   | (4.98)   | (4.06)  | (5.29)   |
| 3-OH <sup>h</sup>               | 621                          | -0.14   | -0.08  | -0.12  | -0.15   | 0.36   |
|                                 | 107                          | (4.45)  | (7.84)   | (4.98)   | (4.06)  | (-1.70)  |
| <i>VI</i>                       | 621                          | 0.33  | 0.18   | 0.29   | 0.36  | 0.35   |
| 3-OCH <sub>3</sub> <sup>g</sup> | 16                           | (4.45)  | (7.84)   | (4.98)   | (4.06)  | 4.15   |
| 3-OCH <sub>3</sub> <sup>h</sup> | 621                          | -0.04   | -0.02  | -0.03  | -0.04   | 0.35   |
|                                 | 96                           | (4.45)  | (7.84)   | (4.98)   | (4.06)  | (-0.45)  |
| <i>VII</i>                      | 643                          | 0.72  | 0.39   | 0.62   | 0.74  | 0.78   |
| 3-CN                            | 46.7                         | (4.56)  | (8.30)   | (5.33)   | (4.42)  | (4.20)   |
| <i>IX</i>                       | 570                          | 0.86  | 0.52   | 0.84   | 0.98  | 0.98   |
| 3-(=O)                          | 36.3                         | (4.19)  | (6.85)   | (4.27)   | (3.66)  | (3.66)   |
| <i>X</i>                        | 760                          | 0.67 <sup>j</sup>   | 0.31 <sup>k</sup>  | 0.64   | —   | 0.84 <sup>l</sup>                                    |
| 4-CN                            | 0                            | (5.14) <sup>j</sup>                                       | (11.03) <sup>k</sup>   | (5.99)   | —   | (4.07)   |
| <i>XI</i>                       | 406                          | 1.37  | 1.06   | —  | —   | 1.13   |
| 2-CN                            | 67.3                         | (3.37)  | (4.39)   | —  | —   | (4.10)   |

<sup>a</sup> Kirkwood-Westheimer<sup>5</sup> sphere in the Tanford modification<sup>31</sup>; <sup>b</sup> Westheimer-Kirkwood ellipsoid<sup>6</sup> in the Tanford modification<sup>31</sup>; <sup>c</sup> Ehrenson ellipsoid<sup>8</sup>; <sup>d</sup> Ehrenson sphere<sup>20</sup>; <sup>e</sup> relative to vacuum,  $\epsilon = 1$ ; <sup>f</sup> the effective dielectric constant as it would be required by the experiment; calculated back from Eq. (1) and the experimental  $\log(K/K^0)$ ; <sup>g</sup> in the conformation with OR as close as possible to COOH; <sup>h</sup> in the conformation with OR as remote as possible from COOH. <sup>j</sup> ref.<sup>17</sup> gives  $\log(K/K^0) = 0.58$ ,  $\epsilon_{cf} = 5.4$ ; <sup>k</sup> ref.<sup>15</sup> gives  $\epsilon_{cf} = 13$ ;  $\log(K/K^0)_{\text{calc}} = 0.30$ ; <sup>l</sup> ref.<sup>15</sup>.



In order to compare our results to the electrostatic theory, several procedures are possible<sup>3</sup>: a) direct comparison of experimental values of  $\log(K/K^0)$  and those predicted by Eq. (1) requires a reasonable cavity model to be constructed which is then tested simultaneously; b) the dependence on  $\epsilon$  can be followed for various solvents and an approximate cavity model, correct in a qualitative sense, may be sufficient; c) the dependence on  $\mu$  can be followed in a series with variable substituents treating  $\epsilon_{ef}$  as an adjustable parameter, a cavity model need not be necessary; d) molecules with the same substituent can be compared, differing sharply in the geometrical parameters  $\Theta$  and/or  $r$ , but the difference in  $\epsilon_{ef}$  cannot be neglected and a cavity model is difficult to apply if the molecules are strongly asymmetric<sup>3</sup>. Our data make

TABLE III

Calculated Relative Dissociation Constants of Substituted Bicyclo[2,2,2]octane-1-carboxylic Acids (80% methyl cellosolve, 25°C)

| Compound<br>Substituent<br>X    | $r$ , pm<br>$\Theta^\circ$ | Sphere <sup>a</sup><br>$\log(K/K^0)$<br>$\epsilon_{ef}^e$ | Ellipsoid <sup>b</sup><br>$\log(K/K^0)$<br>$\epsilon_{ef}^e$ | Ellipsoid <sup>c</sup><br>$\log(K/K^0)$<br>$\epsilon_{ef}^e$ | Sphere <sup>d</sup><br>$\log(K/K^0)$<br>$\epsilon_{ef}^e$ | Experiment<br>$\log(K/K^0)$<br>$\epsilon_{ef}^{e,f}$ |
|---------------------------------|----------------------------|---|--|--|---|--|
| <i>II</i>                       | 572                        | 0.45  | 0.28   | 0.44   | 0.48  | 0.56   |
| 3-Cl                            | 54.1                       | (4.05)  | (6.55)   | (4.13)   | (3.79)  | (3.24)   |
| <i>III</i>                      | 575                        | 0.44  | 0.27   | 0.43   | 0.46  | 0.62   |
| 3-Br                            | 54.5                       | (4.06)  | (6.60)   | (4.16)   | (3.87)  | (2.87)   |
| <i>IV</i>                       | 583                        | 0.40  | 0.25   | 0.39   | 0.41  | 0.42   |
| 3-I                             | 53.4                       | (4.10)  | (6.73)   | (4.26)   | (4.01)  | (3.95)   |
| <i>V</i>                        | 621                        | 0.45  | 0.26   | 0.40   | 0.49  | 0.18   |
| 3-OH <sup>g</sup>               | 25                         | (4.27)  | (7.37)   | (4.73)   | (3.90)  | (10.58)  |
| 3-OH <sup>h</sup>               | 621                        | -0.14   | -0.08  | -0.13  | -0.16   | 0.18   |
|                                 | 107                        | (4.27)  | (7.37)   | (4.13)   | (3.90)  | (-3.41)  |
| <i>VI</i>                       | 621                        | 0.34  | 0.20   | 0.31   | 0.37  | 0.22   |
| 3-OCH <sub>3</sub> <sup>g</sup> | 16                         | (4.27)  | (7.37)   | (4.73)   | (3.90)  | (6.60)   |
| 3-OCH <sub>3</sub> <sup>h</sup> | 621                        | -0.04   | -0.0   | -0.03  | -0.04   | 0.22   |
|                                 | 96                         | (4.27)  | (7.37)   | (4.73)   | (3.90)  | (-0.72)  |
| <i>VII</i>                      | 643                        | 0.75  | 0.42   | 0.65   | 0.78  | 0.80   |
| 3-CN                            | 46.7                       | (4.37)  | (7.76)   | (5.04)   | (4.22)  | (4.09)   |
| <i>IX</i>                       | 570                        | 0.89  | 0.55   | 0.88   | 1.01  | 0.98   |
| 3(=O)                           | 36.3                       | (4.04)  | (6.52)   | (4.10)   | (3.54)  | (3.66)   |
| <i>XI</i>                       | 406                        | 1.40  | 1.08   | —  | —   | 1.20   |
| 2-CN                            | 67.3                       | (3.30)  | (4.29)   | —  | —   | (3.86)   |

<sup>a-h</sup> See Table II.

possible the tests sub (a), (c), (d) while the two solvents are insufficient for a test sub (b).

a) Comparison of theory with experiment is presented in Tables II and III; on the one hand in terms of the relative dissociation constants ( $\log K/K^0$ ) – calculated from Eq. (1) and experimental, on the other hand in terms of  $\epsilon_{ef}$  – calculated from the cavity model and from the experimental pK. The latter test is more sensitive, giving sometimes unrealistic values (e.g. negative) of  $\epsilon_{ef}$ , irrespective of the model in use. In general, the choice of the cavity model is critical while the parameters  $\Theta$  and  $r$  can be determined rather reliably. The new spherical model of Ehrenson<sup>20</sup> gives evidently the best fit (in average 0.07 pK units) and corresponds also rather closely to the actual shape of the molecules (Fig. 1). The original spherical model of Kirkwood and Westheimer<sup>5</sup> and the improved ellipsoidal model of Ehrenson<sup>8</sup> seem to be still satisfactory (deviations 0.10 and 0.12 pK units, respectively), although the pertinent cavities circumscribe the molecules I–IX poorly. There is a shortcoming that for mathematical reasons the diameter of the sphere, or the main axis of the ellipsoid must go through the substituent, in variance with the real geometry. The original ellipsoidal model of Westheimer and Kirkwood<sup>6</sup> fails because the proton and substituent must be located in the foci of the ellipsoid; the resulting cavity is then too thin. The axially unsymmetrical substituents OH and OCH<sub>3</sub> deviate within the framework of any model and will be discussed below.

Summarizing, the electrostatic theory predicts reasonable values of relative dissociation constants for regular-shaped molecules which can be approximated by a simple cavity model (mostly for carboxylic acids, see below). Some arbitrary details of this model are not essential, except the parameter  $d$ , the depth of the pro-

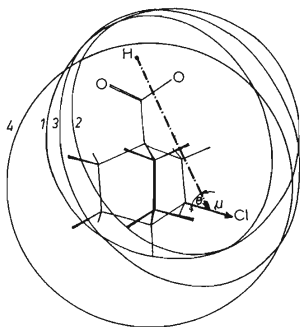


FIG. 1

Fitting of the Molecule of 3-Chlorobicyclo[2,2,2]octane-1-carboxylic Acid by the Cavity Models

1 Kirkwood–Westheimer sphere<sup>5</sup>, 2 Westheimer–Kirkwood ellipsoid<sup>6</sup>, 3 Ehrenson ellipsoid<sup>8</sup>, 4 Ehrenson sphere<sup>20</sup>.

ton and of the substituent dipole under the cavity surface. Although the Tanford<sup>31</sup> value, 150 pm, seems physically reasonable, it appears merely to be an adjustable parameter which can compensate for some shortcomings of the theory and is thus applicable only for certain molecules or certain solvents. Its possible dependence on solvent was already mentioned<sup>41</sup>; the most efficient test would be the application to gas phase acidities where the problems with the effective dielectric constants are almost removed. The gas phase data on bicyclo[2,2,2]octane-1-carboxylic acids are not available, those on 4-substituted benzoic acids<sup>42</sup> have already revealed<sup>14</sup> serious discrepancies when interpreted in terms of Eq. (1). One could draw a conclusion that in solution a compensation for an additional non-electrostatic effect takes place but further examination is still necessary.

c) For the substituent effects within a reaction series, the electrostatic theory predicts that they are proportional to the expression  $\mu \cos \Theta / r^2 \epsilon_{ef}$  with the proportionality constant equal to  $e/2 \cdot 303kT$ . Since  $\epsilon_{ef}$  may vary but little within the series (compare Tables II and III), one can plot<sup>17,19,37</sup>  $\log K$  vs  $\mu \cos \Theta / r^2$  and obtain a mean value of  $\epsilon_{ef}$  from the slope as an adjustable parameter. In a further simplification even the differences in  $r$  and  $\Theta$  are neglected<sup>43,44</sup> (in some particular series  $\Theta$  may *e.g.* equal zero for all derivatives). The  $\log K$  is plotted<sup>45</sup> against the mere substituent dipole  $\mu$ , in this case the slope has no evident physical meaning. In our case (Fig. 2) the former approximation was found acceptable but the latter was not; this is due mainly by the different geometrical parameters of VII and IX. The slopes in Fig. 2

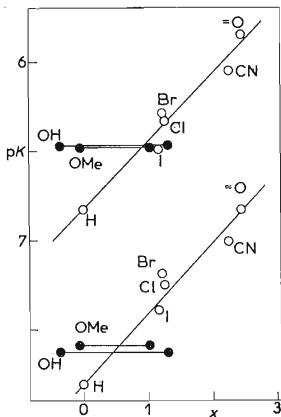


FIG. 2

#### Test of the Electrostatic Theory for Variable Substituents

Dissociation constants of the acids I–IX are plotted vs the substituent characteristic  $x = 10^{11} \mu \cos \Theta / r^2$  ( $\text{Cm}^{-1}$ ); at the top pK's in 50% ethanol, at the bottom — pK's in 80% MCS; ○ simple substituents, ● unsymmetrical substituents.

define a mean effective dielectric constant  $\epsilon_{\text{ef}} = 3.86$  or  $3.91$  in 50% ethanol and 80% methyl cellosolve, respectively, in good agreement with the cavity models. Fig. 2 and similar plots<sup>17,19,45,46</sup> demonstrate some relationships between the effects of substituents on reactivity and their dipole moments, at least for simple, axially symmetrical substituents. However, it was already argued<sup>47</sup> that this relationship is not generally valid for more complex and/of unsymmetrical groups which deserve a closer examination. For instance, the substituents Cl and  $\text{CH}_2\text{Cl}$  possess essentially equal dipole moments while their effects on the dissociation constants are quite different; such differences should be accounted for by the geometrical parameters  $r$  and  $\theta$ . Among our derivatives, there are two (V, VI) with unsymmetrical substituents, OH and  $\text{OCH}_3$ , respectively; in addition their conformation is unknown so that actual values of  $r$  and  $\theta$  are not available. In Tables II and III we give the calculations for the two extreme conformations; the measured values should lie approximately in the middle. Fig. 2 agrees fairly with this assumption. A similar excuse is, however, not possible with 4-substituted bicyclo[2,2,2]octane-1-carboxylic acids but the named substituents still deviate from the correlation. The discrepancy was formally solved<sup>12,17-19,37</sup> by giving the OH dipole arbitrarily the direction<sup>48</sup> from C to O, but it is quite an unrealistic assumption. Similar problems are encountered with other unsymmetrical substituents like  $\text{COCH}_3$ ,  $\text{CONH}_2$ ,  $\text{OCOCH}_3$ . The most complete series of experimental data concerns the dissociation of 4-substituted quinuclidinium ions in water<sup>49</sup>. If we treat these data in the same manner as in Fig. 2, we obtain Fig. 3. Irrespective of the slope the deviations are apparent, particularly for the

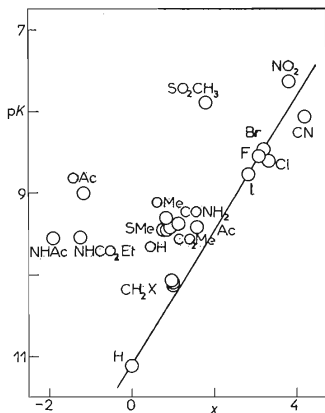


FIG. 3

Test of the Electrostatic Theory for Variable Substituents

The dissociation constants of 4-substituted quinuclidinium ions in water<sup>49</sup> are plotted as in Fig. 2. The straight line has been drawn through the points for simple substituents.

substituents  $\text{OCOCH}_3$ ,  $\text{NHCOCH}_3$ ,  $\text{SO}_2\text{CH}_3$  and further. The direction of these deviations is always in such a sense that the influence of the angle  $\theta$  is overestimated by the theory, in other words the observed effect is intermediate between the predictions of the electrostatic theory and of the through-bonds theory. Most striking is substituent  $\text{NHCOCH}_3$  whose pure electrostatic effect should be acid-weakening, unless the normal conformation<sup>50</sup> (H antiperiplanar to  $=\text{O}$ ) is reversed. A small shift of the substituent effect with reversed conformation – but no change of the sign – was manifested in the  $^{19}\text{F}$ -NMR shifts<sup>51</sup>. A similar overestimating of the angle  $\theta$  by the electrostatic theory was observed<sup>3</sup> even with simple substituents if  $\theta$  was large. A possible explanation of these facts would be a further effect operating in addition to the purely electrostatic forces; for instance a change of the O–H bond energy with substitution<sup>3</sup> can be taken into consideration.

d) The effect of the geometrical parameters  $r$  and  $\theta$  on the relative dissociation constants will be examined here on two levels: within the bicyclo[2,2,2]octane series and quite generally for various rigid molecules. Within the series of 3-substituted bicyclo[2,2,2]octane-1-carboxylic acids *I–VII* the geometrical parameters vary but slightly (Tables II and III), the same applies for the 4-isomers *X*. Therefore, we may compare the experimental ratio of substituents effects (1 : 1.12 for the positions 3- and 4-, respectively) to that calculated for a typical simple substituent. For Br we obtain from Eq. (1) the ratio 1 : 1.17 or 1 : 1.36 according to the cavity model used, Kirkwood–Westheimer sphere<sup>5</sup> or ellipsoid<sup>6</sup>. The result is thus rather sensitive to the model and the difference between isomers is somewhat overestimated – just the opposite of the  $\sigma$ -inductive theory. The value of 1.17 seems reasonable but it includes the  $\epsilon_{\text{eff}}$  values greater for the 4- than for the 3-isomer, while in fact more lines of force must pass through the solvent in the case of 3-derivatives. This effect is counterbalanced by the angle  $\theta$  so that we may confirm the previous finding<sup>3</sup> that the electrostatic theory gives this angle too much weight.

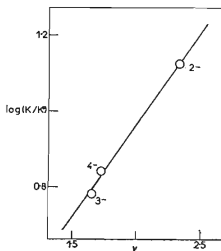


FIG. 4

Test of the Electrostatic Theory for Variable Positions

The relative dissociation constants of X-cyanobicyclo[2,2,2]octane-1-carboxylic acids (50% ethanol) are plotted against the geometrical parameter  $y = 10^{18} \cos \theta / r^2$  ( $\text{m}^{-2}$ ).

An extension of the above reasoning to 2-substituted acids must be based only on the 2-cyano derivative XI. The cyano group is advantageous in consequence of its small volume, but it is not convenient for the cavity models as it breaks the regular shape of the molecule. For the latter reason the spherical cavity model<sup>5</sup> does not work well for this substituent, in particular the relation of the derivatives 3-CN and 4-CN is reversed by the theory (Tables II and III). Curiously enough, the geometrical factors alone give a good linear relationship for the three isomers (Fig. 4) although  $\epsilon_{ef}$  cannot be constant; the straight line goes through the origin of coordinates and its slope implies  $\epsilon_{ef} = 3.98$ . Similar plots with three points were construed for 2-, 3-, and 4-carboxy-N-methylquinuclidinium (or piperidinium) salts<sup>52</sup>; the effect of the unipolar substituent is not angularly dependent and the differences in the effective dielectric constant were simply neglected. Moreover the straight lines pass far from the origin and according to the theory the substituent effects should be proportional to the geometrical factors, not only linearly dependent on them. Therefore, such plots<sup>52</sup> are unable to prove the essential correctness of the electrostatic approach, they are rather at variance with it. A common weakness of these plots and of Fig. 4 is a low statistical weight.\*

A much more significant test can be obtained from literature data for several rigid systems with the same substituent. Since the data are scarce, we were obliged to combine those for substituents Cl and Br, as well as for two solvents: 50% ethanol and 50% methanol. Fig. 5, based on the spherical cavity model<sup>5</sup>, appears to be essentially in accord with the theory, although some deviations are marked. However, most of the points are very close, it means that the model systems were of similar size and one distant point for chloroacetic acid is then of decisive importance. It would be very useful to study molecules of intermediate size between acetic and bicyclo-[2,2,2]octane-1-carboxylic acids, or, on the other hand, still larger than the latter. Some deviations in Fig. 5 (halved points) may be also attributed to the  $\pi$ -inductive effect since the electrostatic theory is strictly valid only for fully saturated systems. Most interesting is the behaviour of ammonium ions differing sharply from carboxylic acids: the substituent effect is *c.* twice as large as theoretically predicted. This is seen in Fig. 5; further discrepancies, even in the sign of the effect, were observed with aminoindanones<sup>3</sup>. There is, of course, no reason why the electrostatic theory should not be applicable to ammonium ions. More probably some parameters, *e.g.* the position of hydrogen of the COOH group or the Tanford<sup>31</sup> value *d*, have been accommodated with a particular respect to carboxylic acids, in order to compensate

\* Under the conditions outlined even the high correlation coefficients are unable to give the quoted results<sup>52</sup> some significance: the common linear regression had to be at least modified by the condition that the straight line goes through the origin. Note further that the correlation coefficient  $r = 0.9997$  with three points is statistically significant at the level  $\alpha = 0.025$  but not at  $\alpha = 0.010$ . Such calculations mean only misusing of statistical formulae.

for some additional non-electrostatic effects (entropy term, unequal O—H bond energies, unequal enthalpies of solvation). Unfortunately the ammonium ions as well as further acids of this type have been little studied in connection with the electrostatic effects and but few rigid model molecules have been synthesized.

In order to summarize the evidence for and against the electrostatic theory, let us firstly restrict ourselves to its original form with a single value of  $\epsilon_{ef}$  and to simple dipolar substituents on a saturated system. Accordingly the extensions giving several discrete values of  $\epsilon_{ef}$  to a molecule<sup>59,\*</sup> or describing a complex substituent as composed of poles and dipoles<sup>60</sup> are set aside. In addition we shall sharply distinguish between the basic assumptions of the theory on the one hand, and a greater or less convenience of the cavity model on the other hand. The very approximate nature of any simple cavity compared with real molecules is beyond discussion<sup>3,63</sup>, even taking into consideration recent refinements<sup>8,20</sup>. Hence attention is to be focused to arguments valid whatever the particular value of the effective dielectric constant

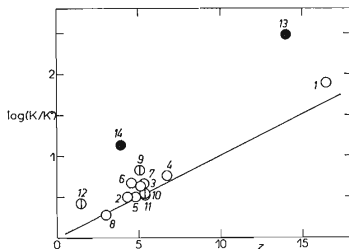


FIG. 5

#### Test of the Electrostatic Theory for Variable Parent Acids

The relative dissociation constants of various chloro (bromo) substituted carboxylic acids (in 50% ethanol or in 50% methanol) are plotted against  $z = 10^{17} \cos \theta / r^2 \epsilon_{ef} (\text{m}^{-2})$  — spherical cavity model<sup>5</sup>. Parent acids: 1 acetic<sup>35</sup>, 2, 3 bicyclo[2,2,2]octane-1-carboxylic (ref.<sup>17</sup> and this work), 4 bicyclo[2,2,1]heptane-1-carboxylic<sup>53</sup>, 5 cyclohexanecarboxylic<sup>37</sup>, 6 adamantane-1-carboxylic<sup>54</sup>, 7 cubanecarboxylic<sup>55</sup>, 8 spiro[3,3]heptane-2-carboxylic<sup>46</sup>, 9 bicyclo[2,2,2]oct-2-ene-1-carboxylic<sup>19</sup>, 10 dibenzobicyclo[2,2,2]octa-2,5-diene-1-carboxylic<sup>19</sup>, 11 tribenzobicyclo[2,2,2]octa-2,5,7-triene-1-carboxylic<sup>56</sup>, 12 4-methylbenzoic<sup>57</sup>, 13 quinuclidinium ion<sup>58</sup>, 14 4-methylquinuclidinium ion<sup>58</sup>. The straight line has the theoretical slope.

\* In this approach<sup>59</sup>, e.g. the part of a molecule bearing the Br substituent is given the dielectric constant of liquid bromine, several other dielectric constants are adjusted empirically. Another procedure<sup>61</sup>, which also represents a *reductio ad absurdum* of the electrostatic theory, defines arbitrarily the distance  $r$  and modified *ad hoc* the laws of electrostatics; it is also at variance with experiments<sup>62</sup>.

may be. Most important in our opinion is the dependence on the dipole angle  $\theta$ . Even if it is somewhat overestimated by Eq. (1), there are convincing proofs that the substituent effect can be even reversed<sup>9,11</sup> for  $\theta > 90^\circ$ , or equal zero<sup>10,12</sup> for  $\theta \approx 0$ . In this point the electrostatic theory is clearly superior to the purely topological description in terms of the  $\sigma$ -inductive effect. Also the required dependence on the distance  $r$ , or on  $r$  and  $\theta$  simultaneously (Figs 4, 5) is mostly confirmed by the experiments but it is not quite contradictory to the predictions of the  $\sigma$ -inductive theory. Note further the difference between carboxylic acids and ammonium ions in Fig. 5. Figs 2, 3 and ref.<sup>17,19,46</sup> show further a relationship between substituent effects and the pertinent dipoles which, of course, can be interpreted in different terms. The solvent effects represent another important aspect of the electrostatic theory since in this point there is virtually no competitive concept. Unfortunately the most suitable model compounds have been investigated only in mixed solvents, but even in pure solvents a disagreement with experiments was observed<sup>41</sup> for all known cavity models. Still more important is the principal variance<sup>14</sup> with ionization equilibria in the gas phase which does not depend of the calculation of  $\epsilon_{ef}$ ; however, data are not available for the best suited models. The solvent dependence and gas phase acidities will be postponed to the next communication<sup>64</sup>. For the present we conclude that the electrostatic approach using a uniform effective dielectric constant and respecting the geometric relations is at least a better approximation than the purely topological concept of transmission through  $\sigma$ -bonds. However, if applied to ionization equilibria, it neglects some additional effects, possibly connected with the bond energy of the bonds to hydrogen. This defect may be partly compensated by particular cavity models with some arbitrary parameters, but only for certain molecules and in certain solvents.

*We are much indebted to Professor S. Ehrenson, Brookhaven National Laboratory, New York, for placing at our disposal the results concerning his new cavity model, and for a fruitful discussion to this point. We thank also Dr M. Synáčková, Dr L. Dolejš, and Dr P. Fiedler (all from Institute of Organic Chemistry and Biochemistry, Prague) for measuring the <sup>1</sup>H-NMR, mass and IR spectra, respectively, and for valuable comments. The elemental analyses were carried out in the Analytical Laboratory of the same Institute (head Dr J. Horáček).*

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