hydro-*endo*-dicyclopentadiene (XV).—To 1.6 g. of potassium metal (0.04 g. atom) was added 30 ml. of toluene, previously dried over sodium. The mixture was heated until the potassium melted and then was allowed to cool slowly with vigorous stirring. A 5.2-g. (0.03 mole) sample of the alcohol XV in 10 ml. of dry toluene was added slowly and the mixture was refluxed for 2 hours with stirring and cooled in an ice-bath; then 6.4 g. (0.045 mole) of methyl iodide was added dropwise. The mixture was heated for an additional hour. The precipitate of potassium chloride was removed by filtration, washed with ethanol, and dissolved in water. The water was extracted with ether, and this extract was added to the toluene–alcohol mixture. The solution was dried over anhydrous magnesium sulfate, and the solvents were removed. The residue, distilled under reduced pressure, yielded 4.1 g. (81%) of product, b.p. 99–101° (8.0 mm.), $n^{28}\text{D}$ 1.4870. The infrared spectrum of this methoxy derivative was the same as that of the product obtained by direct addition of methanol.

Addition of *p*-Thiocresol to 2-Oxa-1,2-dihydro-*endo*-dicyclopentadiene. Preparation of 9-*p*-Thiocresyl-2-oxatetrahydrodicyclopentadiene.—To 13.6 g. (0.1 mole) of the crude bicyclic ether VII was slowly added with stirring 12.4 g. (0.1 mole) of *p*-thiocresol. When the heat of reaction subsided, the mixture was heated to 75° and held at that temperature overnight. The mixture was distilled under vacuum to remove unreacted *p*-thiocresol (b.p. 110–113° (32 mm.)) which solidified in the condenser. The residue was distilled again yielding 20.2 g. (78%) of the thiocresyl derivative, b.p. 148–150° (0.35 mm.). The product solidified after two days and was recrystallized from methanol, m.p. 72.0–72.5°.

Anal. Calcd. for $C_{16}H_{20}OS$: C, 73.80; H, 7.74. Found: C, 73.85; H, 7.80.

In 5 ml. of acetic acid and 5 ml. of acetic anhydride at ice temperature was dissolved 2.6 g. (0.01 mole) of the thiocresyl derivative XXV. To it was added dropwise and with stirring 3 ml. of cold 30% hydrogen peroxide. When heat was no longer evolved, the mixture was heated for one hour on a steam-bath. Cooling the reaction mixture yielded crystals of the sulfone which were recrystallized from methanol. The yield was essentially quantitative, 2.8 g. (96%), m.p. 164–166°.

Anal. Calcd. for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.90. Found: C, 65.52; H, 7.01.

Addition of Phenol to 2-Oxa-1,2-dihydro-*endo*-dicyclopentadiene. Preparation of 9-Phenoxy-2-oxatetrahydrodicyclopentadiene.—A mixture of 13.6 g. (0.1 mole) of the *endo*-ether and 9.4 g. of phenol was added dropwise to 2.0 g. of 98% sulfuric acid maintained at 0°. The reaction was stirred for 2 hours, and then poured into 50 ml. of hot water. The oily layer was washed with hot sodium bicarbonate solution, and distilled under reduced pressure, yielding 2 g. (9%), b.p. 122–124° (0.25 mm.). The oil solidified after one week and the product was recrystallized from methanol; m.p. 62.5–64.5°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.02; H, 7.77.

Bromination of 2-Oxa-1,2-dihydro-*endo*-dicyclopentadiene.—Ten grams (0.074 mole) of the *endo*-ether which had been purified by sublimation, m.p. 85–90°, was dissolved in 40 ml. of chloroform and treated dropwise with stirring with 12 g. (0.075 mole) of bromine in 30 ml. of chloroform. The reaction mixture was stirred overnight and excess bromine was then destroyed by shaking the chloroform solution with aqueous sodium thiosulfate. The chloroform was dried over magnesium sulfate and removed yielding 23.3 g. of a pale yellow viscous liquid which on cooling in an ice-bath gave a precipitate. More chloroform was removed under reduced pressure at room temperature and 12.5 g. (58%) of solid was obtained by cooling a slurry of the crude product in absolute ethanol. A sample was further purified by distillation, b.p. 118–120° (0.3 mm.), and recrystallization from nitroethane, m.p. 101–102°.

Anal. Calcd. for $C_9H_{12}Br_2O$: C, 36.51; H, 4.09. Found: C, 36.66; H, 4.12.

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DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ARKANSAS]

Quantitative Relationships in the Reactions of *trans*-4-X-Cyclohexanecarboxylic Acids and their Methyl Esters[1]

BY SAMUEL SIEGEL AND J. M. KOMARMY[2]

RECEIVED AUGUST 19, 1959

The dissociation constants of a series of *trans*-4-X-cyclohexanecarboxylic acids (X = H, –OH, –OCH$_3$, –Cl, –CO$_2$CH$_3$, –CN and =O) have been measured in water and two mixed solvents at 25°. The rate of reaction of these acids with diphenyldiazomethane and the rate of the basic hydrolysis of the methyl esters in 50% aqueous methanol were also determined, the latter at three temperatures. These data are correlated by an equation of the form $\log k/k_0 = \rho''\sigma''$, *e.g.*, the Hammett equation. The dimensions of substituted cyclohexanecarboxylic acids approximate the dimensions of substituted benzoic acids and the magnitudes of the substituent effects are comparable. The difference in the effect of a substituent upon reactivity in the two series results mainly from the resonance interaction of the substituent with the aromatic ring, an effect which is obviously absent in the saturated compounds. Groups which do not interact strongly with an aromatic ring have about the same quantitative effect upon reactivity in both series. The substituent effects can be calculated with reasonable accuracy by employing the Kirkwood–Westheimer model as modified by Tanford.

A search for quantitative relationships between the structure of organic compounds and their reactivity has received considerable attention.[3–6] Undoubtedly, the Hammett equation correlates the broadest spectrum of reactions in a simple way.[7] The success of this equation has been attributed to the rigidity which the benzene ring imparts to the structure of substituted aromatic compounds and which holds the reactive center and the substituent at a relatively fixed distance.[8] In few aliphatic systems is so simple a relation-

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[1] From the dissertation submitted by J. M. Komarmy in partial fulfillment of the requirements for the Ph.D. degree at the University of Arkansas, January, 1958. Presented in part before the Division of Organic Chemistry, 132nd Meeting of the American Chemical Society, New York, N. Y., September, 1957.

[2] Flint Community College, Flint, Mich.

[3] L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, p. 184.

[4] G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1941.

[5] H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[6] R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

[7] Reference 3, p. 186.

[8] P. D. Bartlett in "Organic Chemistry," Vol. IV, Edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 19–20.

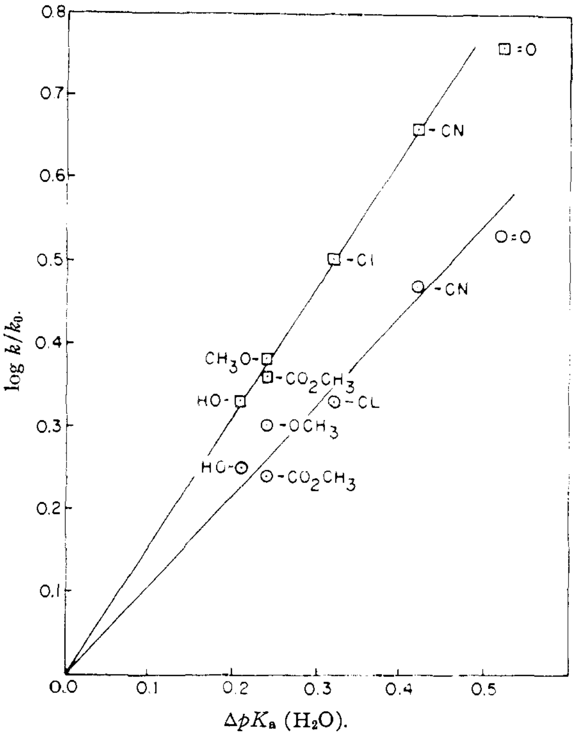

Fig. 1.—The relative dissociation constants of 4-X-cyclohexanecarboxylic acids measured (a) in 50% by volume aqueous ethanol ⊡ and (b) in 50% by weight aqueous methanol ⊙ compared with ΔpK_a measured in water, all at 24.9°.

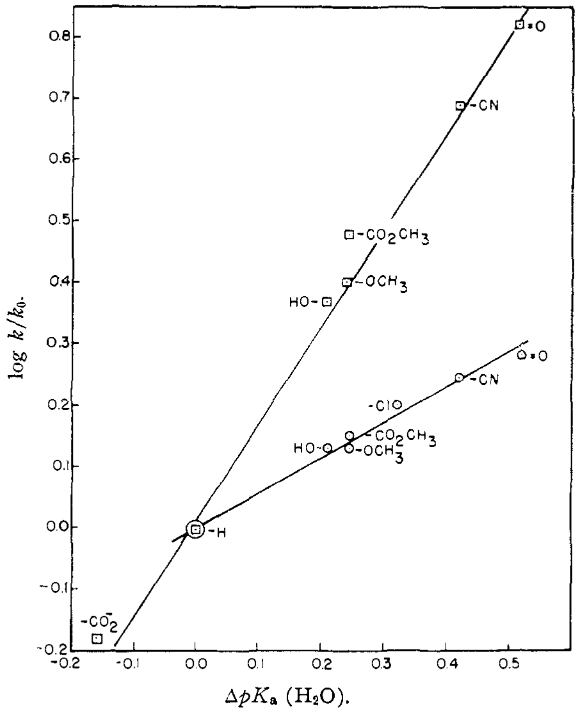

Fig. 2.—The relative rate constants for (a) the alkaline hydrolysis of the methyl esters ⊡ and (b) the reaction of the acids with diphenyldiazomethane ⊙ compared to ΔpK_a of 4-X-cyclohexanecarboxylic acids measured in water.

ship found, a notable exception being the 4-X-bicyclo(2,2,2)octane-1-carboxylic acids and esters.[9] Current theory[10,11] suggests the disubstituted cyclohexanes, particularly the *cis*-1,3- and the *trans*-1,4-isomers (the isomers in which the substituents are both equatorially placed), would have the requisite rigidity. Our preliminary study[12] on reactions of *cis*-3-X-cyclohexanecarboxylic acids and their methyl esters justified this expectation. We now wish to report more extensive measurements on the *trans*-4-X-cyclohexanecarboxylic acids and their methyl esters.

Experimental Results and Discussion

With the exception of *trans*-4-cyanocyclohexanecarboxylic acid and its methyl ester, all of the compounds used in this study have been recorded previously. The acids were purified carefully by crystallization from suitable solvents and the pure stereoisomeric acids were converted to the methyl esters with diazomethane in ether by conventional methods.

The dissociation constants of the acids were measured in water, aqueous methanol (50% by weight) and aqueous ethanol (50% by volume). The technique described by Grunwald[13] was used for the measurements in aqueous methanol. In water, the method was the one described by Davis and Hetzer[14] while a procedure similar to the one used by Roberts was employed for measurements in the aqueous ethanol.[9] The measurements in aqueous ethanol are apparent pK_a's, whereas the others are presumably thermodynamic constants. The reaction of the acids with diphenyldiazomethane in absolute ethanol was measured at 25°[9] and the alkaline hydrolysis of the methyl esters in aqueous methanol (50% by weight) was determined at three temperatures. The results are presented in Tables I, II, III, and in Figs. 1 and 2. Obviously, these data are correlated by an equation like that of Hammett, *e.g.*

$$\log k/k_0 = \rho''\sigma''$$

where k and k_0 refer to the rate or equilibrium constants for reactions of the substituted and the unsubstituted reactants, ρ'' is a constant characteristic of the reaction and σ'' is characteristic of the substituent.

The correlation compares well with the data reported by Roberts and Moreland, and illustrates again that a simple quantitative relationship between structure and reactivity exists for an appropriately limited series of aliphatic compounds. Probably the entropy of reaction is either regular or constant for the members of the series.[3,6] The variation in the rate constants for the hydrolysis of the esters appears to be associated with the change in enthalpy of activation, the entropy of

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[9] J. D. Roberts and W. T. Moreland, Jr., THIS JOURNAL, **75**, 2167 (1953).

[10] C. W. Beckett, K. S. Pitzer and R. Spitzer, *ibid.*, **69**, 2488 (1947).

[11] S. Siegel, *ibid.*, **75**, 1317 (1953).

[12] S. Siegel and W. Duffy, Abstracts of Papers Presented at the 128th National Meeting of the American Chemical Society, Minneapolis, Minn., September, 1955, p. 33-O.

[13] A. L. Bacarella, E. Grunwald, H. P. Marshall and E. L. Purlee, *J. Org. Chem.*, **20**, 747 (1955).

[14] M. M. Davis and A. B. Hetzer, *J. Phys. Chem.*, **61**, 123, 125 (1957).

TABLE I

DISSOCIATION CONSTANTS IN WATER, METHANOL–WATER (50% BY WT.) AND ETHANOL–WATER (50% BY VOL.) AT 24.91 ± 0.05° OF THE *trans*-4-X-CYCLOHEXANECARBOXYLIC ACIDS

X	Water, $K_a \times 10^5$	Methanol-water, $K_a \times 10^6$	Ethanol–water, $K_a \times 10^7$
$-CO_2^-$	0.44[a,b]	..	..
-H	1.26[c]	0.78	3.98
-OH	2.04[c]	1.37	8.41
$-OCH_3$	2.19	1.53	9.55
$-CO_2CH_3$	2.19	1.36	9.02
$-CO_2H$	4.28[a,b]	..	..
-Cl	2.63	1.66	12.7
-CN	3.31	2.31	18.0
=O	4.17	2.64	22.8

[a] Statistical correction, $-CO_2^- = 0.88 \times 10^{-5}$; $-CO_2H = 2.14 \times 10^{-5}$. [b] Reported: $-CO_2^- = 0.38 \times 10^{-5}$; $CO_2H = 6.60 \times 10^{-5}$; R. Kuhn and A. Wasserman, *Helv. Chim. Acta*, 11, 50 (1928). [c] Reported for -H, 1.25×10^{-5}, for -OH, 2.10×10^{-5}; M. Kilpatrick and J. G. Morse, THIS JOURNAL, **75**, 1846 (1953).

TABLE II

REACTIVITIES OF *trans*-4-X-CYCLOHEXANECARBOXYLIC ACIDS TOWARD DIPHENYLDIAZOMETHANE IN ABSOLUTE ETHANOL AT 24.91 ± 0.05°

X	k_2, l. mole^{-1} sec.$^{-1}$
-H	0.357
-OH	.484
$-OCH_3$	.483
$-CO_2CH_3$	.495
-Cl	.564
-CN	.622
=O	.676

TABLE III

RATES OF ALKALINE HYDROLYSIS OF THE METHYL *trans*-4-X-CYCLOHEXANECARBOXYLATES IN METHANOL–WATER (50% BY WT.), 15.02 ± 0.05°, 24 91 ± 0.05° AND 34.90 ± 0.05°

X	k_2, liters moles^{-1} sec.^{1} × 10^{3}		
	15.02°	24.91°	34.90°
-H	0.98	2.34	5.01
$-CO_2^-$	..	3.33[a]	...
-OH	2.33	5.45	12.40
$-OCH_3$	2.55	5.83	11.70
-CN	4.87	11.46	23.44
$-CO_2CH_3$	..	14.12[b]	...
=O	6 12	15.56	29.16

[a] The value at zero ionic strength is estimated to be 1.55×10^{-3}. [b] For comparison with the other esters, the constant should be divided by 2 giving 7.06×10^{-3}.

TABLE IV

ENTHALPIES AND ENTROPIES OF ACTIVATION FOR THE BASIC HYDROLYSIS OF METHYL *trans*-4-X-CYCLOHEXANECARBOXYLATES

X	ΔH	ΔS
-H	14 7	−9.9
-OH	15.0	−9.5
$-OCH_3$	13.8	−9.7
-CN	14.1	−9.8
=O	14.0	−9.6

activation being essentially invariant (Table IV). However, the range of values recorded is small and undue weight should not be attached to this observation.

Those substituents which do not interact strongly with the benzene ring have about the same quantitative effect in both the aromatic and the cyclohexane series investigated (Table V). The largest differences between the substituent constants for *p*-substituted aromatic compounds (σ_p) and the *trans*-4-substituents of the cyclohexanes (σ'') are for groups such as -OH, and $-OCH_3$ for which even the signs are different. These groups powerfully activate the benzene ring toward electrophilic substitution and, according to theory, strongly interact with the benzene ring in its ground state.

TABLE V

COMPARATIVE SUBSTITUENT CONSTANTS

X	4-Cyclohexyl-	4-Bicyclooctyl-1	*p*-Phenyl-[a]	*m*-Phenyl-[a]
-H	0.000	0.000	0.000	0.000
-OH	.227	.283	− .357	− .002
$-CO_2CH_3$	.244	.297[b]	.402	.315
$-OCH_3$	.255	...	− .268	.115
-Cl	.335	0.454[c]	.227	.373
-CN	.440	0.579	.628	.678
=O	.513	...	...	...

[a] From ref. 5. [b] Ethyl instead of methyl. [c] Bromo instead of chloro.

A comparison of the substituent constants for 4-X-cyclohexanecarboxylic acids with those obtained by Roberts and Moreland[9] for the 4-X-bicyclo(2,2,2)octane-1-carboxylic acids is given, also, in Table V. Although following the same order, the substituent constants of the latter are about 30% larger. The difference is readily accommodated by the electrostatic model referred to in the following section, by noting that (1) the substituents in the cyclohexanecarboxylic acids are more distant from the ionizable proton, (2) the component of the molecular dipole along the line joining its center to the ionizable proton is less, and (3) the space between the proton and the dipole contains less hydrocarbon material.

The substituent constant σ'' must also be proportional to the polar substituent constant σ^* estimated by Taft[15] because of the proportionality between the latter and the constants reported by Roberts and Moreland.

The reaction constants ρ'' (Table VI) have been obtained by assuming ρ'' is unity for the dissociation constants in water at 25°. The relationship suggested by Grunwald and Berkowitz[16] predicts a larger value of ρ'' in 50% (by weight) aqueous methanol (>1.24) than observed here while the value for aqueous ethanol, 50% by volume, agrees well with data for substituted benzoic acids (1.46). Because ρ'' and σ'' are inversely related, an error in one set of terms may be compensated by the other. Assuming that the reaction constants for cyclohexanecarboxylic acids are the same as for benzoic acids implies that the susceptibility of the reaction to changes in polarity of the group attached to the reactive center is the same for both series of compounds. Apparently, changes in the polarity of the external environment of benzoic and cyclohexanecarboxylic acids have almost identical

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(15) Reference 6, p. 594.

(16) E. Grunwald and B. J. Berkowitz, THIS JOURNAL, **73**, 4939 (1951).

effects on their dissociation constants, for the ratio of the constants ($K_{A_xB_0}$) is almost independent of the concentration of added neutral salts or a variation in solvent from water to diethylene glycol.[17a] On the other hand, Kilpatrick and Morse[17b] report that the relative dissociation constants of *cis*-3- and *trans*-4-hydroxycyclohexanecarboxylic acids (cyclohexanecarboxylic acid being the reference acid) *decreases* with a decrease in the dielectric constant of the solvent, contrary to expectations based both on theory and the studies of Wooten and Hammett.[18] The anomaly may be associated with the hydroxy group of the substituted acids and the fact that the alcoholic solvents were free of water. In the present study, mixed solvents containing large portions of water were employed, and the relative dissociation constants increased as the bulk dielectric constant of the medium decreased.

TABLE VI

ρ''-VALUES FOR THE REACTIONS STUDIED

Reaction	log K_0		s^a
1. Ionization of acids (water)	−4.900	1.000	. . .
2. Ionization of acids (aq. methanol, 50% by wt.)	−6.108	1.037	0.024
3. Ionization of acids (aq. ethanol, 50% by vol.)	−6.400	1.490	.019
4. Acids with diphenyldiazomethane (100% ethanol at 24.91°)	−0.447	0.540	.021
5. Alkaline hydrolysis of methyl esters (50% by wt. aq. methanol at 24.91°	−2.631	1.586	.013
6. Same as 5 only at 15.02°	−3.009	1.544	.051
7. Same as 5 only at 34.90°	−2.300	1.478	.054

[a] Standard deviation.

The reactions used in the above correlation are characterized as polar reactions and, consequently, the quantitative effect of a substituent upon reactivity which is thus revealed should be accountable in terms of an appropriate form of the electrical-field theory.[19,20]

The electrical-field theory attributes the effect upon the dissociation of a carboxylic acid of replacing a hydrogen atom by a polar group as due to the difference in electrical properties of the substituent compared to hydrogen. The transmission of the electrical effect to the center of action (the ionizable proton in this example) is a function of the material in which the substituent and the reactive center are imbedded. Kirkwood and Westheimer[21] have provided the most elegant mathematical treatment of the effect of polar groups upon the dissociation of carboxylic acids through a model which represents the carboxylic acid or anion as a cavity of low dielectric constant within a continuum, the solvent, of higher dielectric. In spite of limitation, theirs is the most satisfactory quantitative theory of substituent effects that has been devised, particularly with the modification suggested by Tanford[22] that the depth within the cavity at which a charge or a point dipole is located is best taken as a fixed parameter, approximately 1.0 Å. for discrete charges and 1.5 Å. for a point dipole.

In Table VII are presented the results of calculations according to the Kirkwood–Westheimer model as well as the result of employing the Tanford modification.[22] The calculations are based upon the equation

$$\Delta pK_a = \frac{e\mu \cos \zeta}{2.303\, kTR^2D_E}$$

where e is the protonic charge, μ is the dipole moment of the substituent, ζ is the angle between the dipole and the line joining its center with the ionizable proton, k is the Boltzmanm constant, T is the absolute temperature, R is the distance between the center of the dipole and the ionizable proton, D_E is the effective dielectric constant for the molecule and ΔpK_a is the difference in pK_a for the substituted and unsubstituted acids.

TABLE VII

CALCULATED ΔpK VALUES IN AQUEOUS SOLUTION FOR THE CYCLOHEXANECARBOXYLIC ACIDS BY THE KIRKWOOD AND WESTHEIMER METHOD

X	$-OH$	$-OCH_3$	$-CO_2CH_3$	$-Cl$	$-CN$	$=O$
Vol. per molecule[a]	220	252	269	233	233	215
R, Å.[b]	6.57	6.70	7.58	6.61	7.86	6.25
λ[c]	1.43	1.45	1.36	1.44	1.30	1.48
$\mu \times 10^{18}$[d]	1.65	1.29	1.74	2.20	3.71	2.75
D_E[e]	9.8	9.0	14.0	9.5	20.4	8.0
Moment angle to $\overline{R}$[f]	49	33	59	13	12	43
ΔpK calcd.	0.13	0.13	0.06	0.26	0.15	0.32
ΔpK found	0.21	0.24	0.24	0.32	0.42	0.52
ΔpK calcd.[g] ellipsoidal model)	0.15	0.13	0.08	0.27	0.24	0.32
ΔpK calcd.[g] (spherical model)	0.39	0.35	0.29	0.75	0.80	0.80

[a] Calculated by Traube's rule; J. R. Partington, "An Advanced Treatise on Physical Chemistry," Longmans, Green and Co., New York, N. Y. 1953, p. 24. [b] The distance between the center of the dipole and the ionizable proton. The suggestion of R. H. Westheimer and M. W. Shookoff, THIS JOURNAL, 61, 555 (1939), for locating the proton was followed. The centers of the dipole for the $-OH$ and $-OCH_3$ groups were placed in accordance with the model described by Kilpatrick and Morse, *ibid.*, **75**, 1846 (1953), and the center of the $-CO_2CH_3$ group was located in an analogous manner. The paper by E. J. Corey and R. A. Sneen, *ibid.*, **77**, 2505 (1955), was valuable for the calculation of the distance between two points within a molecule of a disubstituted cyclohexane in the "chair" conformation. [c] Calculated assuming the molecule has the shape of a prolate ellipsoid of revolution. [d] C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, Chap. VIII. [e] Obtained by graphical interpolation from the tables in ref. 21. [f] Calculated from geometry and the moment angle given by Smyth in ref. *d*. [g] Calculated using Tanford's suggestion for the location of the center of a dipole relative to the "surface" of the molecule.

The results are not wholly satisfying. Recent discussions of the shortcomings of the Kirkwood–Westheimer model have been presented by others and require no repetition.[9,22] Apparently, the

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(17) (a) M. Kilpatrick, R. D. Eanes and J. G. Morse, THIS JOURNAL, **75**, 588 (1953); (b) M. Kilpatrick and J. G. Morse, *ibid.*, **75**, 1854 (1953).

(18) L. A. Wooten and L. P. Hammett, *ibid.*, **57**, 2289 (1935).

(19) N. Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923).

(20) H. M. Smallwood, THIS JOURNAL, **54**, 3048 (1932).

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

(22) C. Tanford, THIS JOURNAL, **79**, 5348 (1957).

ellipsoidal model is a better approximation to the shape of the substituted cyclohexanecarboxylic acids than is a spherical model. Calculations using the Tanford modification show this strikingly. Interestingly, the reverse seems to apply to the bicyclooctane-1-carboxylic acids, for which the spherical model yields the better fit with experiment.[22] An examination of scale models of the respective carboxylic acids points up this distinction.

To assess the merit of a suggestion that a single value of D_E be used for a series of substituted carboxylic acids,[9,23,24] Fig. 3 is presented. Here ΔpK_a is plotted as a function of the dipole moment and the structural parameters other than the effective dielectric constant D_E. The uncertainty in R^2 and ΔpK_a are suggested by the vertical and horizontal extensions of the indices. The uncertainty in cos ζ is not indicated and is particularly uncertain for the carbomethoxy group and somewhat less so for the hydroxy and methoxy groups. A linear relationship would imply a constant D_E and neglecting the keto group, this relationship is obtained within the over-all experimental uncertainty.

The keto group deviates in the direction of requiring a smaller D_E than for the other substituted acids, an effect which appears in the calculations shown in Table VII. However, specific effects might account for the result such as the polarization of the carbonyl group through the positive end of the solvent dipole,[25] or a direct interaction between the carboxylate and the keto groups.

The substituent effects measured in the cyclohexane series should be classed as polar in distinction to resonance or steric effects.[26] Some authors might prefer to separate the term polar into an "inductive" and a "direct" effect.[9] As described by Ingold,[27] the latter subdivision is quite arbitrary, the term "direct effect" being added in recognition that a change in the polarity of a substituent brings about a change in the electrical field in a distant part of the molecule by a mechanism which is not exclusively the inductive transmission of charge through the chain of atoms joining the respective atomic centers. The electrical field produced by the substituent at a particular point in the molecule is a function of the distribution of matter both within the molecule and its environment.

In the hands of Kirkwood and Westheimer, the electrical field theory treats the same problem by means of an electrostatic model which, by its nature, includes the effects described above through the considered choice of adjustable parameters. The choice of a value for the dielectric constant of the molecular cavity in effect takes into account the induction through the chain of atoms joining the centers of interest. But because the "direct effect" is conceptually so like the electrostatic field theory, it is easy to assume that the two are the same and, thus, a complete theory is, in a sense, taken to be the measure of one of its parts. To avoid this unfortunate situation, it is well to discard the term "direct effect" altogether and retain the earlier concept of the inductive effect which then becomes an alternative and more detailed description of the distribution of electrical charges within a molecule[28] than is provided by the electrostatic model of Kirkwood and Westheimer. Indeed, this veiw has been advanced with more or less emphasis by a number of authors.[26,29,30]

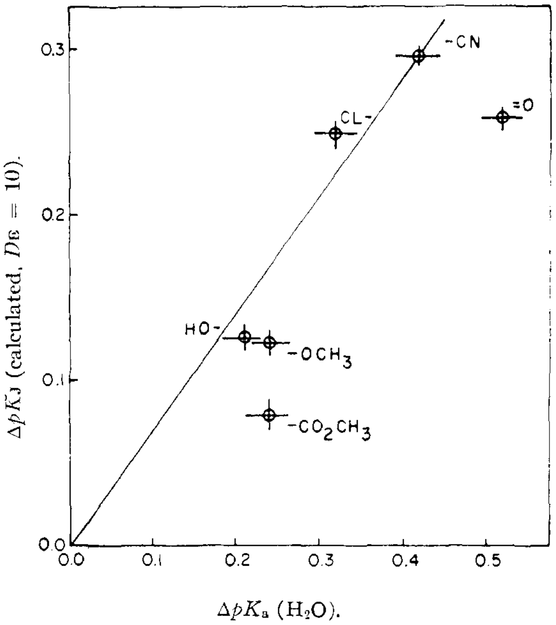

Fig. 3.—Comparison of the relative dissociation constants of the 4-X-cyclohexanecarboxylic acids calculated assuming $D_E = 10$ with the observed ΔpK_a measured in water.

Experimental

Materials.—Reagent grade cyclohexanecarboxylic acid was redistilled under reduced pressure before use. *trans*-4-Hydroxycyclohexanecarboxylic acid was prepared according to the procedure of Campbell and Hunt.[31] *trans*-4-Methoxy and 4-chlorocyclohexanecarboxylic acids were prepared as described by Noyce and Weingarten.[32] 4-Ketocyclohexanecarboxylic acid was prepared from the condensation product of acrylonitrile and ethyl cyanoacetate[33] which was hydrolyzed and the resulting acid cyclized to the keto acid as described by Rubin and Wishinsky.[34]

Hydrogenation of Methyl Terephthalate.—A mixture of methyl terephthalate (0.25 mole, 49 g.), 8–10 g. of Raney nickel, and methanol (80 ml.) were subjected to hydrogenation at a temperature of 160° and 2000 p.s.i. of hydrogen for 3–4 hours. The reaction mixture was filtered and then distilled under reduced pressure. The major fraction was collected between 110–115° (22 mm.), weight 35 g. This material was cooled in the refrigerator and 12.5 g. of the *trans*-methyl hexahydroterephthalate (m.p. 55–65°) separated. The remaining mother liquor (23 g.), containing a

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[23] S. Winstein, E. Grunwald and L. L. Ingraham, THIS JOURNAL, **70**, 821 (1948).

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[25] M. Tamres and S. Searles, Jr., THIS JOURNAL, **81**, 2100 (1959).

[26] See ref. 3, p. 77; and ref. 6, pp. 567–568.

[27] C. K. Ingold, *Chem. Revs.*, **15**, 225 (1934).

[28] Compare ref. 27 with G. W. Wheland and L. Pauling, THIS JOURNAL, **57**, 2086 (1935); and H. H. Jaffé, *J. Chem. Phys.*, **20**, 279 (1952).

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[30] G. W. Wheland, "Advanced Organic Chemistry," Second Edition, J. Wiley and Sons, Inc., New York, N. Y., 1959, Chapter 11.

[31] N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1956).

[32] D. S. Noyce and H. Weingarten, THIS JOURNAL, **79**, 3097 (1957).

[33] H. A. Bruson and T. W. Riener, *ibid.*, **65**, 23 (1943).

[34] M. Rubin and H. Wishinsky, *J. Org. Chem.*, **16**, 443 (1951).

mixture of the *cis*- and *trans*-methyl hexahydroterephthalates, was set aside for isomerization to the *trans*-methyl hexahydroterephthalate.[35]

Isomerization of Dimethyl Hexahydroterephthalate.—A mixture of the *cis*- and *trans*-dimethyl hexahydroterephthalates (153 g.) was refluxed with sodium methoxide (18 g. of Na in MeOH) overnight. The resulting mixture was poured into a large volume of water and extracted with ether. About 81 g. of the *trans*-dimethyl hexahydroterephthalate was recovered (m.p. 65°).

The *trans*-dimethyl 1,4-cyclohexanecarboxylate was hydrolyzed to a mixture of the monoester, the free acid and unreacted ester according to the procedure of Fichter and Holbro.[35] The *trans*- 1,4-cyclohexanedicarboxylic acid was recrystallized from water to a constant melting point; m.p. 309–310°. The *trans*-4-carbomethoxycyclohexanecarboxylic acid was recrystallized from a mixture of ethyl acetate and petroleum ethers; m.p. 124°. The properties of the purified acids are given in Table VIII.

TABLE VIII

PROPERTIES OF THE CYCLOHEXANOIC ACIDS

Acid	M.p., °C. Obsd.	M.p., °C. Lit.	Ref.	Titration, %
Cyclohexanecarboxylic	30–31	31	[a]	100.2
trans-4-OH	147–148	148	31	100.2
trans-4-OCH$_3$	59–60	59–60	32	99.9
trans-4-CO$_2$CH$_3$	124–125	125	35	100.0
trans-4-CO$_2$H	309–310	310	[b]	100.2
trans-4-Cl	159–160	159–159.8	32	100.2
trans-4-CN	151–152	....	..	99.9
4-Keto	67–68	67–68	[c]	100.0

[a] A. Einhorn and H. Meyerberg, *Ber.*, **27**, 2829 (1894). [b] R. S. Stoermer and H. Ladewig, *ibid.*, **47**, 1804 (1914). [c] W. H. Perkin, *J. Chem. Soc.*, **85**, 416 (1904).

Esterification of *trans*-Hexahydroterephthalic Acid.—The *trans*-hexahydroterephthalic acid (48 g.) was dissolved in 200 ml. of absolute methyl alcohol. Concentrated H_2SO_4 (2.7 ml.) was added and the mixture refluxed for 6 hours. The methyl alcohol was removed under vacuum and the remaining oil poured into a large volume of water. The solid obtained (37 g.) was recrystallized from methyl alcohol. The ester was washed again with aqueous $NaHCO_3$ and recrystallized from MeOH; m.p. 69°.[36] Prepared in this way, the ester was free of some unknown impurity which caused previous samples to fluoresce when exposed to ultraviolet radiation.

Preparation of *trans*-Methyl 4-Carboxamidocyclohexanecarboxylate.[37]—A solution of the *trans*-4-carbomethoxycyclohexanecarboxylic acid (28.0 g., 0.15 mole), triethylamine (15.0 g., 0.15 mole) and chloroform (700 ml.) was cooled to 0°. Ethyl chlorocarbonate (16.5 g., 0.15 mole) was added rapidly with continuous agitation for 15 minutes. Anhydrous ammonia was then passed through the solution for 5 minutes. The mixture was stirred at room temperature for one hour and allowed to sit overnight. The chloroform solution was reduced to a volume of about 300 ml., poured into a beaker and allowed to cool. *n*-Hexane was added until the *trans*-methyl 4-carboxamidocyclohexanecarboxylate was completely precipitated (27.5 g., 0.16 mole, m.p. 189–190°).

Eight grams (0.047 mole) of *trans*-methyl 4-carboxamidocyclohexanecarboxylate was dissolved in ether and washed thoroughly with sodium carbonate solution. The ether solution was then dried and the solvent removed. The *trans*-methyl 4-carboxamidocyclohexanecarboxylate remaining was recrystallized from water several times (5.5 g., 0.031 mole, m.p. 194–195°).

Anal. Calcd. for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.31; H, 8.58; N, 7.38.

Preparation of *trans*-Methyl 4-Cyanocyclohexanecarboxylate.[38]—A solution of 28 g. (0.16 mole) of *trans*-methyl 4-carboxamidocyclohexanecarboxylate in excess pyridine was treated with an excess of benzenesulfonyl chloride. The temperature was not allowed to exceed 70° during the addition of the reagent. After the solution was cooled to 25° it was poured into an excess of water. The water solution was acidified and extracted with ether. The ether solution was dried and reduced in volume and allowed to cool. A white solid was obtained which melted at room temperature. The *trans*-methyl 4-cyanocyclohexanecarboxylate, however, was recrystallized from ether several times, the solvent being removed by decantation while the mixture was cold (25.0 g., 0.15 mole).

Partial Hydrolysis of *trans*-Methyl 4-Cyanocyclohexanecarboxylate.—The *trans*-methyl 4-cyanocyclohexanecarboxylate (25.0 g., 0.15 mole) obtained above was hydrolyzed with potassium hydroxide (20.0 g., 0.36 mole) in methyl alcohol (200 ml.) by allowing the mixture to stand three days in room temperature. The volume of the solution was reduced and the remainder poured into water. This water solution was acidified to *p*H 2 and cooled. Approximately 20 g. of a mixture of *trans*-4-cyanocyclohexanecarboxylic acid and *trans*-hexahydroterephthalic acid was obtained after cooling at −15° for several hours. The solid mixture was extracted with chloroform. The chloroform-soluble portion of *trans*-4-cyanocyclohexanecarboxylic acid was recrystallized from chloroform and petroleum ether (5.0 g., 0.03 mole). The compound had a m.p. 151–152° and a neutralization equivalent of 153.8 (calcd. 153.2).

Anal. Calcd. for $C_8H_{11}O_2N$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.40; H, 7.16; N, 8.81.

Preparation of the Methyl Esters of the *trans*-4-X-Cyclohexanecarboxylic Acids.—To an ethereal solution of diazomethane[39] was added 5 g. (approximately 0.035 mole) of the purified cyclohexanecarboxylic acid, until the vigorous bubbling and yellow color disappeared. The ether solution was washed with water, sodium bicarbonate and water again. The ether solution of the methyl ester was dried over magnesium sulfate and the solvent removed. The remaining substituted methyl cyclohexanecarboxylates were distilled at 0.1 m.

The refractive indexes were measured at 25° and are: unsubstituted ester, 1.4505 (lit.[40] 1.4537 (15°)); *trans*-4-hydroxy, 1.4687; *trans*-4-methoxy, 1.4477; *trans*-4-cyano, 1.4588; 4-keto, 1.4589.

Procedure for Measuring Dissociation Constants in Methanol–Water (50% by Weight).—Distilled water was redistilled from alkaline potassium permanganate in an all-glass still protected from atmospheric carbon dioxide by an Ascarite tube. Commercial absolute methanol was used. The 50% by weight methanol–water solution was prepared gravimetrically from calculated amounts of the solvents.

The titrating reagents were prepared in the mixed solvent and standardized using as a primary standard, potassium acid phthalate. Acid–base titrations were done with a 10-ml. calibrated micro buret.

The e.m.f. values of the cell used in determining *p*H was measured with a Beckman model G *p*H meter employing a silver–silver chloride electrode. The apparatus for the measurements and the calculations followed the description of Grunwald and his associates,[41] their "two point" method being used.[13]

Measurement of Dissociation Constants in Water.—To determine pK_a, two independently prepared 0.01 molar solutions (100-ml. portions) were titrated, using glass and saturated calomel electrodes, and with precautions to exclude carbon dioxide. The temperature was 24.91 ± 0.05°. Preliminary adjustments of the apparatus were made with standard potassium hydrogen phthalate buffer solutions. The *p*H data used in computing the pK_a were those recorded at 0.50-ml. intervals from 0.50 to 5.00 ml., inclusive. The following equation was used in the calculation of pK_a.

$$pK_a = pH - \log \frac{(B^-) + (H^+)}{(HB) - (H^+)} + \frac{0.509\sqrt{\mu}}{1 + 1.32\sqrt{\mu}}$$

All of the symbols have their usual well-known significance.[14]

To obtain values of the first and second dissociation con-

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[35] Fr. Fichter and T. Holbro, *Helv. Chim. Acta*, **21**, 141 (1938).

[36] H. A. Smith and T. Fort, Jr., THIS JOURNAL, **78**, 4000 (1956).

[37] J. D. Roberts, W. T. Moreland, Jr., and W. Frazer, *ibid.*, **75**, 637 (1953).

[38] R. R. Stephens, E. J. Bianco and F. J. Pilgrim, *ibid.*, **77**, 1701 (1955).

[39] F. Arndt, *Org. Syntheses*, **15**, 4 (1935).

[40] J. S. Lumsden, *J. Chem. Soc.*, **87**, 97 (1905).

[41] B. Gutbezahl and E. Grunwald, THIS JOURNAL **75**, 561 (1953).

stants of *trans*-1,4-cyclohexanecarboxylic acid, the method described by Speakman was employed.[42]

Apparent Constants in Ethanol–Water Solvent (50% by Volume).—Fifty ml. of 0.10 molar solutions of the 4-X-cyclohexanecarboxylic acids was titrated to the half-point of neutralization. Readings were taken at the half-neutralization point on the *p*H scale of a Beckman model G *p*H meter calibrated against aqueous buffer solutions using glass and saturated potassium chloride–calomel electrodes. The pK_a's were calculated assuming unit activities and *p*H meter readings equal to the logarithm of the reciprocal of the hydrogen ion concentration.[9] The results of the above measurements are shown in Table I.

Alkaline Hydrolysis of *trans*-Methyl 4-X-Cyclohexanecarboxylates in Methanol–Water Solvent (50% by Weight).—The pure ester was dissolved in the methanol–water mixed solvent (50% by weight) to make 250 ml. of about 0.1 molar solutions. Sodium hydroxide solutions of equivalent strength were prepared in each case. Fifty-ml. portions of the base and ester were placed in a thermostat until the desired temperature was achieved. The reaction was started by pouring the ester solution rapidly into the sodium hydroxide solution and shaking thoroughly and the time of mixing recorded.

Five-milliliter samples were withdrawn and titrated after about 3 minutes and at regular intervals until the reaction was completed. The sample was discharged as rapidly as possible into a known excess of 0.02703 *N* hydrochloric acid. The solution was titrated with standard sodium hydroxide using precautions to exclude carbon dioxide.

The concentration of sodium hydroxide at the beginning of the experiment was calculated from the original solutions and the volume of the mixture. All concentrations are expressed in moles per liter. The value of the specific reaction rate constant (k) was determined by finding the slope of the best straight line passing through the points obtained from plotting $1/c$ *vs.* t. The method of least squares was used to obtain the best slope from these points. The results for the hydrolysis of the methyl esters at these temperatures are shown in Table III.

To obtain the hydrolysis constants of *trans*-methyl 4-carbomethoxycyclohexanecarboxylate, the procedure described by Frost and Schwemer was employed.[43] For this purpose, the hydrolysis was performed in a solution 0.200 molar in potassium chloride (in 50% by weight aqueous methanol) to swamp any effects due to changes in ionic strength as the diacid anion was produced. Although the salt is thought to have little effect upon the hydrolysis constant of the first ester group, it affects the second constant appreciably. Consequently, the constant for the hydrolysis of the salt of the monoester was corrected to zero ionic strength by use of the equation[44]

$$\log k = \log k_0 + 2Z_AZ_B\alpha\sqrt{\mu}$$

The constant α (0.82) was evaluated for 25° from universal constants and a value of 56.28 for the dielectric constant of the mixed solvent.[45]

The correction ($\Delta pk = 0.33$) yields the value of 1.55×10^{-3} for k_0, the hydrolysis constant for the ester anion at zero ionic strength. Although this extrapolation is rather large, it is not unreasonable. The use of the above equation for extrapolation is probably justified because of the rather highly aqueous nature of the reaction medium. A more detailed study of salt effects would be required for an accurate extrapolation.[46,47] Fuller details of the measurements and calculations are recorded in reference 1.

Reactivity of the 4-X-Cyclohexanecarboxylic Acids toward Diphenyldiazomethane.—The rates of reaction of the acids with diphenyldiazomethane were measured spectrophotometrically at 24.91 ± 0.05° following the procedure reported by Roberts, McElhill and Armstrong.[48]

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We wish to thank, also, Professor Donald Noyce for providing information on the preparation of *trans*-4-chloro- and 4-methoxycyclohexanecarboxylic acids prior to publication.

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[42] J. C. Speakman, *J. Chem. Soc.*, 855 (1940).

[43] A. A. Frost and W. C. Schwemer, THIS JOURNAL, **74**, 1268 (1952).

[44] S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 427.

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[48] J. D. Roberts, E. A. McElhill and R. Armstrong, THIS JOURNAL, **71**, 2923 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

The Relative Stabilities of *cis* and *trans* Isomers. VII. The Hydrindanes[1,2]

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The equilibrium constant for the reaction *cis*-hydrindane ⇄ *trans*-hydrindane has been measured in the liquid phase over the temperature range 466–638°K. From the data the thermodynamic quantities for the isomerization under these conditions were calculated to be: ΔH^{552} −1070 ± 90 cal./mole; ΔS^{552} −2.30 ± 0.10 e.u. The applicability of the method to the determination of the thermodynamic constants for such a reaction on a small scale has been established.

Introduction

Knowledge concerning the relative stabilities of *cis* and *trans* isomers of fused ring compounds is of general interest and is especially important in natural product work where stereochemistry is often assigned by analogy with related simpler systems. A previous paper described the determination of the thermodynamic quantities for the *cis–trans* isomerization of the fundamental decalin system, and discussed the usefulness of such data.

The relative "stability"[3] of the *cis* and *trans* isomers in various hydrindane systems is affected by many variables and cannot be summarized in any simple way. This complexity, relative to the decalins, results in part from the fact that the parent hydrindanes are of nearly equal stability, and minor structural changes can have appreciable effects.

The pertinent thermodynamic data available

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[2] Paper VI, THIS JOURNAL, **81**, 4080 (1959).

[3] "Stability" is always used in this paper in reference to free energy and not to enthalpy.