CONTRIBUTION TO THE CORRELATION OF STERIC STRUCTURE WITH DISSOCIATION CONSTANTS IN ORGANIC COMPOUNDS. II. CARBOXYLIC ACIDS

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The correlation of dissociation constants of carboxylic acids with steric structure has been studied and the sign of operative primary steric effect in some compounds determined. Primary steric effect has been found to cause a fall in acid strength, when non-aqueous solvents are used. On the basis of the latter, conformational analyses of a few compounds were carried out. It has been stated that certain anomalies, recorded in literature, exist only in an aqueous solution due to specific effects unknown so far. For the detection of hydrogen bonds formation in carboxylic acids a new method was suggested.

In part I, the correlation of steric effect with basicity has been studied in the field of β-substituted aliphatic amines and orto-aromatic amines [1].

Although the correlation of dissociation constants with steric structure has been more intensively investigated in the field of carboxylic acids than in the case of amines, some of the problems remained unsolved.

The quotient of the first and second dissociation constants of dicarboxylic acids has been applied lately to stereochemical considerations [3], [4], [5], [6] according to the well-known BJERRUM formula [2]. After laying down the ruling principles in the case of monocarboxylic acids, the application of the corresponding dissociation constants was greatly extended in order to determine the steric relation of carboxyl to the adjacent group [7], [8], [9], [10]. This could be carried out easiest in the field of unsaturated carboxylic acids [11], [12], [13], [14] since the *cis*-modification had been found to have higher dissociation constants than the corresponding *trans* stereoisomer. Thus, on the basis of dissociation constants, one can distinguish *cis* and *trans* modifications. Data of saturated carboxylic acids, however, does not allow a similarly unequivocal deduction. The question is: which of the two stabilities may be supported to a greater extent by steric effects acting in an aqueous solution; in the equilibrium of

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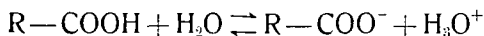
the stability of the undissociated carboxylic acid or rather that of the carboxylate anion will be more promoted. In other words, what will be the pro-

portion between proton cleavage and reassociation. Consequently, two inconsistent views dealing with the problem have been simultaneously developed in the chemical literature, according to which steric hindrance may increase or decrease, respectively, the dissociation constant of saturated carboxylic acids.

Obviously, the solvent effect has to be taken into account; this problem, however, will be discussed in detail later on.
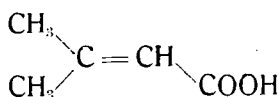
Dissociation constants of geometrically isomeric carboxylic acid

1. *Olefinic-carboxylic acids.* The effect of double bond on dissociation constants has been the subject of many interesting investigations [12], [13], [16]. In the course of the present experiments olefinic bond has been found to give rise to increased acidity, owing to its electron-attractive nature. This effect, however, is weaker in the field of α, β unsaturated acids, than in the γ compounds, which may be explained in terms of mesomeric effects. Similarly extensive investigations on the correlation of steric structure with dissociation constants in the field of stereoisomeric carboxylic acids made it clear that dissociation constants of β-alkyl substituted geometric isomers decrease as compared to those of acrylic acid. INGOLD [14] explained this type of variation of the dissociation constants in terms of secondary steric effects. Accordingly, steric pressure would twist carboxyl group out of the olefinic plane in *cis* compounds. This effect, by weakening the mesomeric effect leads to the increase in strength of acidity, compared to that of the *trans* compound. Obviously, dissociation constants depend partly on primary steric effects and electronic effects as well, though generally no such effects are taken into account in this respect. The reason of this is that the proportion of primary and secondary effects can be analysed only with difficulty. This problem, however, is quite important, since in the knowledge of the primary steric effect of a given group the principal problem, mentioned in the introductory part, may be solved.
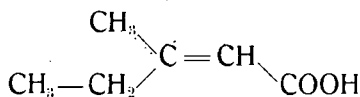
Since no more data were available, analysis could be carried out only in one case.

$$\begin{array}{c} R_1 \\ \\ R_2 \end{array} C = CH \begin{array}{c} \\ COOH \end{array}$$
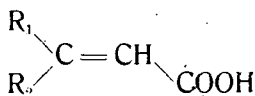
The increase of the bulk of R_2 group in a given system owing merely to secondary steric effect ought to increase the dissociation constant, since the mesomeric effect decreases. Similar results were anticipated as to the outcome of inductive and hyperconjugative effects in CH_3, C_2H_5 order. In contrary to expectation, the dissociation constants of β-*cis* methyl and β-*cis* ethyl crotonic acids were as follows [15].

$$CH_3 \atop CH_3 \diagup C = CH \diagdown COOH \qquad\qquad CH_3 \atop CH_3-CH_2 \diagup C = CH \diagdown COOH$$

$$K = 0,76 \cdot 10^{-5} \qquad\qquad\qquad K = 0,71 \cdot 10^{-5}$$

These data indicate that methyl groups, when displacing ethyl groups, cause a decrease in acid strength — instead of strengthening it — which makes

clear that primary steric effects as a dissociation hindering factor are of con-siderable importance.

2. *Cyclo-pentane carboxylic acid.* In the field of saturated compounds — when an alkyl group is fixed by a ring system in a *cis* position to carboxyl group — acidity exhibits a falling tendency. This may be seen from the follow-ing example.

The dissociation constant of *meso-cis*-2,5-dimethyl *cyclo*pentane carb-oxylic acid containing two *cis* positioned methyl groups is smaller, than that of *dl*-2,5-dimethyl-*cyclo*-pentane, in which compound only one *cis* placed methyl group can be found. The *K* value for *meso-trans*-2,5-dimethyl-*cyclo*-pentane carboxylic acid — having no methyl group in a *cis* position with respect to carb-oxyl — is greater [17]. The dissociation constant of *meso-cis*-dimethyl com-pound is even lower, than that of c-pentane-carboxylic acid. Data are compiled in Fig. 1.

The dissociation constant of *meso-trans*-dimethyl c-pentane carb-oxylic acid in water is higher than that of c-pentane carboxylic acid, which is analogous to the examples. discussed in the field of dialkyl acetic acid.

H. C. LOCHTE and P. BROWN used in their experiments α-substi-tuted c-pentane carboxylic acids measuring the dissociation constants in aqueous dioxane [18]. Though the application of these two factors sim-plifies the question, the steric effect arising under such condition may be seen quite clearly from the data cited by the authors.
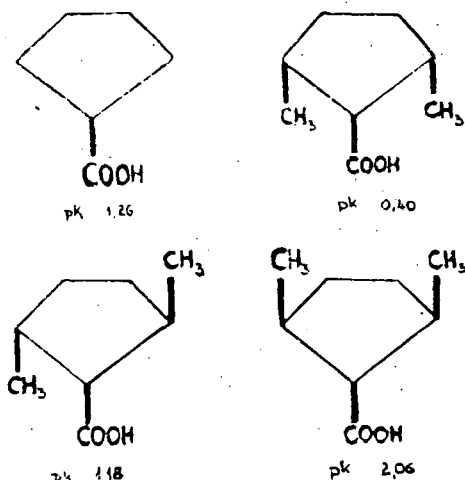

Fig. 1.

Table 1

Dissociation constants of some c-pentane-carboxylic acid in 25% aqueous dioxane at 25° C

Compound	$10^5 K$
c-Pentane carboxylic acid	0,126
1, 2, 2-Trimethyl c-pentane carboxylic acid	0,0348
1, 2, 2, 3-Tetramethyl c-pentane carboxylic acid	0,0353

Saturated aliphatic carboxylic acids

The correlation of steric structure with dissociation constants in the field of saturated carboxylic acids has been less studied. DIPPY compared butyric acid to *cis* and *trans* crotonic acids in order to gain some explanation of the so

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called »anomal« dissociation constant of the former and drew the conclusion that the constellations of carboxyl and methyl groups are similar to that of *cis* crotonic acid, which strengthens acidity compared to propionic acid. Obviously, the increase in acid strength in this case may be attributed either to the primary steric effect or to the existence of hydrogen brigde between the carboxyl and methyl groups. Since the latter could not be proved and olefinic carboxylic acids have been found to decrease acidity — instead of increasing it — propionic acid — and not butyric acid — has to be considered as anomalous. This can be interpreted neither in terms of polar nor of steric effects. The improbability of the existence of a hydrogen bridge is strongly supported by the fact that the above mentioned anomaly exists only in an aqueous solution. In alcohol and also in aqueous alcohol of a certain concentration, acidity varies according to the inductive effect. The existence of an intramolecular H-bridge in pure water is less probable than that of an intermolecular H-bridge by comparison with aqueous ethanol. Changes of the dissociation constant, however, show reverse effects.
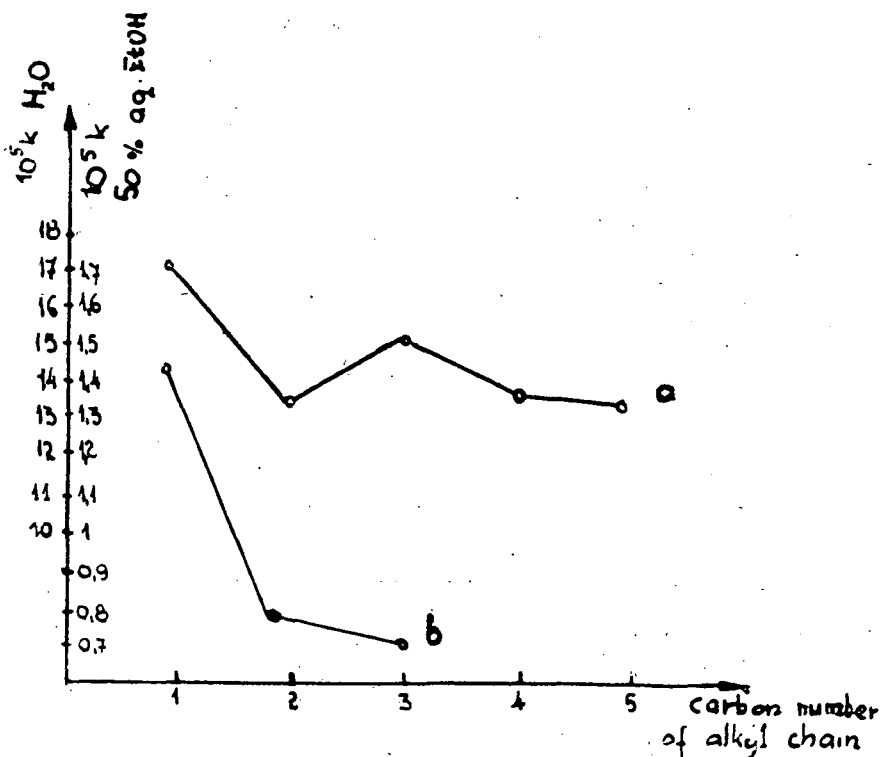

Fig. 2. Correlation of dissociation constants of saturated aliphatic carboxylic acids with the number of carbon atoms in water (a) and in aqueous alcohol (b)

The formation of a hydrogen-bridge is less probable in water, than in aqueous alcohol, which holds even for hydrogen bonds arising from a phenolic hydroxyl group.

Table 2

Dissociation constants of benzoic and o-hydroxybenzoic acids

Compound	Water	25 % Aqueous EtOH
Benzoic acid	$10^5 K = 6{,}27$	$10^5 K = 2{,}29$
o-Hydroxybenzoic acid	$10^5 K = 105$	$10^5 K = 63{,}8$
o-Hydroxybenzoic acid/benzoic acid	16,8	27,9

Above data indicate that the dissociation constants of o-hydroxy-benzoic acid in aqueous alcohol increase a greater extent, than those of benzoic acid. Thus, on the basis of dissociation constants measured in water and in aqueous alcohol of different concentration, the formation of a H-bond may be traced.

Recently HAMMONTH studied [19] the correlation of dissociation constants with steric effect in saturated aliphatic carboxylic acids. He found that the increase of the bulk of substituents causes K to fall gradually. Thus the strength of methyl i-butyl neopentyl acetic acid is by 26 times smaller, than that of acetic acid, and also essential weaker than trimethyl acetic acid. Though this statement is in agreement with that already discussed in the field of geometrically isomeric carboxylic acids according to which primary steric effect decreases acidity, we wish to add some more remarks to this problem. Data reported by HAMMONTH refer to water–ethanol systems, in which solvent anomalies, being traceable in pure water, can not be revealed. Primary steric effects have been found to appear only in the field of trialkyl acetic acids in pure water. In the system of R_1—R_2—R_3—CCOOH, by increasing the bulk of any substituent, a permanent diminution of the dissociation constant could be observed.

When the bulks of substituents are increased in the order

$$CH_3 < C_2H_5 < HC(CH_3)_2 < C(CH_3)_3$$

the inductive effect becomes simultaneously enhanced, which similarly brings about a fall in K. This, however, makes somewhat questionable the role of steric effect in establishing the permanent diminution in dissociation constants. The existence of steric effect is strongly supported by the following fact. The introduction of a third methyl group into dimethyl acetic acid should reduce the value of K to an extent, which corresponds to the inductive effect of a methyl group. Consequently — taking into consideration only the inductive effect alone — the difference of the values K of dimethyl- and trimethyl-acetic acids should be equal or rather higher — because of the different inductive effects of methyl and ethyl groups — than in the field of methyl-ethyl- and dimethyl-ethyl-acetic acids, resp. Inspection of data reveals, however, that in the latter case the introduction of methyl group causes greater alterations.

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Table 3

$10^5 K$ values of a few substituted acetic acid in water at 25° C

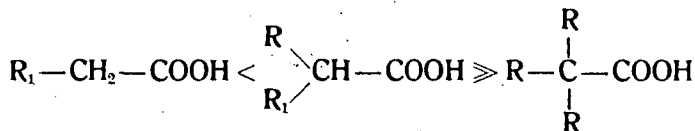| Compound	$10^5 K$	Quotient
Dimethyl acetic acid	1,38	1,55
Trimethyl acetic acid	0,891	
Ethyl, methyl acetic acid	1,67	
Dimethyl, ethyl acetic acid	0,957	1,75

J. F. J. Dippy: Chem. Rev., **25**, 151 (1939)

Hitherto only steric effects, giving rise to diminution in dissociation constants of various α-trialkyl substituted carboxylic acids, have been discussed. These findings, however, do not hold for derivatives of dialkyl substituted acetic acid. The fall of the acid strength with increasing R-bulks in a smaller degree was expected, but the reverse is actually the case. The dissociation constants show an increase instead of decrease in acid strength, by enhancing the bulks of the alkyl groups.
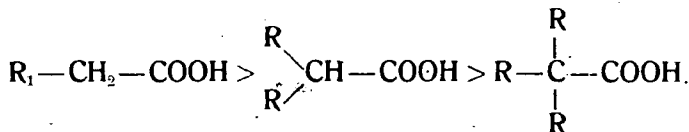
Table 4

Dissociation constants of substituted acetic acid derivatives in water at 25° C

Compound	$10^5 K$
Propionic acid	1,33
Dimethyl acetic acid	1,38
i-Valeric acid	1,67
Diethyl acetic acid	1,77
di-n-Propyl acetic acid	2,85

The above data are in contrast to the effect as well as to the inductive effect. Thus, the generally accepted order of falling strength

$$R_1-CH_2-COOH < \begin{array}{c} R \\ \diagdown \\ \diagup \\ R_1 \end{array} CH-COOH \gg R-\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}}-COOH$$
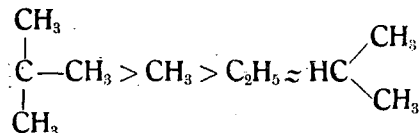
is no more valid. Moreover in the knowledge of all the examples on this subject the following sequence of strength, measured in pure water, has to be considered:

$$R_1-CH_2-COOH > \begin{array}{c} R \\ \diagdown \\ \diagup \\ R \end{array} CH-COOH > R-\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}}-COOH.$$
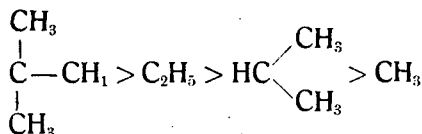
An explanation for this was given by DIPPY in the case of the sequence of propionic, isobutyric and trimethylacetic acids, according to which, the al-

terations of dissociation constants are similar to those of the corresponding para-substituted carboxylic acids. This is the necessary outcome of hyperconjugative and inductive effects. Thus, the substituents being attached directly to the carboxyl group, would represent the following order of falling strengths.

$$\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 > CH_3 > C_2H_5 \approx HC\begin{smallmatrix}CH_3\\ \\ CH_3\end{smallmatrix}$$

Apart from this sequence which proved to be correct for p-alkyl substituted benzoic acids, if acetic acid is taken into account as well, the following order is given regarding the diminution of K for formic acid

$$\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_1 > C_2H_5 > HC\begin{smallmatrix}CH_3\\ \\ CH_3\end{smallmatrix} > CH_3$$

Even if the hyperconjugative effect would also be considered, the dissociation constant of diethyl acetic acid higher than that of dimethyl acetic acid could not be explained. Accordingly, diethyl acetic acid should have a dissociation constant approximately equal to that of *cyclo*-pentane-carboxylic acid. However, the p_K values are as follows:

c-pentane carboxylic acid   1,26
diethyl acetic acid   1,77.

These data show, that steric and polar effects, as discussed in the field of tertiary alkyl derivatives, do not give adequate explanations. Perhaps also the interaction of solvent effect with carboxylic acid should be considered, regarding the dissociation constant, which results in the stabilization of ionic form and is in connection with the polarity of solvent. Thus, for instance, the dissociation constant of butyric acid in water is of higher value, than that of i-valeric acid, whereas in water-alcohol solutions alterations are as seen below.

Table 5. [20]

$10^5 K$-Values of butyric and i-valeric acid in aqueous EtOH of different concentrations

Compound	EtOH %					
	0	20,3	35	50,1	65,1	79,9
Butyric acid	4,82	5,31	5,70	6,15	6,65	7,22
i-Valeric acid	4,78	5,29	5,75	6,22	6,76	7,35

Beyond a certain concentration of alcohol, the alteration of dissociation constants corresponds to that of the inductive effect — as in the field of propionic, butyric acids is already observed. On the basis of the above mentioned correlations of this type proved to exist more distinct in a water-alcohol solvent,

than in pure water. This may be explained by the different solvent effects exerted upon H-bonds (arising e. g. in associations of carboxilic acids). Since the proportion of associated molecules depends partly on the structure of carb-oxylic acid, this may be recognized as an other intervening factor in the de-termination of the dissociation constant.

Thus, the correlation of dissociation constants with configuration and con-formation, resp., reveals a lot of problems, not yet solved, accordingly, they ought to be dealt with more criticism. In the field of α-trisubstituted carboxy-lic acids the decrease in dissociation constant brought about by steric effects seems to be generally accepted. Thus, conclusions may be drawn from steric features.

For instance, the dissociation constant of tetramethyl succinic acid $(K = 3,14.10^{-4})$ is higher, than that of succinic acid $(K = 6,6.10^{-5})$. The expla-nation given is that the molecule reflects of the two possible conformations of tetramethyl succinic acid this one, in which carboxyl groups are close to each other and where the H-bridge formation enhances the dissociation con-stant. Similar conclusions were drawn by Mc DANIEL and BROWN [21] on com-paring the first dissociation constant to the second one.

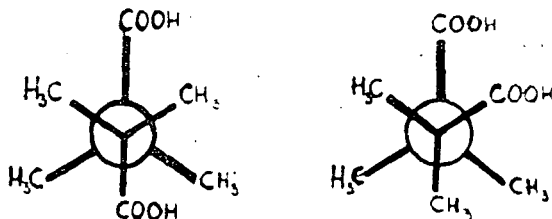*Fig. 3*

In a solvent, which does not contain pure water, polar and steric effects cause smaller anomalies. The dissociation constants of cis- and trans-2,2,6-tri-methyl c-hexane carboxylic acids, respectively, were measured by LOCHTE and BROWN [18]. The conformations of the compound are illustrated below.

In both energetically stable forms (a, c) the increase of hindering groups from three (being present in *trans* modification) to four in *cis* compounds brings about a significant diminution in the dissociation constant. It is worth to men-tion, that K for c-hexane-carboxylic acid $(K = 0,174.10^{-5})$ and for *trans* 2,6-trimethyl c-hexane carboxylic acid exhibits smaller decrease even in the case of increasing number of hindering groups from zero— to three than that of *cis* compound by comparison with the *trans* form when an increase of hindering groups from three to four takes place. These findings show unequivocally that final confirmations regarding the correlation of steric structure with dissocia-tion constants and with solvent effects, respectively, require further extensive investigations.
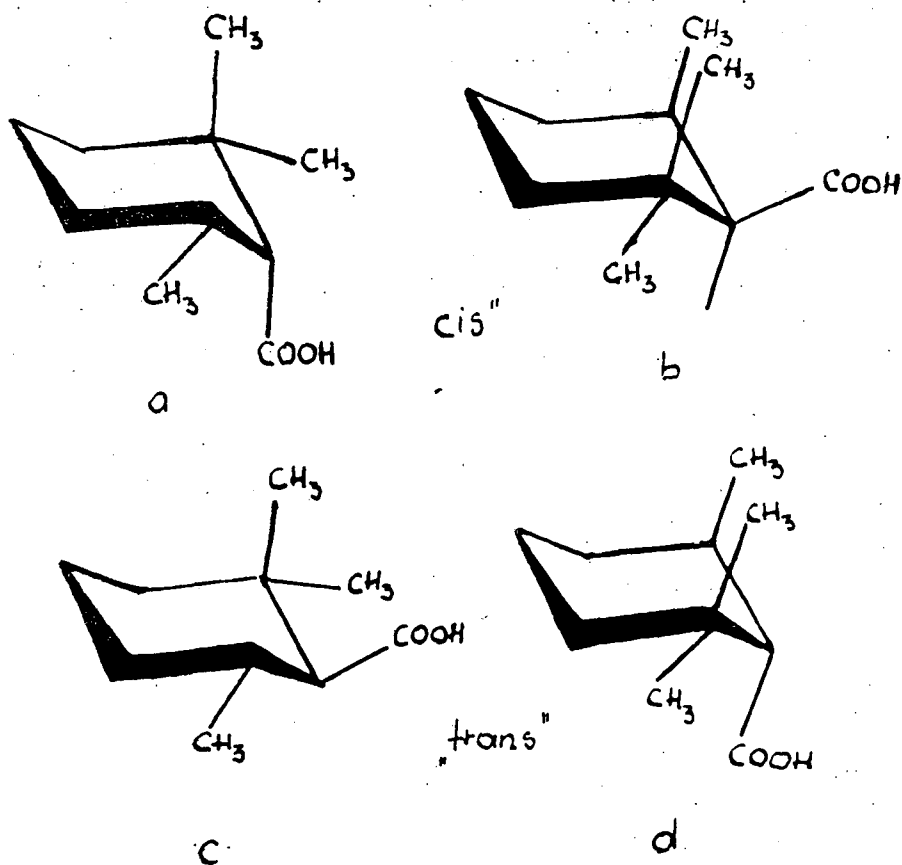
Fig. 4

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