Prom. Nr. 3763

ACIDITY OF CYCLOHEXANECARBOXYLIC ACIDS, CYCLOHEXYLAMINES AND RELATED COMPOUNDS

THESIS

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Dedicated to my dear parents

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I am very indebted to my respected

Prof. Dr. W. Simon

under whose direction this work has been carried out, for his invaluable advice, stimulation and assistance.

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1. INTRODUCTION

In the last twenty-five years there has been a great development in the application of physico-chemical methods in the elucidation of the structure of organic compounds. The term "Instrumental methods of analysis" has been widely used for these methods *).

This work deals with the application of several of these techniques:

Acidity measurements
Infrared spectroscopy
Thermoelectric molecular weight determinations

to cyclohexanecarboxylic acids, cyclohexylamines and related compounds. The purpose is to correlate the experimental data with the structure and stereochemistry of such compounds.

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*) For the terminology "Instrumental methods of analysis" see S.Z. Lewin, Analytic. Chem. 33, 23 A (1961).

2. ACID-BASE EQUILIBRIUM

2.1. DEFINITION OF THE ACIDITY CONSTANT

According to J.N. Brønsted [1)] and T.M. Lowry [2)] acid-base equilibria can be formulated as follows:

$$AH + LH \rightleftharpoons A^{\ominus} + LH_2^{\oplus} \qquad (1)$$

In Equation (1), LH is the solvent, AH the acid to be investigated and $A^{\ominus}$ the base formed from AH by removal of a proton. The acidity constant of the acid AH is defined by

$$K(AH) = \frac{a_{A^{\ominus}} \cdot a_{LH_2^{\oplus}}}{a_{AH}} = C_{LH_2^{\oplus}} \cdot \frac{C_{A^{\ominus}}}{C_{AH}} \cdot f_{LH_2^{\oplus}} \cdot \frac{f_{A^{\ominus}}}{f_{AH}} =$$

$$= K_C(AH) \cdot f_{LH_2^{\oplus}} \cdot \frac{f_{A^{\ominus}}}{f_{AH}} \qquad (2)$$

where a is the activity, C the concentration and f the activity coefficient.

K(AH) is the thermodynamic acidity constant (dissociation constant), while $K_C(AH)$ does not include any activity coefficient. $K_C(AH)$ is therefore dependent on the concentration and is called "classical dissociation constant", sometimes "apparent acidity constant". The acidity of the acid AH is measured by the magnitude of K(AH), although for practical reasons its negative decimal logarithm is to be preferred:

$$pK(AH) = -\log K(AH) \qquad (3)$$

For the acidity constant K(AH), the following relationship is valid:

$$\Delta F = 2.303\ RT\ pK(AH) + 2.303\ RT \log a_{LH} \qquad (4)$$

Assuming that the activity, a_{LH}, of the solvent LH remains constant, the pK(AH) value of the acid AH is proportional to the change in free-energy, ΔF, of the acid-base reaction of Equation (1).

All the factors that affect the stability of the acid AH and/or the anion $A^{\ominus}$ influence therefore the acidity of the acid AH [3, 4]. These effects are: resonance effects, steric effects, electrostatic and inductive effects, solvation effects and hydrogen bond formation.

2.2. DETERMINATION OF THE ACIDITY CONSTANT. SELECTION OF THE SOLVENT

In the systematic determination of dissociation constants for qualitative analysis of organic natural products, two main restrictions must be considered: a) It should be possible to carry out the measurements on small quantities of sample (about 1 mg). b) Owing to the low solubility of most organic compounds in water, the determinations must be carried out in non-aqueous solvents. Solvents used so far include: alcohol and alcohol/water [5 - 9], ethylene glycol mixed with other organic solvents [10 - 12], acetonitrile [13 - 15], dimethylformamide [16 - 18], cyclohexanone [19], dioxane/water [20 - 22], benzene [24], nitrobenzene [13, 25], acetone [26, 27], pyridine [28, 29], glacial acetic acid [30, 31] and methylcellosolve [32, 33].

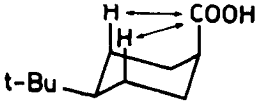
Under these conditions, the thermodynamic dissociation constants must be abandoned in favor of "apparent acidity constants" K^*. These constants K^* no longer have the well-defined thermodynamic significance of an equilibrium constant in the sense of equations (2) - (4). Standardization (solvent, concentration, determination procedure, temperature and pressure are kept constant) leads however to pK^* values which depend only on the structures of the compounds under investigation.

A standard method has been developed for the determination of apparent dissociation constants in the system methylcellosolve/water (80:20 % by weight) [34 - 40], and is used in the present work. The apparent acidity constants in this system are represented by K^*_{MCS} ($pK^*_{MCS} = -\log K^*_{MCS}$).

3. ACIDITY OF CYCLOHEXANECARBOXYLIC ACIDS

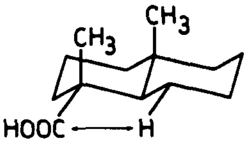
3.1. DIFFERENCES IN THE ACIDITY OF CYCLOHEXANECARBOXYLIC ACIDS WITH EQUATORIAL AND AXIAL POSITION OF THE CARBOXYL GROUP *)

It is experimentally found that cyclohexanecarboxylic acids with equatorial position of the carboxyl group clearly differ in their acidity from their axial isomers [41-45]. As may be seen in Table 1, the difference in the free-energies of cyclohexanecarboxylic acids with axial and those with equatorial carboxyl groups is about 1,6 kcal./mole; the difference for the corresponding anions is about 2.2 kcal./mole [42 - 45]. The fact that the acidity of the axial isomer is 0.5 pK^*_{MCS} units lower than that of the equatorial isomer can be attributed to hindrance of solvation of its anion by about 0.6 kcal./mole relative to the anion of the equatorial isomer [42, 43, 49] [cf. also 50)]. This additional hindrance of solvation is essentially due to interaction with axial substituents in the γ-positions with respect to the axial carboxyl group (1,3-interactions) [cf. Formula (5)].



(5)

From the assumption that the effects of these 1,3-interactions are additive, it follows that each 1,3-interaction is responsible for an increment in the pK^*_{MCS} value of 0.25 units. Interactions between equatorial substituents can be geometrically equivalent to the 1,3-axial-axial-interactions, so that an increment in the pK^*_{MCS} value of 0.25 units can also be assumed for such 1,3-interactions [cf. Formula (6)] .



(6)

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*) cf. P.F. Sommer, Ph.D. Thesis, Eidgenössische Technische Hochschule, Zürich 1961.

Table 1 Differences in the Free-energies of Cyclohexanecarboxylic Acids and Their Corresponding Anions, and ΔpK Values at 25° C.

SOLVENT	$\Delta\Delta F = \Delta F_{axial} - \Delta F_{equatorial}$ [kcal./mole]		$\Delta pK = pK_{axial} - pK_{equat.}$		Ref.
	$C_6H_{11}COOH$	$C_6H_{11}COO^{\ominus}$	from ΔΔF	*)	
Water	1.7 ± 0.2	2.4 ± 0.4	0.5	-	42)
Methylcellosolve/water (80 : 20 % by weight)	1.6 ± 0.3	2.2 ± 0.3	0.4	0.48	43)
				0.48	46)
Ethanol/water (50 : 50 % by volume)	1.5	2.1	0.4	0.50	45)
Dimethylformamide/water (66 : 34 % by volume)				0.44	42)

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*) The values in this column are the differences in the pK values of cis- and trans-4-t-butylcyclohexane-1-carboxylic acids, and were determined potentiometrically. The values in the other columns were obtained from thermodynamic data in combination with dissociation constants of unsubstituted or alkyl-substituted acids.

These assumptions will allow the estimation of pK^{*}_{MCS} values of cyclohexanecarboxylic acids or the determination of the axial or equatorial position for the carboxyl group [41, 52, 53, 55].

Another effect that influences the acidity of these acids is the presence of substituents in the α-position relative to the carboxyl group, such as a methyl group or a ring-closure. These substituents, which are present in many natural products, influence the pK^{*}_{MCS} value by means of their polar effect. Some indication of the effect of substituents R on the acidity of carboxylic acids of the type R-COOH is given in Figure 1, in which pK^{*}_{MCS} values are plotted as a function of Taft's polar substituent constants σ^{*} [54].

If a hydrogen atom on the carbon atom α to the carboxyl group is replaced by a methyl group, or if ring fusion takes place in the α-position, σ^{*} changes by -0.10 to -0.12 units [54], corresponding to a mean increment in pK^{*}_{MCS} of 0.22 units [cf. Fig. 1] .

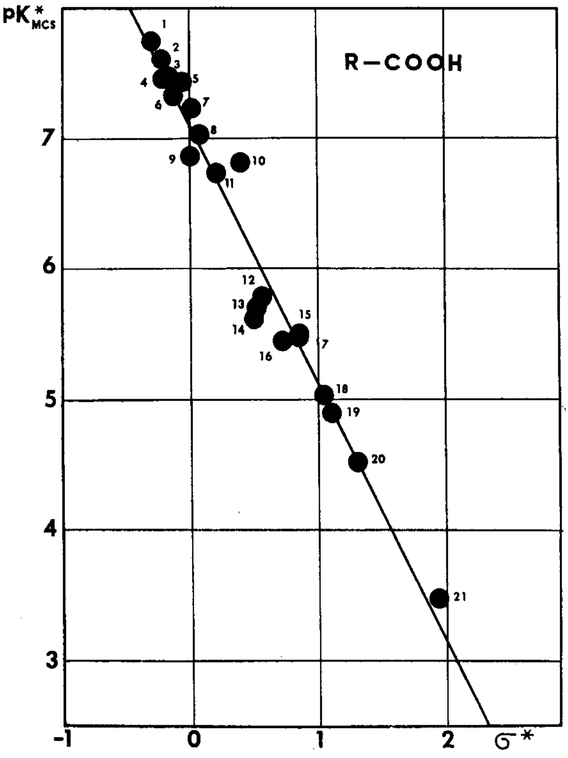

Figure 1 pK^*_{MCS} values of acids R - COOH as a function of the polar substituent constants σ^*.

1: Pivalic acid
2: Diethylacetic acid
3: Cyclohexanecarboxylic acid
4: α -Methylbutyric acid
5: Cyclohexylacetic acid
6: Isovaleric acid
7: γ -Phenylbutyric acid
8: β -Phenylpropionic acid
9: Acetic acid
10: Diphenylacetic acid
11: Phenylacetic acid
12: Glycolic acid
13: Methoxyacetic acid
14: Formic acid
15: Iodoacetic acid
16: Mandelic acid
17: Phenoxyacetic acid
18: Chloroacetic acid
19: Fluoroacetic acid
20: Cyanoacetic acid
21: Dichloroacetic acid

3.2. RULE FOR THE ESTIMATION OF ACIDITY CONSTANTS IN CYCLOHEXANE-CARBOXYLIC ACIDS

Since the pK^*_{MCS} value of cyclohexanecarboxylic acid *) is 7.44, the pK^*_{MCS} values of such acids can be estimated, under certain assumptions, using the following rule [41, 52, 53]:

$$pK^*_{MCS} = 7.44 + 0.25\,a + 0.22\,b \qquad (7)$$

where a: number of 1,3-interactions

$$b: \begin{cases} b = 1 & \text{for an } \alpha\text{-CH}_3 \text{ or for ring-closure in the } \alpha\text{-position;} \\ b = 0 & \text{for } \alpha\text{-H} \end{cases}$$

3.3. CONDITIONS FOR THE APPLICABILITY OF THIS RULE

The assumptions for the applicability of Equation (7) are the following:

1. The carboxyl group is a substituent in a cyclohexane skeleton in the chair conformation.
2. If there exists a conformational equilibrium, Equation (7) is only applicable when the population of one conformer may be neglected within the limits of accuracy of the pK^*_{MCS} determination. For instance, the free-energy difference between the two epimeric cyclohexanecarboxylic acids is about 1.6 - 1.7 kcal./mole [42, 43]. As may be seen in Table 2, the equilibrium contribution of the cyclohexanecarboxylic acid with axial carboxyl group is therefore only about 5 %. The effect of this small contribution on the pK^*_{MCS} value is only 0.02 pK^*_{MCS} units, which

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*) Since the equilibrium contribution of the epimeric cyclohexanecarboxylic acid with an axial carboxyl group is only 5 %, it may be neglected within the limits of accuracy of the pK^*_{MCS} determinations (standard deviation s = 0.07 units [23]), [cf. 3.3.] .

is well within the accuracy of the pK^*_{MCS} determination. 1-Methylcyclohexanecarboxylic acid has a pK^*_{MCS} value of 7.87. The calculated [Equation (7)] pK^*_{MCS} values for the two conformers of this acid are 7.66 and 8.16 respectively. *The experimental value confirms that there is an equilibrium between the two* conformers and that the population of each conformer is about 50 %, which is *in perfect agreement with what should be expected from the free-energy differ*ences between equatorial and axial carboxyl (1.6 - 1.7 kcal./mole) and methyl *(1.5 - 1.9 kcal./mole) groups respectively* 100).

3. Unfortunately no model compounds are available to select a value for the COOH: CH_3-1,3-*interactions as well as other COOH-1,3-interactions. The same value of* 0.25 pK^*_{MCS} units was therefore taken for such COOH : CH_3-1,3-interactions.
4. *The rule has to be applied with care when polar groups, which may strongly* affect the acidity of the acid, are present in the molecule near the carboxyl group [cf. 3.7. d)] .

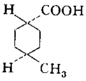
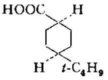
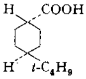
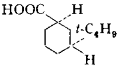
Table 2 Relation between Percentage of More Stable Isomer at Equilibrium, and Free-energy Difference at 25° C 51).

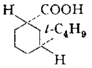
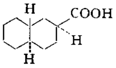
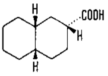
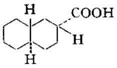
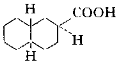
Population of favored state, %	67	75	80	83	91	95	99	99.9	99.99
- ΔF, kcal./mole	0.41	0.65	0.82	0.95	1.4	1.8	2.7	4.1	5.5

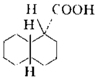
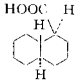
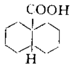
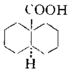
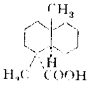
3.4. MEASURED AND CALCULATED pK^*_{MCS} VALUES

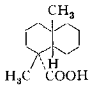
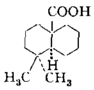
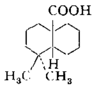
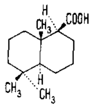
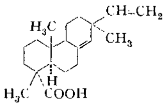
Table 3 summarizes the measured pK^*_{MCS} values compared with the values calculated with Equation (7), for seventy acids whose structure is completely unequivocal.

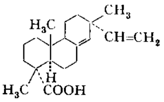
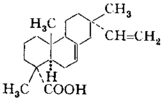
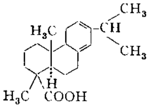
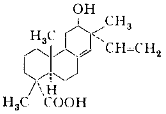
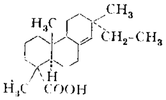
Table 3 Comparison of Calculated and Measured pK^{*}_{MCS} Values of Cyclohexanecarboxylic Acids

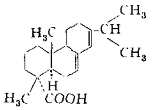
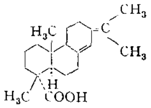
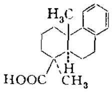
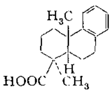
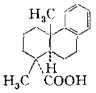
ACID		a	b	pK^{*}_{MCS} calc.	pK^{*}_{MCS} exper.	Bibliography; origin of the acid
trans-4-Methyl-cyclohexane-carboxylic acid	I 	0	0	7.44	7.42	43) J. Sicher
cis-4-t-Butyl-cyclohexane-carboxylic acid	II 	2	0	7.94	7.91	43) J. Sicher
trans-4-t-Butyl-cyclohexane-carboxylic acid	III 	0	0	7.44	7.43	43) J. Sicher
trans-3-t-Butyl-cyclohexane-carboxylic acid	IV 	2	0	7.94	7.96	43) J. Sicher

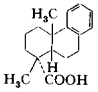
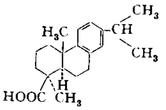
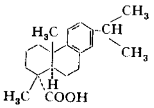
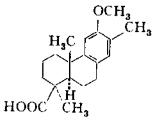
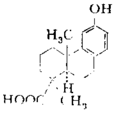
ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography; origin of the acid
cis-3-t-Butyl-cyclohexane-carboxylic acid	V 	0	0	7.44	7.44	43) J. Sicher
trans-Decalin-2β-carboxylic acid	VI 	2	0	7.94	7.88	58) J. Sicher
cis-Decalin-2α-carboxylic acid	VII 	0	0	7.44	7.52	59) W.G. Dauben
trans-Decalin-2α-carboxylic acid	VIII 	0	0	7.44	7.51	59) W.G. Dauben
cis-Decalin-2β-carboxylic acid	IX 	0	0	7.44	7.56	59) W.G. Dauben

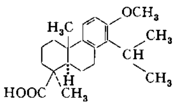
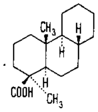
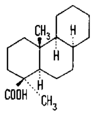
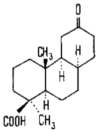
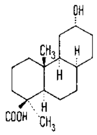
ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography; origin of the acid
cis-Decalin-1 α-carboxylic acid	X 	1	0	7.69	7.72	59) W.G. Dauben
trans-Decalin-1 β-carboxylic acid	XI 	1	0	7.69	7.58	59) W.G. Dauben
cis-Decalin-9-carboxylic acid	XII 	2	1	8.16	8.17	60) P.D. Bartlett
trans-Decalin-9-carboxylic acid	XIII 	4	1	8.66	8.58	60) P.D. Bartlett
4,9-Dimethyl-4-carboxy-trans-decalin	XIV 	1	1	7.91	8.00	61) P.C. Dutta

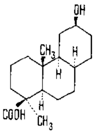
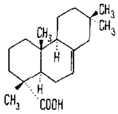
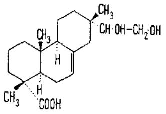
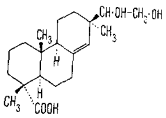
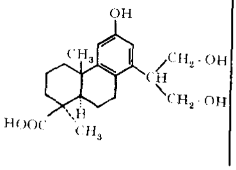
ACID		a	b	pK^{*}_{MCS} calc.	pK^{*}_{MCS} exper.	Bibliography; origin of the acid
4,9-Dimethyl-4-carboxy-cis-decalin	XV 	1	1	7.91	7.96	61) P.C. Dutta
4,4-Dimethyl-9-carboxy-trans-decalin	XVI 	4	1	8.66	8.86	62) R.F.C. Brown
4,4-Dimethyl-9-carboxy-cis-decalin	XVII 	2	1	8.16	8.30	62) R.F.C. Brown
5,5,9-Trimethyl-1-carboxy-trans-decalin	XVIII 	1	0	7.69	7.80	63) A. Eschenmoser
Pimaric acid	XIX 	1	1	7.91	7.90	64) D. Arigoni

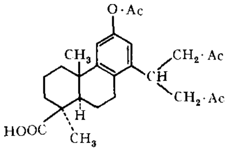
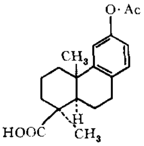
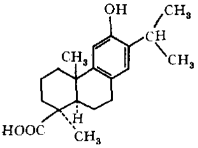
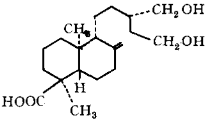
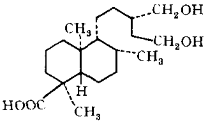
ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
Sandaraco-pimaric acid	XX 	1	1	7.91	7,94	65) O.E. Edwards
Isopimaric acid	XXI 	1	1	7.91	7.98	66) R.V. Lawrence
Levopimaric acid	XXII 	1	1	7.91	7.90	67) R.V. Lawrence
6 β-Hydroxy-sandaraco-pimaric acid	XXIII 	1	1	7.91	7.85	68) O.E. Edwards
Dihydro-sandaraco-pimaric acid	XXIV 	1	1	7.91	8.05	68) O.E. Edwards

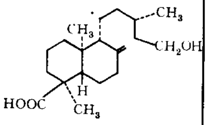
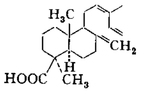
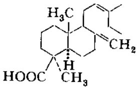
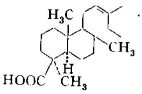
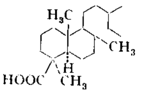
ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
Abietic acid	XXV 	1	1	7.91	7.93	69) B.G. Engel
Neoabietic acid	XXVI 	1	1	7.91	7.94	70) R.V. Lawrence
trans-Deoxy-podocarpic acid	XXVII 	3	1	8.41	8.45	71) P.C. Dutta
cis-Deoxy-podocarpic acid	XXVIII 	2	1	8.16	8.00	71) P.C. Dutta
Deisopropyl-dehydroabietic acid	XXIX 	1	1	7.91	7.80	71) 72) M. Ohta

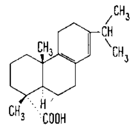
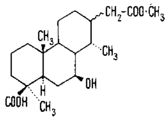
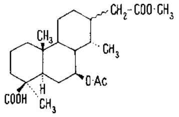
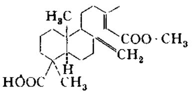
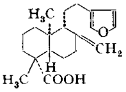
ACID		a	b	pK^{*}_{MCS} calc.	pK^{*}_{MCS} exper.	Bibliography ; origin of the acid
Deisopropyl-allo-dehydro-abietic acid	XXX 	1	1	7.91	7.91	72) M. Ohta
	XXXI 	3	1	8.41	8.46	73) P.C. Dutta
Dehydro-abietic acid	XXXII 	1	1	7.91	7.92	74) O. Jeger
O-Methyl-7-methyl-podocarpic acid	XXXIII 	3	1	8.41	8.43	75) R.H. Bible
Podocarpic acid	XXXIV 	3	1	8.41	8.44	76) 77) B.G. Engel

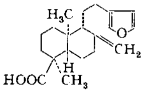
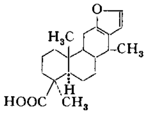
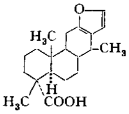
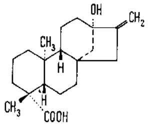
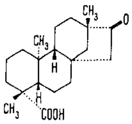
ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
	XXXV 	3	1	8.41	8.47	78) R.C. Cambie
	XXXVI 	3	1	8.41	8.59	57) O.E. Edwards
	XXXVII 	3	1	8.41	8.59	57) O.E. Edwards
	XXXVIII 	3	1	8.41	8.57	77) R.H. Bible
	XXXIX 	3	1	8.41	8.63	77) R.H. Bible

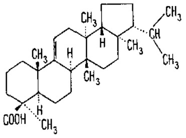
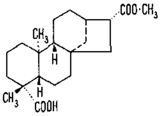
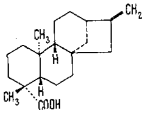
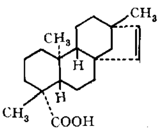
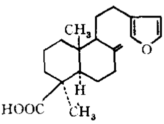
ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
trans-anti-cis-Perhydro-podocarpic acid	XL 	3	1	8.41	8.65	77) R.H. Bible
	XLI 	1	1	7.91	7.98	89) O.E. Edwards
	XLII 	1	1	7.91	8.00	89) O.E. Edwards
Palustric acid	XLIII 	1	1	7.91	7.89	89) O.E. Edwards
Pododacric acid	XL IV 	3	1	8.41	8.44	79) R.C. Cambie

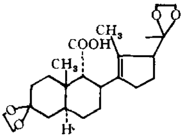
ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
Pododacric acid triacetate	XLV 	3	1	8.41	8.42	79) R.C. Cambie
O-Acetyl-podocarpic acid	XLVI 	3	1	8.41	8.26	79) R.C. Cambie
13-Isopropyl-podocarpic acid	XLVII 	3	1	8.41	8.41	79) R.C. Cambie
	XLVIII 	1	1	7.91	7.83	80) C.A. Henrick
	XLIX 	1	1	7.91	7.98	80) C.A. Henrick

ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
	L 	1	1	7.91	7.88	80) C.A. Henrick
Communic acid	LI 	3	1	8.41	8.29	81) 82) H. Erdtman
Dihydro-communic acid	LII 	3	1	8.41	8.64	82) H. Erdtman
Tetrahydro-communic acid	LIII 	3	1	8.41	8.65	82) H. Erdtman
Hexahydro-communic acid	LIV 	3	1	8.41	8.61	82) H. Erdtman

ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
Palustric acid	LV 	1	1	7.91	7.89	83) R.V. Lawrence
	LVI 	3	1	8.41	8.30	84) B.C. Engel
	LVII 	3	1	8.41	8.37	84) B.C. Engel
Agathic acid monomethyl ester	LVIII 	3	1	8.41	8.50	85) B.C. Engel
Daniellic acid	LIX 	3	1	8.41	8.60	86) G. Ourisson

ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
Polyalthic acid	LX 	1	1	7.91	7.93	70) T.R.Govindachari
Vouacapenic acid	LXI 	3	1	8.41	8.52	87) F.E. King
Vinhaticoic acid	LXII 	1	1	7.91	8.01	87) F.E. King
Steviol	LXIII 	3	1	8.41	8.58	88) E. Mosettig
Isosteviol	LXIV 	3	1	8.41	8.52	88) E. Mosettig

ACID		a	b	pK^*_{MCS} calc.	pK^*_{MCS} exper.	Bibliography ; origin of the acid
Davallinic acid	LXV 	3	1	8.41	8.60	90) K.Nakanishi
	LXVI 	3	1	8.41	8.52	91) C.A. Henrick and P.R. Jefferies
	LXVII 	3	1	8.41	8.55	92) C.A. Henrick and P.R. Jefferies
	LXVIII 	3	1	8.41	8.59	93) K.H. Overton
Lambertianic acid	LXIX 	3	1	8.41	8.51	94) W.G. Dauben

ACID		a	b	pK^{*}_{MCS} calc.	pK^{*}_{MCS} exper.	Bibliography ; origin of the acid
	LXX 	3	0	8.19	8.20	95) O. Jeger

3.5. APPLICATION OF THE LEAST SQUARE METHOD TO THE EXPERIMENTAL VALUES

The least square method was applied to the seventy experimental values [cf. Table 3] to adjust the parameters for the 1,3-interactions and for the substitution in the α-position in order to check the validity of Equation (7).

The following Equation was obtained by this procedure:

$$pK^{*}_{MCS} = 7.44 + 0.27\ a + 0.24\ b \qquad (8)$$

This result supports the validity of the empirical rule given by Equation (7).

The obvious question arises whether the increment in the pK^{*}_{MCS} value caused by a COOH : CH_3-1,3-interaction is of the same magnitude as the one for the COOH : H-1,3-interaction. To test this, another least square approach was applied using three different increments for the substitution in α-position, the COOH : H - and the COOH : CH_3-1,3-interactions. The following Equation, which indicates a slightly larger increment for the COOH : CH_3-1,3-interaction was obtained [cf. 3.7. c)] :

$$pK^{*}_{MCS} = 7.44 + 0.25\ a + 0.33\ b + 0.23\ c \qquad (9)$$

where a : number of COOH : H-1,3-interactions

b : number of COOH : CH_3-1,3-interactions

$$c : \begin{cases} c = 1 & \text{for an } \alpha\text{-CH}_3 \text{ or for ring-closure} \\ & \text{in the } \alpha\text{-position ;} \\ c = 0 & \text{for } \alpha\text{-H} \end{cases}$$

3.6. STANDARD DEVIATION OF THE CALCULATED VALUES FROM THE MEASURED ONES

Table 4 summarizes the standard deviations of the calculated [Equations (7), (8) and (9)] pK^*_{MCS} values from the measured ones, as well as the largest deviations for each of the three equations.

Table 4

Equation used	Standard deviation [pK^*_{MCS} units]	Largest deviation [pK^*_{MCS} units]
(7)	0.11	0.24
(8)	0.09	0.22
(9)	0.09	0.26

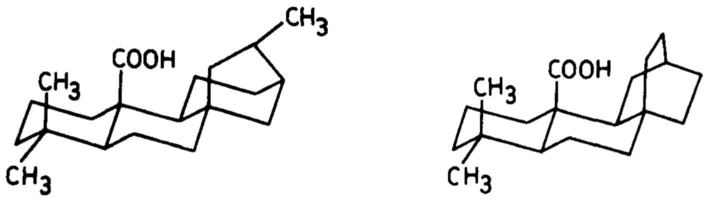
3.7. COMMENTS

a) As shown in Table 3, Equation (7) allows the estimation of the acidity constants of cyclohexanecarboxylic acids and related compounds with a remarkable precision.

b) Small deviations from the ideal chair conformation in the decalin skeleton [cf. XXI, XXV, XLI and XLII] do not seem to affect the applicability of Equation (7).

c) The difference between the increment in the pK^*_{MCS} value for a COOH : CH_3-1,3-interaction and a COOH : H-1,3-interaction [cf. 3.5.] is significant at the 95 % confidence limit, although according to the space requirement of a methyl group (van der Waals radius 2.0 Å 47)) in relation to the hydrogen atom (van der Waals radius 1.2 Å 47)) a much larger difference should be expected. A possible explanation for this fact is that in all the acids studied with a COOH : CH_3-1,3-interaction, the involved axial carboxyl or methyl group is in the terminal ring, so that by distortion of the ring from the ideal chair conformation 48) to the twist (skew-boat) form, the hindrance of solvation of the corresponding anion may be reduced. This distortion, which actually is also present in the acid molecule, seems to be so large as to make the resulting hindrance of solvation of the anion due to the COOH : CH_3-1,3-interaction in the distorted system as large as the one for a COOH : H-1,3-interaction in a non-distorted ring. This is in perfect agreement with observations in triterpenes having methyl groups at C-4 and C-10 [cf. 97)] .

A confirmation of this working hypothesis can be found in the fact that acids with a rigid skeleton, in which the steric hindrance of solvation can not be reduced by distortion of the ring, have a much larger pK^*_{MCS} value than expected 56, 57) [cf. Fig. 2] .



pK^*_{MCS} (exper.) : 9.49 *)
pK^*_{MCS} (calc.) : 8.91

pK^*_{MCS} (exper.) : 9.42 **)
pK^*_{MCS} (calc.) : 8.66

Figure 2 Acids with a rigid 1,3-interaction

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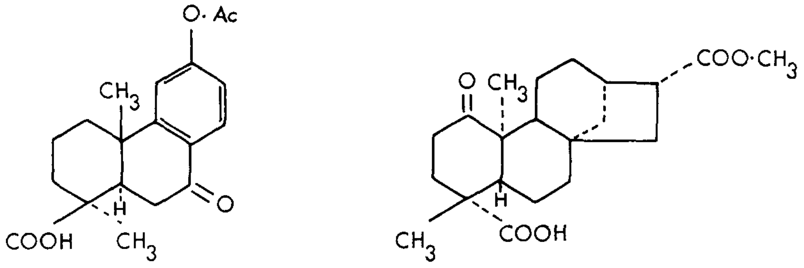
*) I am indebted to C. Djerassi for samples of this acid [cf. 56)] .

**) I am indebted to O.E. Edwards for samples of this acid [cf. 57)] .

d) As may be seen in Fig. 3 the presence of a polar group in the molecule near the carboxyl group can affect very strongly the pK^*_{MCS} value of the parent acid so that Equation (7) is not applicable.



pK^*_{MCS} (exper.) : 7.59 *)
pK^*_{MCS} (calc.) : 8.41

pK^*_{MCS} (exper.) : 7.58 **)
pK^*_{MCS} (calc.) : 8.41

Figure 3 Acids with a polar substituent near the carboxyl group

e) The rule expressed by Equation (7) has been used with success for the determination of the structure in many cyclohexanecarboxylic acids [cf. 55), 56), 57), 78), 84), 88), 90), 91), 96)] . Definite assignments would hardly have been possible by other methods, and would certainly have required considerably more effort.

---

*) I am indebted to R.C. Cambie for samples of this acid [cf. 99)] .

**) I am indebted to C.A. Henrick for samples of this acid.

4. ACIDITY OF THE CONJUGATE ACIDS OF CYCLOHEXYLAMINES

4.1. EXPERIMENTAL pK^*_{MCS} VALUES

In analogy to cyclohexanecarboxylic acids, the conjugate acids of cyclohexylamines with equatorial position of the functional group clearly differ in their acidity from their axial isomers [43, 58, 98]. There are unfortunately no data available in the literature on the free-energy differences between equatorial and axial amino groups. It can be assumed that this difference is smaller than the one for carboxyl groups. An estimation of this free-energy difference using experimental pK^*_{MCS} values is very unsatisfactory because of the small differences in the acidity between axial and equatorial isomers.

Table 5 summarizes the measured pK^*_{MCS} values of some conjugate acids of cyclohexylamines and N,N-dimethylcyclohexylamines *).

4.2. APPLICATION OF THE LEAST SQUARE METHOD TO THE EXPERIMENTAL VALUES

The least square method was applied to the experimental pK^*_{MCS} values of Table 5 in order to obtain an Equation to estimate the pK^*_{MCS} values of such acids. For this least square approach only the acids with a population of the favored conformer of more than 95 % were taken into account. The acids LXXII, LXXIV, and LXXXIII were therefore excluded.

The following Equation was obtained:

$$pK^*_{MCS} = 9.58 - 0.13\,a - 0.84\,b \qquad (10)$$

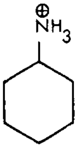
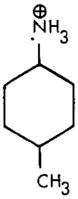
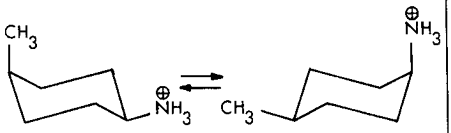
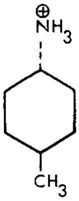
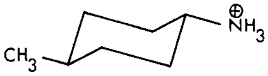
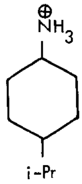
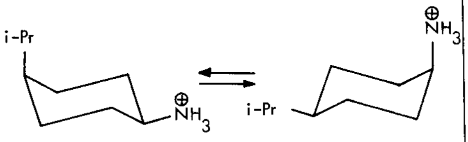
where a : number of 1,3-interactions

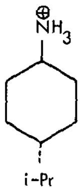
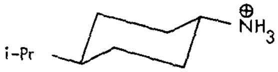
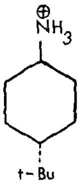
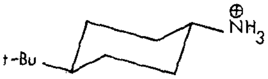
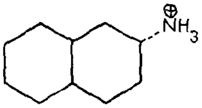
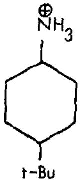
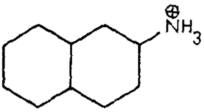
b : $\begin{cases} b = 1 & \text{for the N,N-dimethyl compounds} \\ b = 0 & \text{for the compounds without methyl groups attached to the nitrogen atom} \end{cases}$

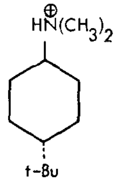
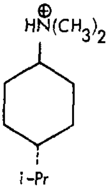
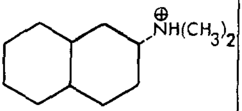
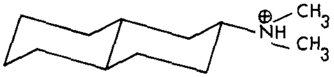
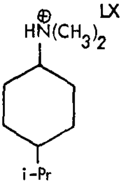
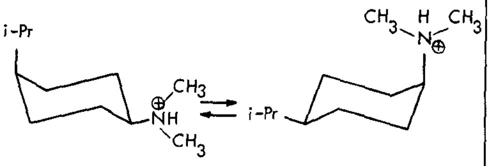
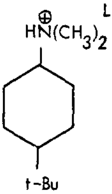
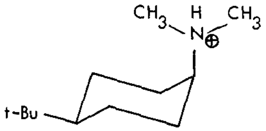
---

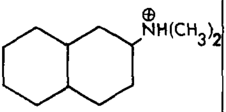
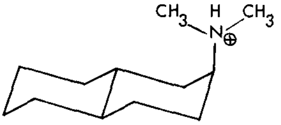
*) I am very indebted to J. Sicher for samples of these compounds [cf. 58)] .

Table 5 Experimental pK^*_{MCS} Values of Some Cyclohexylamines

ACID			pK^*_{MCS} exper.
	LXXI		9.57
	LXXII		9.49
	LXXIII		9.56
	LXXIV		9.53

ACID		pK^*_{MCS} exper.
 LXXV		9.55
 LXXVI		9.58
LXXVII 		9.62
 LXXVIII		9.29
LXXIX 		9.37

ACID		pK^*_{MCS} exper.
LXXX 		8.73
LXXXI 		8.74
LXXXII 		8.73
LXXXIII 		8.60
LXXXIV 		8.47

	ACID	pK^*_{MCS} exper.
LXXXV 		8.47

The standard deviation of the calculated [Equation (10)] pK^*_{MCS} values from the measured ones is 0.02 pK^*_{MCS} units.

4.3. COMMENTS

a) The number of acids available to obtain Equation (10) was unfortunately too small to generalize the validity of this Equation. The small standard deviation obtained seems however to allow the application of Equation (10) at least to very closely related compounds.

b) As expected the 1,3-interactions destabilize the acids with axial functional group relative to the equatorial isomers so that the increments in the pK^*_{MCS} values due to the 1,3-interactions are negative. The effect is however much smaller than in the case of cyclohexanecarboxylic acids.

c) The increment in the pK^*_{MCS} values caused by methyl groups attached to the nitrogen atom is not additive *). Equation (10) can therefore only be used to estimate the pK^*_{MCS} values of cyclohexylamines and N,N-dimethylcyclohexylamines. The application of Equation (10), with an adequate value of b, to N-methylcyclohexylamines has to be studied.

d) In analogy to the cyclohexanecarboxylic acids and to the conjugate acids of cyclohexylamines it is to be expected that cyclohexanols with equatorial position of the hydroxyl group also differ in their acidity from the axial isomers,

---

*) The pK^*_{MCS} values of methylamine, dimethylamine and trimethylamine are, for instance, 9.94, 8.28 and 8.31 respectively $^{106)}$.

the axial isomer being the weaker acid. The small acidity of these alcohols requires acidity measurements in a very basic solvent such as liquid ammonia. No routine method is so far available for acidity measurements in liquid ammonia. It is however to be expected that rules of the type of Equations (7) and (10) for the estimation of pK^{*}_{MCS} values can be obtained.

5. OTHER PHYSICO-CHEMICAL METHODS TO DIFFERENTIATE BETWEEN THE EQUATORIAL AND AXIAL POSITION OF THE CARBOXYL GROUP IN CYCLOHEXANECARBOXYLIC ACIDS

The obious question arises whether there exist other routine physico-chemical methods allowing the differentiation between the equatorial and axial position of the carboxyl group in cyclohexanecarboxylic acids. The methods studied in this connection are described in the present chapter.

5.1. MONOMER-DIMER EQUILIBRIUM

If cyclohexanecarboxylic acids with an axial position of the carboxyl group experience an additional hindrance in the solvation due to 1,3-interactions, a steric inhibition in the dimerization is to be expected.

$$2\ R - COOH \rightleftharpoons (R - COOH)_2 \qquad (11)$$

To test this hypothesis, thermoelectric molecular weight determinations in very dilute solutions in methylene chloride were carried out *).

The equilibrium constant K_D for the monomer-dimer equilibrium (11) is then expressed by

$$K_D = \frac{C X / 2}{C^2 (1 - X)^2} = \frac{X}{2 C (1 - X)^2} = \frac{MW (MW - M)}{C (2 M - MW)^2} \qquad (12)$$

where X : ratio of the number of "molecules" in the dimeric form to the total number of the "molecules" present.

C : total molar concentration of acid molecules.

M : molecular weight of the monomer.

MW : measured molecular weight.

---

*) For a description of the apparatus and the method used cf. Ch. Chylewski, PH.D. Thesis, Eidgenössische Technische Hochschule, Zürich 1964.

For practical reasons the negative decimal logarithm of the equilibrium constant K_D was used:

$$pK_D = -\log K_D \tag{13}$$

Table 6 summarizes the experimental equilibrium constants for different cyclohexanecarboxylic acids.

5.2. INFRARED MEASUREMENTS

5.2.1. Carbonyl frequencies of Cyclohexanecarboxylic Acids

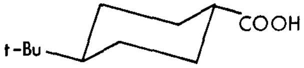
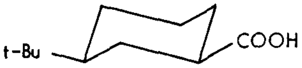
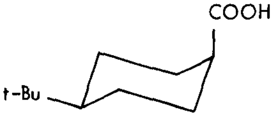
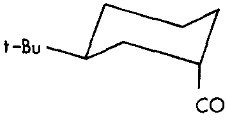
Infrared spectra of different cyclohexanecarboxylic acids were taken to see whether the 1,3-interactions influence the carbonyl stretching frequency. The spectra were recorded in a very dilute solution in carbon tetrachloride to observe clearly the monomer as well as the dimer absorption band. Table 7 summarizes the $\tilde{\nu}_{CO}$ frequencies of the acids measured.

Comparing acids XXIX and XL on one hand, and acids II and III on the other one, it is clear that practically no effect on the carbonyl frequencies due to 1,3-interactions is observed. The small frequency shifts observed in acids XII, XIII, XXIX and XL are caused by the inductive effect of the methyl group or ring junction in α-position [cf. 5.2.2.] *).

---

*) Bory and Fétizon studied the infrared spectra in the region 1250 - 1100 cm^{-1} of a series of terpenoid carboxylic acid methyl esters 105). They observed differences in the absorption between the esters with axial position of the ester group relative to those with an equatorial one. The authors however point out the difficulty in generalizing the results.

Table 6 Monomer-dimer Equilibrium Constants K_D for Some Cyclohexanecarboxylic Acids in Methylene Chloride at 30° C.

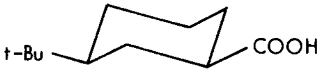
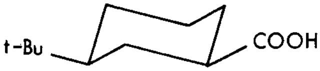
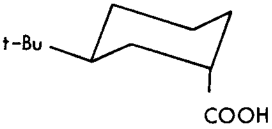
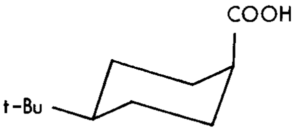
ACID	Concentration [mole/l.]	pK_D
	0.024	-1.88 ± 0.07*)
	0.028	-1.87 ± 0.07
	0.024	-1.79 ± 0.07
	0.023	-1.62 ± 0.07
	0.026	-1.80 ± 0.07

As shown in Table 6 the effect of the axial or equatorial position of the carboxyl group on the monomer-dimer equilibrium is too small to allow the use of this method for structural elucidation.

---

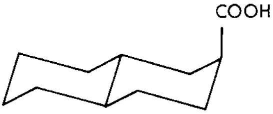
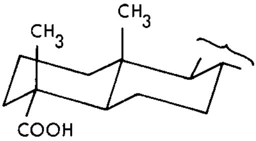
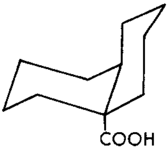
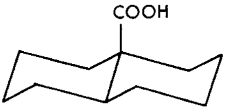
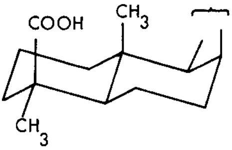
*) Standard deviation at the 95 % confidence level.

Table 7 Carbonyl Frequencies of Some Cyclohexanecarboxylic Acids *)

ACID	$\tilde{\nu}_{CO}$ $[cm^{-1}]$	
	Monomer	Dimer
	1752	1706
V 	1752	1706
III 	1752	1706
VIII 	1752	1705
IV 	1751	1702
II 	1751	1703

---

*) The concentration was 0.005 mole/l. and the cell-thickness 3 mm.

ACID	$\tilde{\nu}_{CO}$ $[cm^{-1}]$	
	Monomer	Dimer
 VI	1751	1701
 XXIX	1743	1695
 XII	1743	1694
 XIII	1747	1696
 XL	1741	1694

5.2.2. Infrared Spectra of the Silver Salts

Carboxylate anion frequencies are more strongly influenced by the environment of the anion than the carboxyl frequencies. Silver salts are very suitable for studies of the corresponding anions because of their easy preparation 101).

Carboxylate anions give rise to two absorption bands between 1610 cm^{-1} and 1550 cm^{-1} and between 1400 cm^{-1} and 1300 cm^{-1}, which correspond to the anti-symmetrical and symmetrical vibration of the $COO^{\ominus}$ structure 102). Of these bands, the former is much more characteristic, since on one hand it is stronger and on the other many skeletal vibrations may occur in the range 1400 - 1300 cm^{-1}.

Table 8 includes the carboxylate frequencies of a few silver salts of cyclohexane-carboxylic acids.

As may be seen in Table 8, no effect is observed on the carboxylate frequencies due to 1,3-interactions. In order to test whether steric effects can influence the carboxylate frequencies, spectra of several silver salts of carboxylic acids were taken using the potassium bromide sampling technique. The anti-symmetrical carboxylate frequencies are plotted in Figure 4 as a function of Taft's polar substituent constants 54).

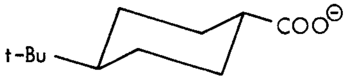
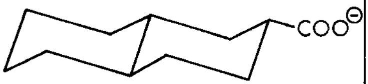
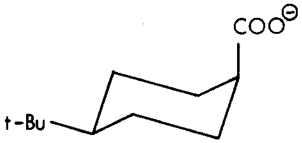
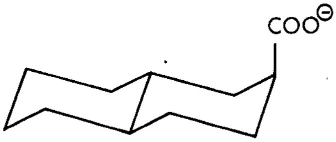
As shown in Figure 4, there exists a linear relationship between the anti-symmetrical carboxylate vibration frequencies and the polar substituent constants σ^*. No steric effects on the carboxylate frequencies whatsoever can be observed in the salts studied [see salts 1, 2, 3 and 4] .

The relationship in Figure 4 can be expressed by the following Equation:

$$\sigma^* = 0.0260 \cdot \tilde{\nu}_{as} - 41.02 \qquad (14)$$

The linear regression expressed by Equation (14) is significant at the 99 % confidence level and can therefore be used to estimate polar substituent constants σ^* ($\tilde{\nu}_{as}$ in cm^{-1}).

<u>Table 8</u> Carboxylate Frequencies of Some Silver Salts of Cyclohexanecarboxylic Acids (KBr disc)

SALT	$\tilde{\nu}_{as}$ $[\mathrm{cm}^{-1}]$	$\tilde{\nu}_{s}$ $[\mathrm{cm}^{-1}]$
	1570	1401
	1572	1403
	1570	1403
	1571	1401
	1571	1400

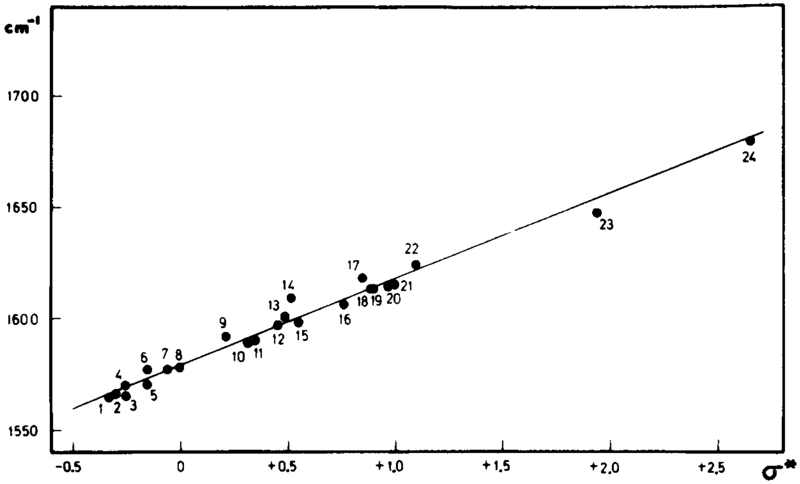


Figure 4 $\tilde{\nu}_{as}$ carboxylate frequencies of silver salts of carboxylic acids as a function of Taft's polar substituent constants σ^*.

Silver salts of

1 : α,α-Dimethylvaleric acid
2 : Pivalic acid
3 : Levopimaric acid
4 : 1-n-Propylvaleric acid
5 : Cyclohexanecarboxylic acid
6 : Capric acid
7 : Cyclohexylacetic acid
8 : Acetic acid
9 : Phenylacetic acid
10 : Tropic acid
11 : α,α-Dimethylglycolic acid
12 : Lactic acid
13 : Formic acid
14 : Methoxyacetic acid
15 : Glycolic acid
16 : Mandelic acid
17 : Phenoxyacetic acid
18 : α-Bromobutyric acid
19 : α-Chloropropionic acid
20 : Benzilic acid
21 : Bromoacetic acid
22 : Fluoroacetic acid
23 : Dichloroacetic acid
24 : Trichloroacetic acid

6. 2-HYDROXYCYCLOHEXANECARBOXYLIC ACIDS

So far only cyclohexanecarboxylic acids without other functional groups near the carboxyl group have been considered. Since many natural products containing such groups have other functional groups in the molecule, it is of interest to extend the study to cyclohexanecarboxylic acids with additional functional groups in the molecule.

6.1. ACIDITY OF 2-HYDROXYCYCLOHEXANECARBOXYLIC ACIDS

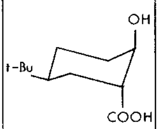
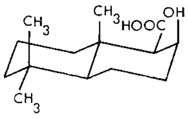
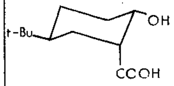
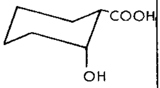
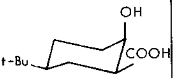
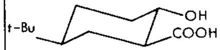
Table 9 shows the experimental pK^*_{MCS} values of several 2-hydroxycyclohexanecarboxylic acids as well as the pK^*_{MCS} values of the corresponding acids without hydroxyl group.

The "overall" effect of the hydroxyl group on the pK^*_{MCS} values of the 2-hydroxycyclohexanecarboxylic acids can be considered to be mainly due to three factors: the inductive effect (this operates only through the bonds and corresponds to a displacement of electronic charge caused by the different electronic-withdrawing effect of the two atoms forming a bond 107)), the field effect of the hydroxyl group (a dipole may interact with a charge directly through the space 107)) and the effect of intramolecular hydrogen bond formation between the hydroxyl and the carboxyl group, or between the hydroxyl and the carboxylate anion. Regarding the magnitude of the field effect, there is some uncertainty. According to the Kirkwood and Westheimer treatment 108, 109) this field effect is in the order of magnitude of only 0.1 pK units in the 1,2-diaxial-hydrocyclohexanecarboxylic acid [the dielectric constant for the solvent system methylcellosolve/water (80 : 20 % by weight) is 32.0 110)] . A field effect will therefore be neglected in this molecule.

The inductive and residual (field effect and hydrogen bond formation) contribution of a hydroxyl group are represented by $\Delta pK^*_{Ind.}$ and $\Delta pK^*_{Resid.}$ respectively. The total change in the pK^*_{MCS} value due to the hydroxyl group is therefore:

$$\Delta pK^*_{Total} = \Delta pK^*_{Ind.} + \Delta pK^*_{Resid.} \qquad (15)$$

Table 9 pK^*_{MCS} Values of 2-Hydroxycyclohexanecarboxylic A

	LXXXVI  	LXXXVII  	LXXXVIII  	LXXXIX  	XC  	XCI  	XCII 
pK^*_{MCS}	7.57	6.43	6.62	6.60	6.67	6.86	6.90
pK^*_{MCS} of the corresponding acids without OH	7.96	7.80	7.96	7.44	7.44	7.44	7.44
ΔpK^*_{Total}	- 0.39	- 1.37	- 1.34	- 0.84	- 0.77	- 0.58	- 0.54
$\Delta pK^*_{Ind.}$	- 0.39	- 0.39	- 0.39	- 0.39	- 0.39	- 0.39	- 0.39
$\Delta pK^*_{Res.}$	-	- 0.98	- 0.95	- 0.45	- 0.38	- 0.19	- 0.15

The inductive effect of the hydroxyl group is to a first approximation independent of the stereochemistry. The different ΔpK^{*}_{Total} values observed in the 2-hydroxycyclohexanecarboxylic acids of Table 9 have therefore to be attributed mainly to differences in the field effect and to intramolecular hydrogen bond formation of different strength. Both effects vary with the mutual steric arrangement of the two groups.

In the hydroxy-acid LXXXVI, in which both the carboxyl and the hydroxyl group are axial, the contribution of the hydroxyl group to the pK^{*}_{MCS} value is assumed to be due to the inductive effect of the substituent. This contribution, $\Delta pK^{*}_{Ind.}$, is assumed to be the same for all the other 2-hydroxycyclohexanecarboxylic acids studied.

The optimal condition for the formation of intramolecular hydrogen bonding is claimed to be reached if the hydrogen atom finds itself a link in a six-membered planar ring 104). In an ideal cyclohexane chair conformation, the torsion angles between the hydroxyl and the carboxyl groups in the remaining hydroxy-acids studied (LXXXVII, LXXXVIII, LXXXIX, XC, XCI and XCII) should be identical. The same holds for the corresponding field effects.

A very interesting situation is presented by the large $\Delta pK^{*}_{Resid.}$ of the acids LXXXVII and LXXXVIII. This can be explained on the basis of ring distortion. In acid LXXXVII there is a large steric interaction between the axial methyl group and the hydroxyl, the latter being "bent out" of the axial position with a consequent distortion of the ideal chair conformation of the ring. The two functional groups are therefore brought more closely together in a more favored configuration for hydrogen bond formation. This could also increase the field effect. The same happens in acid LXXXVIII, in which the interactions of the carboxyl group with the axial hydrogens are relieved by a "bending" of the C-CO bond out of the axial direction leading to a "flattened" chair 103). Another possibility is a preferred rotational conformation of the axial carboxyl, particularly suited for intramolecular hydrogen bond formation 58).

In acids LXXXIX and XC there exist also interactions between the axial hydrogens and the axial hydroxyl group. In these cases however the hydroxyl group having smaller steric requirements than a carboxyl group, is less extensively "bent out" of its axial orientation in the ideal chair conformation. The remaining acids, XCI and XCII, have no steric reasons for being twisted into a more planar configuration.

In an ideal chair conformation and in the solvent system methylcellosolve/water there seems therefore to be practically no tendency to intramolecular hydrogen bond formation between the hydroxyl and the carboxyl group.

6.2. MONOMER-DIMER EQUILIBRIUM

If 2-hydroxycyclohexanecarboxylic acids are capable of intramolecular hydrogen bonding, an inhibition in the dimerization relative to the corresponding cyclohexanecarboxylic acids without hydroxyl group is to be expected. To test this hypothesis, thermoelectric molecular weight determinations in very dilute solutions in methylene chloride were carried out [cf. 5.1.] .

Table 10 summarizes the experimental equilibrium constants for four different 2-hydroxycyclohexanecarboxylic acids.

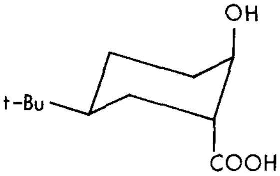
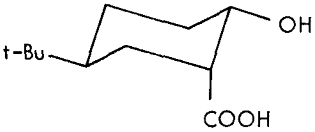
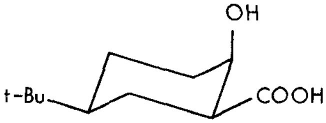
As shown in Table 10, the acid LXXXVI has the same monomer-dimer equilibrium constant as the corresponding cyclohexanecarboxylic acid without hydroxyl group [cf. Table 6] . The acid LXXXVIII has the lowest monomer-dimer equilibrium constant. The equilibrium constants of the two other acids, XC and XCI, are intermediate values between those of acids LXXXVI and LXXXVIII. These results are in perfect agreement with what should be expected on the basis of the acidity measurements.

6.3. INFRARED STUDY OF THE INTRAMOLECULAR HYDROGEN BONDING IN 2-HYDROXYCYCLOHEXANECARBOXYLIC ACIDS

Infrared spectroscopic determination of intramolecular hydrogen bonding in bifunctional derivatives is known to be a versatile method for determining the mutual spatial relationship between the two groups which are linked by a hydrogen bridge 103). There are two parameters which provide this information. The first one is the magnitude of the separation of the absorption bands due to the bonded and the free functional groups (hydroxyl or carbonyl frequencies). The other parameter is the value of the apparent molecular extinction coefficients, or preferably the integrated intensities of the two bands. The above approach has been used on several occasions 111 - 115) [cf. 132)] .

The low pK^{*}_{MCS} values of acids LXXXVII - XC [cf. 6.1.] could be explained assuming an intramolecular hydrogen bond between the hydroxyl and the carboxylate anion. The steric requirements for such a hydrogen bond are similar to those for a hydrogen bond between the hydroxyl and the carbonyl group in the free acid molecule.

Table 10 Monomer-dimer Equilibrium Constants K_D for Some 2-Hydroxycyclohexanecarboxylic Acids in Methylene Chloride at 30° C.

ACID	Concentration [mole/l.]	pK_D
LXXXVI 	0.025	-1.78 ± 0.07 *)
LXXXVIII 	0.023	-0.92 ± 0.07
XC 	0.026	-1.50 ± 0.07
XCII 	0.023	-1.41 ± 0.07

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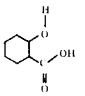
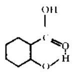
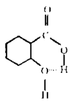
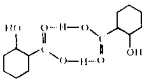
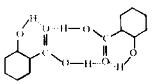
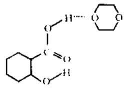
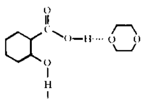
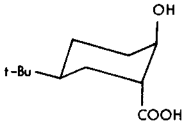
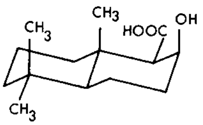
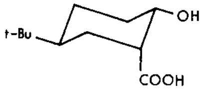
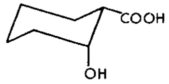
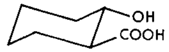
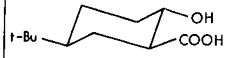
*) Standard deviation at the 95 % confidence level.

Table 11 Carbonyl Absorption Frequencies of 2-Hydroxycyclohexanecarboxylic Acids in Carbon Tetrachloride*).

ACID	$\tilde{\nu}_{CO}$ $[cm^{-1}]$						
	Free Monomer 						
LXXXVI 	1748			1702			1730
LXXXVII 		1728	1754		1685	1707	
LXXXVIII 		1733	1762	1696		1713	
LXXXIX 		1737		1698		1715	
XC 		1737		1698		1715	
XCI 		1737		1703		1717	
XCII 		1739		1702		1718	

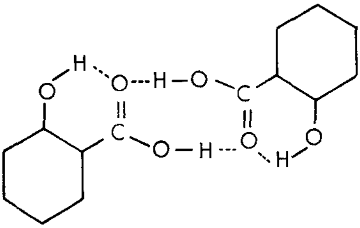
*) The concentration was 0.005 M or 0.0015 M and the cell-thickness 3mm or 10 mm respectively.

Leer - Vide - Empty

There should therefore exist a correlation between the acidity of such acids and the carbonyl frequency shift in the hydrogen bonded carboxyl group relative to the free monomer, the field effect being assumed to be roughly constant in the acids LXXXVII-XCII [cf. 6.1.] .

As can be seen in Table 11, the acids LXXXVII and LXXXVIII, having the lowest pK^*_{MCS} values of the series [cf. Table 9] , show the largest carbonyl frequency shifts in the hydrogen bonded carboxyl group relative to the free monomer. The assignment of the absorption bands in Table 11 has been made using dioxane to differentiate between inter- and intra-molecular hydrogen bonds 118). Dioxan and similar compounds form complexes with hydroxyl groups 119 - 124), effectively disrupting even strong intermolecular hydrogen bonds. Strong intramolecular hydrogen bonds, on the other hand, are almost unaffected by dioxane.It is thus possible to establish the type of hydrogen bonding by measuring the carbonyl frequencies of a compound in carbon tetrachloride and in dioxane/carbon tetrachloride solutions.

The carbonyl absorption frequency of the free carboxyl group in the 2-hydroxycyclohexanecarboxylic acids studied is unfortunately not known exactly, the only exception being the acid LXXXVI. It could be assumed to a first approximation to be roughly constant for all of them. The dipole-dipole interaction between the hydroxyl and the carboxyl group, varying with the different steric arrangements, can however influence it. It is known that the molecule with the hydroxyl of the carboxyl group internally bonded to another oxygen in the molecule has a carbonyl frequency higher than that of the "free" carboxyl 125 - 127). The "free " carboxyl frequency of the hydroxy-acids LXXXVII - XCII is to be assumed about 1750 cm^{-1} as it is experimentally obtained in acid LXXXVI [cf. Table 11] . The acid LXXXVII is the only one that in analogy to salicyclic acid 118, 128) forms a dimer of the type shown in Formula (16). The carbonyl frequency of this especies is 1685 cm^{-1},


(16)

As shown in Table 11, the frequency shift caused by the dioxane complex formation is 18 - 22 cm^{-1}, what is in perfect agreement with results found in the literature [118, 129, 130].

The results obtained in carbon tetrachloride (dielectric constant 2.23 [131]) can not be directly compared with those obtained in the acidity measurements in methylcellosolve/water (80 : 20 % by weight) (dielectric constant 32.0 [110]) [cf. 6.1.] . The agreement found in the results for the two solvent systems points out however that the steric arrangements in the 2-hydroxycyclohexanecarboxylic acids are roughly the same in both solvent systems.

7. EXPERIMENTAL

7.1. CYCLOHEXANECARBOXYLIC ACIDS

The acids under investigation were kindly placed at our disposal by the authors cited in the last column of Table 3 [cf. 3.4.]. 1-Methylcyclohexanecarboxylic acid was provided by J. Sauer, University of Munich. I am very grateful to them. Cyclohexanecarboxylic acid was obtained from FLUKA AG.

7.2. CONJUGATE ACIDS OF CYCLOHEXYLAMINES

The cyclohexylamine hydrochlorides studied in Chapter 4 were kindly provided by J. Sicher, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science, Prague, to whom I am very indebted.

7.3. 2-HYDROXYCYCLOHEXANECARBOXYLIC ACIDS

The acids LXXXVI, LXXXVIII, XC and XCII were provided by J. Sicher. The acids LXXXIX and XCI were placed at our disposal by J. Pascual, Faculty of Science, University of Barcelona. The acid LXXXVII was provided by E. Eschenmoser, Laboratory for Organic Chemistry, Eidgenössische Technische Hochschule, Zurich. I am very grateful to them.

7.4. DETERMINATION OF THE ACIDITY CONSTANTS

A standard method used for the determination of apparent acidity constants in the system methylcellosolve/water (80 : 20 % by weight), using samples of 0.1 mg to 1.0 mg has been described elsewhere 34, 35, 36, 38, 39, 40). The compound to be investigated was titrated according to a predetermined program using a glass-electrode/calomel-electrode combination which was conditioned in water and calibrated with aqueous buffer solutions. The apparent pH of the solution at half-neutralization of the functional group to be determined was assumed to be equal to the pK^*_{MCS}. 1 ml of a $3 \cdot 10^{-3}$ to $4 \cdot 10^{-3}$ M solution was normally titrated at 25° C. at a constant speed, the neutralization curve being plotted simultaneously.

7.5. THERMOELECTRIC MOLECULAR WEIGHT DETERMINATIONS *)

A review on the method with a comprehensive literature has been published elsewhere 116, 117). The method depends upon the measurement of the steady state temperature difference between a drop of solvent and one of solution suspended in a solvent saturated atmosphere at a fixed temperature.

The concentration used was 3 mg/ml. in methylene chloride and the fixed temperature 30° C. The standard deviation of the method is 2.0 % 117).

7.6. INFRARED MEASUREMENTS

All the infrared measurements were carried out using a Perkin-Elmer infrared grating spectrophotometer, Model 125. The accuracy in the range 1800 - 1600 cm^{-1} is ± 0.5 cm^{-1}. All spectra were calibrated using water vapour absorption bands. The measurements were carried out in carbon tetrachloride and dioxane/carbon tetrachloride (4 % or 1.25 % by volume with 3 mm or 10 mm cell-thickness respectively).

7.7. PREPARATION OF THE SILVER SALTS

The silver salts were prepared by adding 0.005 mole of the carboxylic acid to 12 ml. of water containing a few drops of phenolphtalein solution, then titrating to the pink end-point with 1 N sodium hydroxide solution. Silver nitrate solution (0.005 mole in 1 ml. hot water) was then added dropwise with stirring and the precipitated silver salt was filtered and rinsed with water, methanol and ether, then dried at 25°C and 30 Torr.

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*) cf. Ch. Chylewski, Ph. D. Thesis, Eigenössische Technische Hochschule, Zürich 1964.

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SUMMARY

1. A rule for the estimation of the pK^{*}_{MCS} values of cyclohexanecarboxylic acids has been studied using additive increments for the carboxyl : hydrogen- and carboxyl : methyl-1,3-interactions. The rule has been applied to seventy acids and may be used in the determination of the structure of cyclohexanecarboxylic acids.
2. A similar rule has been worked out for the estimation of the acidity of the conjugate acids of cyclohexylamines and related compounds.
3. Other physico-chemical methods such as monomer-dimer equilibrium studies and infrared measurements have been applied to cyclohexanecarboxylic acids to differentiate between the equatorial and axial position of the carboxyl group. No positive results have been obtained with these methods, leading to the conclusion that the pK^{*}_{MCS} determination so far is the only simple routine method that enables this differentiation.
4. The acidity of a series of 2-hydroxycyclohexanecarboxylic acids have been studied. The acidity of these acids is influenced by intramolecular hydrogen bond formation. This intramolecular hydrogen bond formation is found to be dependent on the relative position of the two functional groups. Significant intramolecular hydrogen bond formation was found only in those cases where the ring system is distorted from the ideal chair conformation. The hydrogen bond formation was confirmed by infrared measurements.

ZUSAMMENFASSUNG

1. Eine Regel zur Abschätzung von pK^*_{MCS}-Werten von Cyclohexancarbonsäuren basierend auf additiven Inkrementen für Carboxyl:Wasserstoff- und Carboxyl:Methyl-1,3-Wechselwirkungen ist untersucht worden. Die Regel ist auf 70 Verbindungen angewendet worden und lässt sich in der Strukturbestimmung von Cyclohexancarbonsäuren einsetzen.

2. Eine analoge Regel ist zur Abschätzung der Aciditätskonstanten der korrespondierenden Säuren von Cyclohexylaminen und verwandten Verbindungen abgeleitet worden.

3. Andere physikalisch-chemische Methoden wie infrarot-spektroskopische Untersuchungen sowie Messungen von Dimerisierungsgleichgewichten mittels Vaporometrie sind eingesetzt worden, um zwischen äquatorialer und axialer Lage von Carboxylgruppen zu differenzieren. Aus den negativen Ergebnissen folgt, dass die Messung von Aciditätskonstanten gegenwärtig die einzige einfache Routinemethode ist, die diese Differenzierung zulässt.

4. Die Acidität einer Reihe von 2-Hydroxycyclohexancarbonsäuren ist untersucht worden. Ihre Acidität wird in hohem Masse durch intramolekulare Wasserstoffbrückenbildung beeinflusst, die von der relativen Lage der beiden funktionellen Gruppen abhängt. Ausgeprägte Wasserstoffbrückenbildung tritt nur dann auf, wenn eine Deformation aus der idealen Sesselkonformation angezeigt ist. Die Wasserstoffbrückenbildung ist durch infrarotspektroskopische Untersuchungen bestätigt worden.

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