Tetrahedron Letters No.13, pp. 1401-1407, 1966. Pergamon Press Ltd.
Printed in Great Britain.

ROTATIONAL ORIENTATION OF CARBOXYL GROUPS IN CYCLOHEXANE SYSTEMS

REVISION OF SIMON'S pK_a-RULE

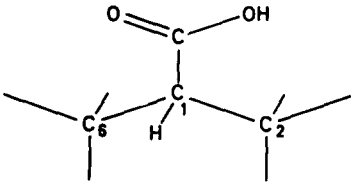
H. van Bekkum, P.E. Verkade, and B.M. Wepster

Laboratory of Organic Chemistry

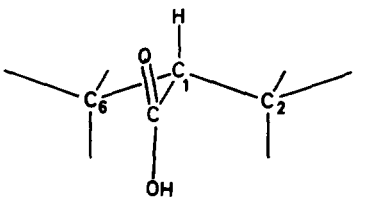
Technical University, Delft, Netherlands

(Received 25 January 1966)

In recent years we have measured the pK_a values of a large number of cyclohexanecarboxylic acids (1). The results have led us to accept the conformations I and II as the preferred ones for axial and equatorial carboxyl groups, respectively.



I



II

In I the plane of the carboxyl group is parallel to the plane through the axial C_3-H and C_5-H bonds; the angle of rotation about the C_1-COOH bond is defined as $\varphi = 90^\circ$. In II the carbonyl bond eclipses the C_1-H bond; the angle of rotation is defined as $\varphi = 0^\circ$.

It may be noted that, although the evidence for I and II comes (mainly) from the pK_a values, I is plausible a priori in view of atomic distances, and II in view of its resemblance to the known conformation of acetaldehyde (2).

In what follows the same rotational orientation will be assumed to hold for COOH and COO^-.

The different orientation of carboxyl in I and II with respect to C_1-H implies that the effect, ΔpK_a, of any substituent in 1-axial position on 1-equatorial carboxyl will be different from that of the same substituent in 1-equatorial position on 1-axial carboxyl. Table I shows this to hold for 1-methyl and 1-bromo substitution.

TABLE I

pK_a values[a] of 1-bromo- and 1-methyl-4-t-butylcyclohexanecarboxylic acids

Substitution	Position of			pK_a	ΔpK_a	$\Delta\Delta pK_a$
	COOH	Me/Br	t-Bu			
4-t-Bu	e		e	6.22	-0.39	0.23
4-t-Bu-1-Me	e	a	e	6.61		
4-t-Bu	a		e	6.68	-0.16	
4-t-Bu-1-Me	a	e	e	6.84		
4-t-Bu	e		e	6.22	1.47	0.22
4-t-Bu-1-Br	e	a	e	4.75		
4-t-Bu	a		e	6.68	1.69	
4-t-Bu-1-Br	a	e	e	4.99		

a. Thermodynamic values in 50 vol. % ethanol-water at 25°.

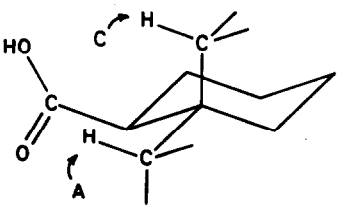
Again, the increase in acid strength when substituting equatorial methyl by equatorial bromine (1.85 pK_a units) is equal to that of substituting axial methyl by axial bromine (1.86 pK_a units). This may be seen as a strong indication that the rotational orientation of carboxyl is identical in the four 1-substituted acids in question. We accept $\varphi = 90^\circ$ for this orientation on the basis of our data. The tabulated $\Delta\Delta pK_a$ values then reflect only the

consequences of the rotation of equatorial carboxyl from $\varphi = 0^{o}$ to $\varphi = 90^{o}$.

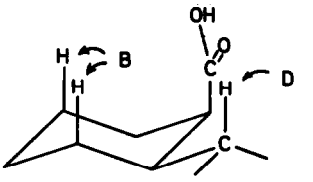
An extrapolation of this to aliphatic acids would seem valid. Isobutyric acid will be conformationally equivalent to II. Introduction of the third methyl group to give pivalic acid should have the same effect as the introduction of a 1-axial methyl group in trans-4-t-Bu-cyclohexanecarboxylic acid. This we found to be true; the acid-weakening effects are 0.35 and 0.39 pK_a units, respectively. Our analysis also implies that, quite apart from saturation and other effects, additivity of substituent influences in mono-, di-, and tri-substituted acetic acids, esters, etc., is illusory.

A further consequence of the occurrence of preferred carboxyl orientations is a strong variation in the acid-weakening effects caused by γ-hydrogen from γ-C-H bonds parallel to the C_1-COOH bond, and due to steric hindrance to solvation and, in many cases, the rotational re-orientation of carboxyl.

Table II contains some examples. For the discussion we define the relevant "internal" and "external" interfering hydrogen as "γ-syn hydrogen", and their interactions with carboxyl, as being of types A, B, C, and D. These types are illustrated by III and IV and are arranged in order of decreasing angle - 90^{o}, 60^{o}, 30^{o}, and 0^{o} - between the plane of carboxyl and the plane including C_1 and the C-H bond in question.



III



IV

TABLE II

pK_a values[a] of 2-methylsubstituted cyclohexanecarboxylic acids

Substitution	Conf.[b]	pK_a	φ ; γ-syn H[c]	φ ; γ-syn H[d]
2-Me	ee	6.20	0° ; A	
2-Me	ea	6.45	0° ; C	60° ; A
2-Me-4-t-Bu	eee	6.22	0° ; A	
2-Me-4-t-Bu	aee	7.17	90° ; 2B,D	0° ; A,2C
2-Me-4-t-Bu	eae	6.38	0° ; C	60° ; A
2,6-di-Me	eee	6.22	0° ; 2A	
2,6-di-Me	aee	7.09	90° ; 2B,2D	0° ; 2A,2C
2,4,6-tri-Me	eeee	6.24	0° ; 2A	
2,4,6-tri-Me	aeee	7.22	90° ; 2B,2D	0° ; 2A,2C
1,2-di-Me	eae	6.73	0° ; A; 1-Me	
1,2-di-Me	aee	6.93	90° ; 2B,D; 1-Me	
decalin-1-COOH[e]	eee	6.28	0° ; A	
decalin-1-COOH[e]	aee	7.08	90° ; 2B,D	0° ; A,2C
decalin-9-COOH	aea	6.91	90° ; 2B; 1-Me	
decalin-9-COOH	aee	7.40	90° ; 3B,D; 1-Me	60° ; 2A,2C; 1-M

a. See legend Table I.

b. Predominant conformation; the position of substituents is given in order of numbering, with COOH first.

c. Rotational orientation and γ-syn interactions on the basis of conformations I and II.

d. Most probable orientation and the corresponding interactions, if different from those in the preceding column.

e. Gift from Prof. N.B. Chapman and Drs. J. Shorter and K.J. Toyne, University of Hull, which we acknowledge gratefully.

One type A interaction is present in ee-2-methylcyclohexanecarboxylic acid and in eee-decalin-1-carboxylic acid. Only very small effects on pK_a are observed, even when two such interactions are created as in eee-2,6-dimethylcyclohexanecarboxylic acid.

Two B-interactions are present with the standard axial carboxyl (I), e.g. in (ae) cis-4-t-butylcyclohexanecarboxylic acid. The reason for the acid-weakening with respect to equatorial carboxyl can be regarded as twofold: the rotation from $\varphi = 0^\circ$ to $\varphi = 90^\circ$ and the two B-interactions.

Type C interaction would occur in eae-2-methyl-4-t-butylcyclohexanecarboxylic acid. However, this interaction will be evaded by rotation, even though this means a deviation from $\varphi = 0^\circ$.

Type D interaction might be expected in aee-2-methyl-4-t-butylcyclohexanecarboxylic acid and in aee-decalin-1-carboxylic acid. Strong acid-weakening is observed. Once more rotational re-orientation is likely, the carboxyl accepting one A- and two C-interactions, with $\varphi = 0^\circ$. This explains why a second equatorial methyl group, as in aeee-2,4,6-trimethylcyclohexanecarboxylic acid, exhibits such a small effect; only an additional A-interaction is then introduced.

In recent years Simon et al. (3,4,5,6) have given rules correlating and predicting pK_a values of systems as discussed above. In these rules, in a given solvent, one increment is assigned to 1-methyl substitution, and one increment to any γ-syn hydrogen. In other words, the rotational orientation of carboxyl is not taken into account. The following rules, based upon the above, satisfy our experimental data considerably better.

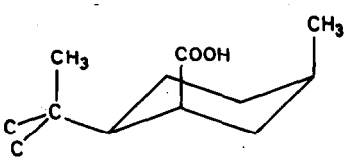
In 50 % ethanol, pK_a values can be estimated by starting out from the pK_a value of equatorial carboxyl with $\varphi = 0^\circ$ ($pK_a = 6.22$), and adding the increments:

1. $\varphi = 90^\circ$: + 0.23; $\varphi = 60^\circ$: + 0.14
2. γ-syn hydrogen, type A: + 0.02; type B: + 0.13; type C: + 0.45; type D: unknown but larger than type C
3. 1-methyl substitution, $\varphi = 90^\circ$: + 0.18

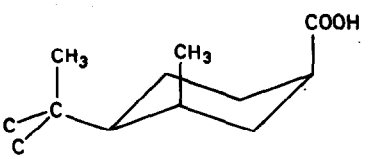
   $\varphi = 0^\circ$: + 0.40

In cases where the rotational orientation of carboxyl is uncertain, the orientation leading to the minimum increment should be chosen. If a hydrogen atom in γ-position is replaced by substituents, further increments will have to be considered.

Apart from affecting the rotational orientation of carboxyl the interactions in question can also be of importance with regard to the chair-chair equilibrium. Thus, in cis-2-methylcyclohexanecarboxylic acid the chair-form with methyl axial and carboxyl equatorial predominates. A more spectacular example is found with the anion of cis-1,2-dimethylcyclohexanecarboxylic acid in which the eaa-conformation, with two axial methyl groupe, prevails. Both cases are further illustrations of the non-additivity of conformational energies (7).



V



VI

Finally we give an example in which comparable interactions involving γ-syn methyl groups produce even more profound effects. Introduction of a 5-cis-methyl group in ae-2-t-butylcyclohexanecarboxylic acid (pK_a = 7.36), giving V, increases the acid strength (pK_a = 7.04). This can be understood only if the cyclohexane ring of V is largely in a flexible conformation, thus avoiding the larger part of the unfavourable interactions. In contrast, aae-3-methyl-4-t-butylcyclohexanecarboxylic acid, VI, which at first sight would seem equivalent to V, behaves normally (pK_a = 6.87).

Similar conclusions have been reached by Prof. J. Sicher et al. at the Czechoslovak Academy of Sciences, Prague. This work, of which Prof. Sicher has kindly informed us, is to be published simultaneously with the present paper in this journal.

REFERENCES

1. Preliminary paper: H. van Bekkum, P.E. Verkade, and B.M. Wepster, Koninkl. Ned. Akad. Wetenschap., Proc. B64, 161 (1961).
2. Cf. E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, Conformational Analysis, p. 19. Interscience Publishers, New York (1965).
3. P.F. Sommer, V.P. Arya, and W. Simon, Tetrahedron Letters, No. 20, 18 (1960).
4. P.F. Sommer, C. Pascual, V.P. Arya, and W. Simon, Helv. Chim. Acta 46, 1734 (1963).
5. C. Pascual and W. Simon, Helv. Chim. Acta 47, 683 (1964).
6. W. Simon, Angew. Chem. 76, 772 (1964).
7. Cf. R.D. Stolow, J. Am. Chem. Soc. 86, 2170 (1964).