**Tetrahedron Letters No.13, pp. 1393-1399, 1966. Pergamon Press Ltd.
Printed in Great Britain.**

CONFORMATIONAL EQUILIBRIA IN THE 2-METHYLCYCLOHEXANE-CARBOXYLIC ACIDS. PREFERRED ROTATIONAL CONFORMATIONS OF THE CARBOXYL ON THE CYCLOHEXANE RING+

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(Received 25 January 1966)

Although a great deal is known about chair-to-chair conformational equilibria in monosubstituted cyclohexanes (1), there is only scant information about analogous equilibria in 1,2-disubstituted cyclohexane derivatives. Such data are clearly of intrinsic interest; in addition, they afford information on the mutual interactions between substituents. The carboxyl group is of particular interest because it is a non-centrosymmetrical group and its "effective steric bulk" will be expected to depend sensitively on its detailed steric environment (2).

As has been shown (3,4), it is possible to determine chair-to-chair conformational equilibrium constants in mobile dissociating cyclohexane systems by confrontation of the

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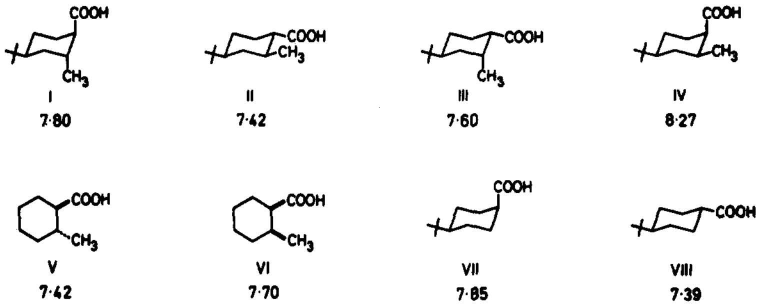
+During discussions at the Bürgenstock Conference on Stereochemistry (May 1965) it was learned that closely related work had been going on in the Laboratory of Organic Chemistry at the Technical University, Delft, and in this Laboratory, and concurrent publication was agreed upon, cf. accompanying paper (5).

dissociation constant, K_R, of the "mobile" compound under study, with the dissociation constants, K_e and K_a, of the corresponding conformationally "biased" compounds. The formulae $K_{COOH} = (K_e - K_R)/(K_R - K_a)$ [1] and $K_{COO^-} = (K_a/K_e)K_{COOH}$ [2] then give values of K_{COOH} and K_{COO^-}, the conformational equilibrium constants of the acid and the dissociated species, respectively.

pK_a-Values in "80 %" Methyl Cellosolve at 25°C



Scheme 1

In order to study the important case of the 2-methylcyclohexanecarboxylic acids V and VI we have synthesised, by methods to be reported subsequently, the four stereoisomeric 4-tert.butyl-2-methylcyclohexanecarboxylic acids I - IV, which we look upon as the conformationally biased species. From the dissociation constants (Scheme 1), and formulae [1] and [2], we estimate the conformational equilibrium constant, K_{COOH}, for *cis*-2-methylcyclohexanecarboxylic acid (VI) as being 0.37 ± 0.1, which corresponds to about 0.6 ± 0.2 kcal.mole^{-1} in favour of conformer COOH^{e} (Scheme 2). Similarly, for the dissociated species, the conformational equilibrium constant, K_{COO^-}, corresponds to about 1.5 kcal.mole^{-1}, again in favour of conformer COO$^{-\,e}$. If one assumed additivity of A-values,

VI

Scheme 2

the free energy corresponding to the equilibrium of the acid VI would be[+] $A_{Me} - A_{COOH} = 1.7 - 1.15 = 0.55$ kcal. mole^{-1}, but now in favour of conformer COOH^{a}. The difference between the value thus computed and that actually found is hence greater than 1 kcal.mole^{-1}.[++] For the dissociated acid the deviation from A-value additivity is even larger, about 1.5 kcal.mole^{-1}. A powerful destabilising feature must hence be operating in the COOH^{a} conformer.

Interesting conclusions pertinent to the nature of this destabilising feature follow from a confrontation of the

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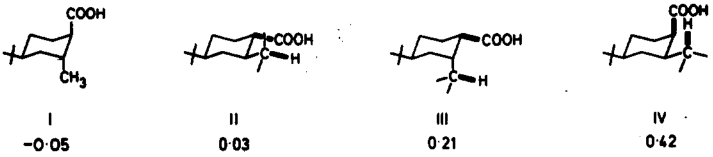
[+] The value 1.15 for carboxyl was newly determined from dissociation data; it is somewhat lower than that reported earlier (3,4,6) but close to that recently found by other methods (7,8). The A-value for the carboxylate anion is 1.8.

[++] The dissociation constant of II is identical with that of trans-2-methylcyclohexanecarboxylic acid V, confirming that the latter exists in the di-equatorial conformation exclusively, or almost so.

pK_a values of the acids I - IV, with those of the appropriate 4-tert.butylcyclohexanecarboxylic acids VII and VIII. The differences in pK_a of the 2-methyl acids I - IV and the appropriate "parent" cyclohexanecarboxylic acids, VII and VIII, denoted as ΔpK_{Me} , are given in Scheme 3. The ΔpK_{Me} values reflect the effects which the methyl group (cf. Scheme 3), in the four different mutual positions, exhibits on the dissociation properties of the carboxyl. As will be seen, the values of ΔpK_{Me} differ considerably from one acid to the next; a particularly high value of ΔpK_{Me} was found for the acid IV.

Values of pK_a Increments, ΔpK_{Me} due to Introduction of 2-Methyl Group



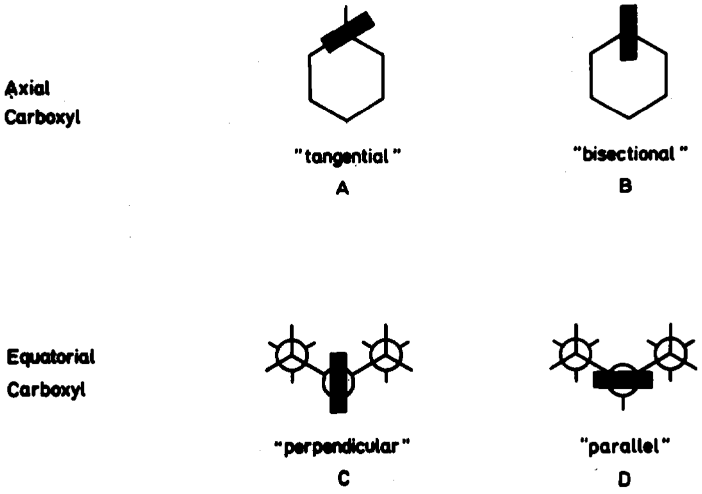
Scheme 3

The conformational equilibrium data, as well as the ΔpK_{Me} values, may be rationalised if we make the a priori reasonable assumption that both for the axial and the equatorial carboxyl there exists a particular preferred rotational conformation, namely A and C, respectively, (Scheme 4) and that deviations from these preferred rotational conformations, enforced by the introduction of the vicinal methyl group, may involve considerable energy demands, which, moreover, differ as between isomers. The ΔpK_{Me} values may then be regarded as depending, in part, on the magnitude of these demands.

Consideration of the formulae in Scheme 3 makes it plausible why the acid weakening effect should be largest in the case of the isomer IV : the "quasi-synaxial hydrogen" of the methyl group here will tend to force the carboxyl into the highly unfavourable "bisectional" conformation B. Analogously, the "quasi-synaxial hydrogen" in III will interfere with the preferred "perpendicular" conformation C of the equatorial carboxyl more seriously than does the "quasi-synaxial hydrogen" in II, and will hence be expected to have a larger acid weakening effect, although in both the latter instances the effect would be much smaller than in the case of IV. The fact that "synaxial" hydrogens in different positions have different effects on the pK_a values of the carboxyl shows that simple empirical rules for the calculation of pK_a values which do not take this feature into account, such as the rule of Simon (9), will require some modification.

The feature responsible for the highly strained nature of the $COOH^a$ conformer of cis-2-methylcyclohexanecarboxylic acid (VI) is also seen to be a consequence of the fact that the carboxyl in this conformer must exist either in a now highly congested "tangential" (A), or the - anyhow strained - "bisectional" (B) conformation. A semi-

Rotational Conformations of the Carboxyl Group



Scheme 4

quantitative estimate of the strain resulting from such a situation may be obtained from the direct equilibration of the esters corresponding to the acid II and IV. The equilibrium in this system corresponds to 2.2 kcal.mole^{-1} in favour of the isomer II, which is at least 1 kcal. mole^{-1} in excess of what would be predicted on the basis of additivities of A-values. This hence is a minimum value for the magnitude of the strain involved.

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