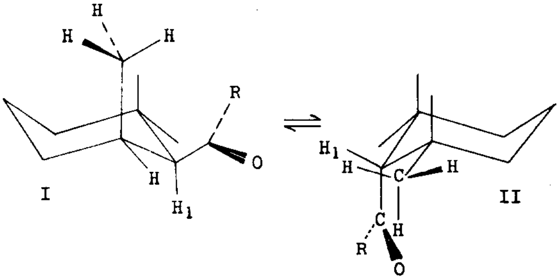
Tetrahedron Letters No.6, pp. 645-650, 1968. Pergamon Press. Printed in Great Britain.

HYDROLYSIS OF THE METHYL 2-METHYLCYCLOHEXANECARBOXYLATES; CONFORMATIONAL ANALYSIS OF SOME CYCLOHEXANECARBOXYLIC DERIVATIVES

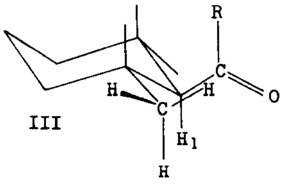
Lars H. Hellberg (1a) and Robert Peiffer (1b)
San Diego State College, San Diego, California 92115
Thomas L. Jacobs
University of California, Los Angeles, California 90024
and Russell Reed
Thiokol Chemical Corporation, Brigham City, Utah 84302

(Received in USA 28 June 1967)

It has been reported (2) that cis-2-methyl-1-acetylcyclohexane [a] exists largely (at least 89%) in the conformation Ia (rather than 58% IIa- 42% Ia, approximately, assuming additivity of A-values (2,3) and ignoring other considerations), and [b] it reacts faster (33:1) towards hydroxylamine than its trans isomer (IIIa, neglecting the diaxial conformation). Considerations published earlier (4,5) of the ionization constants of a series of alkylated 2-methylcyclohexanecarboxylic acids were in agreement with [a]: it was concluded that cis-2-methylcyclohexanecarboxylic acid exists largely (66-78%) in the Ib conformation due to destabilization of the (normally) preferred "tangential" conformation of the carboxyl shown in IIb (rather than 72% IIb- 28% Ib, based on A-values) (4,5). These reports prompt us to describe some earlier kinetic results (7) similar to those given in [b].



I ⇌ II



III

a: R = CH_3
b: R = OH
c: R = OCH_3

The pseudo first-order rate constants for the acid-catalyzed hydrolysis of the methyl cis- (Ic $\rightleftharpoons$ IIc) and trans- (IIIc) 2-methylcyclohexanecarboxylates in 60% (by wt.) aqueous dioxane establish their relative reactivity to be approximately k_{cis}/k_{trans} = 5/1 (see TABLE; data for methyl cyclohexanecarboxylate, IV, included for comparison; see also ref. (9)). This order of reactivity reportedly has also been observed for esterification of Ib $\rightleftharpoons$ IIb and IIIb but with no data supplied (2). This contrasts with the relative reactivity of methyl cis- (V, CO_2CH_3 axial) and trans- (VI, CO_2CH_3 equatorial) 4-t-butylcyclohexanecarboxylates in acid hydrolysis in 50% (by vol.) aqueous dioxane of k_V/k_{VI} = 1/4.7 (at 90°) (8). Thus, in conjunction with the earlier reports (2,4,5) on structurally similar compounds, these kinetic data suggest that methyl cis-2-methylcyclohexanecarboxylate exists to a large extent (though not calculable here) in the conformation Ic (rather than 73% IIc- 27% Ic, assuming additivity of A-values only (3,9)).

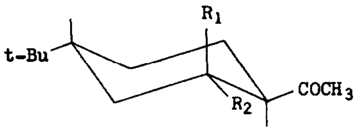
TABLE

	$k_1 \times 10^7$ (l. mole^{-1} sec.$^{-1}$)^a				
	25.00°	40.00°	60.00°	E^a (kcals./mole)	$\Delta S^{\ddagger}$ (e.u.)
Ic $\rightleftharpoons$ IIc	18.2 ± 0.6	69.5 ± 4 64. ± 2	325 ± 12 322 ± 11	16.00 ± 1.00	-33.3 ± 3.0
IIIc	3.4 ± 0.3 (2.92 ± 0.06)^b	13.0 ± 0.9	68 ± 7^c 73 ± 10.5^c	17.20 ± 1.75	-32.8 ± 5.2
IV	163. ± 5.	596. ± 10.	2665 ± 63	15.55 ± 0.45	-30.5 ± 1.4

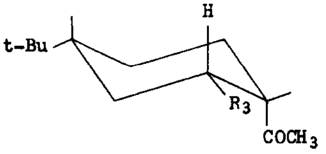
[a] Initial ester conc. ~0.05 M; [HCl] ~0.2 N. Each rate run involved an average of seven periodic determinations of organic acid present in sealed ampoules of the reaction system. The data at 40° and 60° were corrected for solvent expansion. All data were corrected for slight solvent decomposition except that of IV (60°) by means of solvent blanks. The errors are standard deviations. [b] Initial ester conc. was ~0.10 M. [c] There was some evidence of a slight downward drift in the individual rate constants in these runs.

Several observations have been recorded that suggest that k_{cis}/k_{trans} (for Ic $\rightleftharpoons$ IIc: IIIc) will be larger than k_V/k_{VI}, regardless of the percentage of each conformation in Ic $\rightleftharpoons$ IIc. First of all, data from the oximation studies (2) are as follows (all relative rate ratios): k_{VII}/k_{IX} = 1/13.8, k_{VIII}/k_{IX} = 1/471 and k_X/k_{XI} = 1/65.5 (some uncertainty exists here, however, since the formation of the tetrahedral reaction intermediate, a carbinolamine, in oximation is an equilibrium reaction, not a rate-controlling one as in the ordinary ester hydrolysis mechanism ($A_{Ac}2$) (12)). If such effects are also operative in the methyl 2-methylcyclohexanecarboxylates in at least the order of diminution indicated, they suggest the following:

[1] an axial (a-) 2-methyl adjacent to an equatorial carbomethoxyl reduces reaction rate



VII R_1 = CH ,
R_2 = H
VIII R_1 = H,
R_2 = CH_3
IX R_1 = R_2 = H

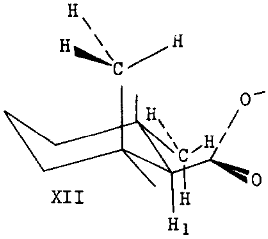


X R_3 = CH_3
XI R_3 = H

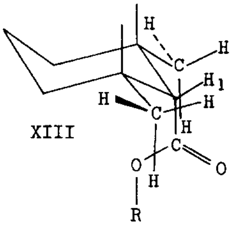
less than an equatorial (e-) 2-methyl so that Ic should react faster than IIIc; examination of Dreiding models of Ic and IIIc (torsion $\angle$ H_1—C_1—C=O = 60° and 0°, respectively) (13) suggests that the carboxyl carbon in Ic is more open to approach (at 90° to the plane of the protonated carbomethoxyl) by a water molecule from the C_6 side than is the same atom in IIIc (openness from the C_2 side in both esters appears to be the same) (15).

[2] an e-2-methyl reduces the rate of reaction at an adjacent 1-a-carbomethoxyl markedly less than at a 1-e-carbomethoxyl. Even though axial carbomethoxyl with no 2-substituent is slower than equatorial (presumably because axial hydrogens at positions 3 and 5 are hindering), the added hindrance of an e-2-methyl would reverse the relations and IIc would react more rapidly than IIIc; the difference might be quite small, however.

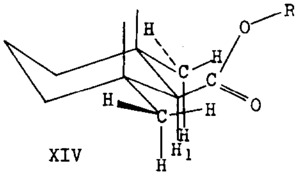
That such effects do appear to occur in ester hydrolysis is found in the relative rates of acid-catalyzed hydrolysis in 60% (by wt.) aqueous dioxane of the methyl 2,6-dimethylcyclohexanecarboxylates (7,16). Support of the first effect (a-2-methyl vs. e-2-methyl next to 1-e-CO_2CH_3) is seen in the rate ratio of k_{XIIa}(*racemic*)/k_{XIVa}(*meso trans*) = 11/1 (at 144°). This relative order of reactivity has also been observed in the hydrolysis of *racemic-* and *meso trans-* 2,6-dimethylcyclohexyl phenyl ketimine hydrochlorides (17). Dreiding models of XIIa and XIVa (torsion $\angle$ H_1—C_1—C=O = 30° and 0°, respectively) (13), as well as Stuart-Briegliеb models, are consistent with the carboxyl carbon in XIIa being more open to the approach of a water molecule than in XIVa (15). The second effect (a-1-CO_2CH_3 vs. e-1-CO_2CH_3, both with e-2-methyl) is supported by the rate ratio k_{XIIIa}(*meso cis*)/k_{XIVa}(*meso trans*) = 2.3/1 (144°), in complete contrast to the ratio observed for V and VI (see above), where no adjacent methyls are present. In this discussion no assessment of the more subtle effects, if any, of ring flattening caused by an axial substituent, bringing *cis*-1,2-substituents closer to each other than *trans*-1,2-substituents (18), on the relative reactivities has been attempted.



XII



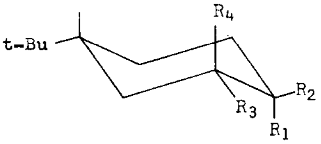
XIII



XIV

a: $R = CH_3$
b: $R = H$

In contrast to the kinetic studies just discussed, the relative acidities (thermodynamic control) of alkylated 2-alkylcyclohexanecarboxylic acids appear to be primarily determined by steric hindrance to solvation of charge on the oxygens of the anions formed on ionization (19). This includes effects arising 1: from ring flattening caused by an axial substituent (see above) (18) and 2: from the a-3,5-hydrogens hindering solvation of an a-1-CO_2^- (where such occurs in a compound or conformation). Thus, trans-4-t-butylcyclohexanecarboxylic acid, XV, IIIb, and XIVb are very similarly acidic (all substituents equatorial), with cyclohexanecarboxylic acid only slightly less so. In contrast, XVI (an a-2-methyl) is a weaker acid while XVII and XIIIb (both with a-1-CO_2H), of like acidity, are weaker yet; the acidity of Ib $\rightleftharpoons$ IIb is intermediate to those of XVI and XVII (all measurements in aqueous alcoholic solvents) (4-6).



XV $R_2 = CO_2H$ $R_3 = CH_3$ $R_1 = R_4 = H$
XVI $R_2 = CO_2H$ $R_4 = CH_3$ $R_1 = R_3 = H$
XVII $R_1 = CO_2H$ $R_3 = CH_3$ $R_2 = R_4 = H$

Our results ($pK_{H_2O}^{25^\circ}$ XIVb, 4.66; XIIb, 4.96; XIIIb, 5.64) (20) are in accord with the above observations. However, superimposed is an effect seemingly peculiar to water (though perhaps damped in mixed solvents and thus not as noticeable) that enhances the acidities of 2-methylcyclohexanecarboxylic acids. For example, the acidity of XIVb exceeds that of IIIb ($pK_{H_2O}^{25^\circ}$ 4.73) (21), both of which in turn are more acidic than trans-4-methylcyclohexanecarboxylic acid (conformationally homogeneous) ($pK_{H_2O}^{25^\circ}$ 4.88) (21). This effect in water has remained unexplained (21,22) and appears to be real, despite the comment of Sicher et al. (23). Whether this effect arises from 1: some sort of entropy effect (bulk effect, differential solvation, etc.), resulting in a less negative entropy of ionization in water because of the 2-methyl substituent, earlier proposed (24) but not observed (25) for n-butyric acid (pK_{H_2O} smaller than that for propionic acid), from 2: the weak inductive effect (acid-weakening) of the 2-methyl being swamped by some sort of field effect of the methyl's hydrogens ($C^{\delta-} - H^{\delta+}$) (less likely perhaps) (26,27) or from other factors (25) as yet unidentified can only be speculated upon at this point.

Acknowledgement. We wish to thank the National Science Foundation for support of R. P. under the Undergraduate Research Participation Program. We thank Professor Arne Fredga, Uppsala, for discussion, and the American-Scandinavian Foundation for a travel grant-in-aid.

References

(1) (1a) On leave, Chemical Institute, Uppsala University, Uppsala, Sweden, 1966-1967.
(1b) National Science Foundation Undergraduate Research Fellow, 1962-1964.

(2) A. Heymes and M. Dvolaitzky, Bull. Soc. Chim. France, 2819 (1966).

(3) E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis," Interscience, New York, 1965, pp. 36-50 and 436-444, and references therein.

(4) J. Sicher, M. Tichy and F. Sipos, Tetrahedron Letters, 1393 (1966) and Coll. Czech. Chem. Commun., 31, 2238 (1966). See, however, references (3) and (6) (Table I, footnote a) for other A-values of carboxyl and discussion of their reliability.

(5) H. van Bekkum, P. E. Verkade and B. M. Wepster, Tetrahedron Letters, 1401 (1966).

(6) E. L. Eliel and F. J. Biros, J. Am. Chem. Soc., 88, 3334 (1966).

(7) L. H. Hellberg, Ph.D. Thesis, University of California, Los Angeles, 1958.

(8) N. B. Chapman, J. Shorter and K. J. Toyne, J. Chem. Soc., 2543 (1961).

(9) An average A-value of 1.1 kcals./mole (from equilibrium determinations) (3) was used for CO_2CH_3; more recently, an average value of 1.3 kcals./mole has been reported. (10) No A-value of CO_2CH_3 from kinetic data has been reported; the reason is seen in (8) and (11) and in work in this (San Diego State) laboratory (F. Kester, Undergraduate Research Report, June, 1960): methyl cyclohexanecarboxylate (IV) always reacted somewhat faster than methyl trans-4-t-butylcyclohexanecarboxylate in aqueous dioxane under both acidic and basic conditions. This raises questions about the solvent, aqueous dioxane (see ref. (3), p. 78, footnote; note mention of the relative reactivities of these esters in aqueous methanol being in the reverse, "expected," order), about the conformational make-up of IV in such a solvent and about the effect of this solvent on the conformational equilibria of the other esters discussed herein.

(10) M. Tichy, F. Sipos and J. Sicher, Coll. Czech. Chem. Commun., 31, 2889 (1966).

(11) E. A. S. Cavell, N. B. Chapman and M. D. Johnson, J. Chem. Soc., 1413 (1960).

(12) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Rinehart-Winston, New York, 1959, Chapt. 9.

(13) The carbomethoxyl rotational conformations in Ic-IIIc and XIIIa-XIVa are those proposed for the carboxyls of the corresponding acids (4,5); that of XIIa is proposed based on principles used for the others. For comment on the proposed carboxyl conformations, see ref. (14).

(14) J. D. Dunitz and P. Strickler, Tetrahedron Letters, 3933 (1966).

(15) Of course, kinetic considerations do not rule out intervention of less stable carbomethoxyl rotational conformations, some of which are undoubtedly separated from that shown for each ester by small energy barriers (14).

(16) Robert Peiffer, Undergraduate Research Thesis (San Diego State), August, 1964. Details of the kinetics, etc., from this study and ref. (7) will be presented elsewhere.

(17) J. B. Culbertson, D. Butterfield, O. Kolewe and R. Shaw, *J. Org. Chem.*, *27*, 729 (1962).

(18) R. A. Wohl, *Chimia* (Aarau), *18*, 219 (1964).

(19) Such an explanation also accounts for the relative reactivity observed in some epimeric pairs of cyclohexane- and *trans*-decalincarboxylic acids toward diphenyldiazomethane, insofar as this applies to a transition state in which only partial charge development on the oxygens has taken place during the rate-determining proton transfer. However, unexpected rate enhancements for the faster member of some of the pairs has so far eluded satisfactory explanation; cf. N. B. Chapman, A. Ehsan, J. Shorter and K. J. Toyne, *J. Chem. Soc.*. (B), 256 (1967).

(20) R. Reed, Ph.D. Thesis, University of California, Los Angeles, 1948.

(21) J. F. J. Dippy, S. R. C. Hughes and J. W. Laxton, *J. Chem. Soc.*, 4102 (1954).

(22) R. D. Stolow, *J. Am. Chem. Soc.*, *81*, 5806 (1959).

(23) See ref. (4) (C.C.C.C.), p. 2244 (footnote).

(24) H. C. Brown, M. D. Taylor and S. Sujishi, *J. Am. Chem. Soc.*, *73*, 2464 (1951).

(25) C. R. Allen and P. G. Wright, *J. Chem. Ed.*, *41*, 251 (1964).

(26) H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, *86*, 1161 (1964).

(27) R. C. Fort and P. von R. Schleyer, *J. Am. Chem. Soc.*, *86*, 4194 (1964).