procedure was used for the conversion of *p*-bromotoluene into *p*-deuteriotoluene ($n^{26}\text{D}$ 1.4936, bp 105–108°, d_1 92% and d_0 8%), *via* the Grignard reagent.[26] The deuteriotoluene was then converted by procedures routinely available for toluene to benzyl bromide,[27] benzaldehyde,[28] benzoin,[29] benzil,[30] and tetracyclone[23] sequentially into the desired dideuteriotetracyclone, d_2 83%, d_1 16%, d_0 1%, mp 217–218° (lit.[23] 219°).

Acknowledgments. We are grateful for the assistance of Dr. Manning P. Cooke and Mr. Ned A. Moore. This work was supported through Contract SD-100 of the University of North Carolina Materials Research Center with the Advanced Research Projects Agency.

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(27) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **29**, 573 (1946); C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(28) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949).

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Conformational Analysis. XV. The Conformational Enthalpy, Entropy, and Free Energy of the Carboxyl, Carboxylate, Carbomethoxy, Carbonyl Chloride, and Methyl Ketone Groups[1,2]

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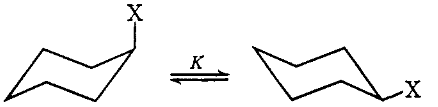
Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. *Received September 18, 1967*

Abstract: The following thermodynamic parameters for conformational equilibria in cyclohexyl compounds (axial $C_6H_{11}X \rightleftharpoons$ equatorial $C_6H_{11}X$) have been determined: X = COOH, *n*-dodecane solvent, $\Delta H°$ −1.64 ± 0.03 kcal/mol, $\Delta S°$ −0.85 ± 0.05 cal/deg mol, $\Delta G°_{25}$ −1.38 ± 0.04 kcal/mol; aqueous diethylene glycol dimethyl ether solvent (mole fraction H_2O 0.1), $\Delta H°$ −1.56 ± 0.05 kcal/mol, $\Delta S°$ −0.68 ± 0.10 cal/deg mol, $\Delta G°_{25}$ −1.36 ± 0.08 kcal/mol; (mole fraction H_2O 0.5), $\Delta H°$ −1.71 ± 0.03 kcal/mol, $\Delta S°$ −0.87 ± 0.06 cal/deg mol, $\Delta G°_{25}$ −1.46 ± 0.05 kcal/mol; X = COO^-, $\Delta H°$ −2.13 ± 0.06 kcal/mol, $\Delta S°$ −0.56 ± 0.13 cal/deg mol, $\Delta G°_{25}$ −1.96 ± 0.10 kcal/mol; X = $COOCH_3$, $\Delta H°$ −1.12 ± 0.04 kcal/mol, $\Delta S°$ +0.50 ± 0.11 cal/deg mol, $\Delta G°_{25}$ −1.27 ± 0.08 kcal/mol; X = COCl, $\Delta H°$ −1.39 ± 0.05 kcal/mol, $\Delta S°$ −0.32 ± 0.11 cal/deg mol, $\Delta G°_{25}$ −1.29 ± 0.09 kcal/mol; X = $COCH_3$, $\Delta H°$ −1.17 ± 0.01 kcal/mol, $\Delta S°$ +1.16 ± 0.03 cal/deg mol, $\Delta G°_{25}$ −1.52 ± 0.02 kcal/mol. The rationale of the data is discussed.

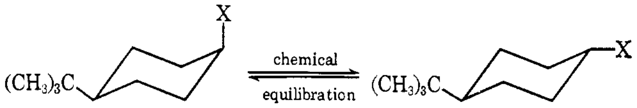
By now, a large number of conformational equilibria[3] of the type shown in eq 1 have been studied by a variety of methods[3,4] and the conformational free



(1)

energies, $-\Delta G°$, derived from the equilibrium constants K have been summarized quite recently for all the known cases.[5] In contrast, very little is known about the derived parameters of conformational enthalpy ($-\Delta H°$) and conformational entropy ($\Delta S°$). We have undertaken a program of study to obtain such parameters for a select number of nonconically symmetrical substituents.

Of the various methods of determining conformational equilibria,[4] the ones most often used have been the kinetic method, the nuclear magnetic resonance method, and the method of equilibrating model compounds, such as 4-*t*-butyl-substituted homologs of the cyclohexyl compounds to be studied (eq 2). It has been found, over



(2)

the years, that, because of systematic difficulties, the kinetic method often does not give reliable results,[6,7] and the nmr method is also subject to limitations which have been discussed in detail elsewhere.[1] It is therefore fortunate that the equilibration method (eq 2) proved applicable to the groups investigated in the present study: the carboxyl group (COOH), its derivatives, the carboxylate (COO^-), carbomethoxy ($COOCH_3$), and carbonyl chloride (COCl) groups, and the methyl ketone ($COCH_3$) group. The method gives equilibrium constants of sufficient accuracy and precision to obtain quite precise values of $\Delta H°$ and $\Delta S°$. Values for $\Delta G°_{25}$ were obtained directly in the case of the CH_3CO group and were calculated from the $\Delta H°$ and $\Delta S°$ values obtained at higher temperatures in the case of the other groups.

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(1) Paper XIV: E. L. Eliel and R. J. L. Martin, *J. Am. Chem. Soc.*, **90**, 689 (1968).

(2) From the Ph.D. dissertation of M. C. Reese, University of Notre Dame, 1966. Presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 30, 1966.

(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1965.

(4) *Cf.* E. L. Eliel, *Angew. Chem.*, 77, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965).

(5) J. A. Hirsch, "Table of Conformational Energies—1967," in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1967.

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

(7) J. L. Mateos, C. Perez, and M. Kwart, *Chem. Commun.*, 125 (1967).

The only assumption of the equilibration method is that the conformational equilibrium shown in eq 1 and the configurational equilibrium shown in eq 2 have the same equilibrium constant. Empirical support for this assumption has been summarized;[4] in essence, the assumption implies that the axial and equatorial conformations shown in eq 1 are not differentially affected, as far as their free energy is concerned, by the introduction of a 4-*t*-butyl substituent (eq 2). Recently some theoretical support for this assumption has come forth;[8] the analogous assumption for a 3-*t*-butyl substituent is apparently not warrented.[4,8]

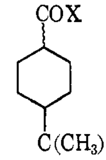
Several previous determinations[3–5,9–12] for the $COOCH_3$ and $COOC_2H_5$ groups had given $-\Delta G^\circ$ values ranging from 1.05 to 1.2 kcal/mol and while the present work was in progress, two additional determinations for $COOC_2H_5$ were published[13,14] giving $-\Delta H^\circ$ 1.09 and 1.10 kcal/mol, ΔS° 0.4 and 0.37 cal/deg mol, and $-\Delta G^\circ_{25}$ 1.21 and 1.24 kcal/mol. In contrast, earlier $-\Delta G^\circ$ values[3–5] for COOH were considerably higher, ranging from 1.5 to 1.7 kcal/mol. This unexplained apparent difference of the ΔG° values of COOR and COOH provided additional impetus for the present work; however, more recent studies[9,15,16] of the COOH group have led to a downward revision of its $-\Delta G^\circ$ value to 1.15–1.2 kcal/mol.[9,15,16] It must be mentioned that all of the previous determinations of $\Delta G^\circ_{\mathrm{COOH}}$ were by methods (pK measurements, indirect equilibration methods, kinetic method) which are less direct than the one chosen in the present investigation.

Previous investigations[3–5] of the carboxylate (COO^-) group in aqueous solvents have given values for $-\Delta G^\circ$ in the range of 2.0 to 2.8 kcal/mol but the recent revisions[9,15] have brought this value down to 1.8–1.9 kcal/mol. There are no published values in the literature for COCl;[17a] a value for $COCH_3$ of 1.5 kcal/mol was published[17b] after the present work was completed.

Results

Of the required compounds, *cis*- and *trans*-Ia–d had been described in the literature and were prepared by known methods. The methyl ketones *cis*- and *trans*-Ie were prepared by catalytic reduction of 4-*t*-butylacetophenone over rhodium on alumina followed by oxidation of the carbinols formed by chromic acid and were separated by preparative gas chromatography.

Equilibration was effected at at least four temperatures for each compound in vapor-Stats employing liquids with boiling points ranging from 56 to 344°, except that equilibrations at 25° were effected in a thermostat; temperatures always stayed within ±1° of the value reported. The solutions of the substances investigated ranged from 0.44 to 1.10 *M* in concentration and were introduced into the vapor-Stat in sealed ampoules. The use of more dilute solutions would have been desirable but would have diminished the precision of the analytical method. Carboxylic acids and their salts were equilibrated thermally, as were the acid chlorides. The equilibration of the acids Ia is probably an autocatalyzed reaction proceeding *via* the enediolate $C_6H_{10}{=}C(OH)_2$; the equilibration of the acid chloride Id probably proceeds through a similar intermediate, $C_6H_{10}{=}CCl(OH)$, and may be catalyzed by adventitious HCl. The salt Ib was presumably equilibrated through the enolate dianion $C_6H_{10}COO^{2-}$. Enolates are probably also involved in the equilibration of the esters Ic and the methyl ketones Ie by methanolic sodium methoxide.



Ia, X = COOH
b, X = COO^-
c, X = $COOCH_3$
d, X = COCl
e, X = $COCH_3$

All equilibria (except two; *cf.* Table II, footnote *c*) were approached from both sides so that completeness of equilibration could be checked. At the completion of reaction, the solutions were subjected to gas chromatographic analysis. The acids were converted to their methyl esters by treatment with excess diazomethane and were analyzed as such. The anions were analyzed similarly after prior acidification and extraction of the acids into ether. The acid chlorides were converted into di-*n*-butyl esters and analyzed in this form. The methyl esters and methyl ketones were analyzed as such. In all cases gas chromatographic response ratios were measured and control experiments were carried out to establish the reliability of the analytical procedures.

The enthalpy values (ΔH°) were obtained from the slope of a computer-drawn, least-squares plot of ln K *vs.* $1/T$. Entropy values (ΔS°) were obtained from the intercept ($1/T = 0$) of the same plot. The conformational free energy at 25°, ΔG°_{25}, was calculated as $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$. In all cases the points of ln K *vs.* $1/T$ defined a straight line very closely, indicating the absence of difficulties due to differences in heat capacity of the diastereoisomers or due to changes in molecular association with temperature (which would have caused changes in ΔH° with temperature). Four or more points were obtained for each compound; for the critical case of COOH, K was recorded at six temperatures. The results are shown in Table I, the raw data being given in Table II in the Experimental Section. A typical plot (for COOH) is shown in Figure 1.

Discussion

The conformational free energy of the COOH group found in the present investigation (1.36–1.46 kcal/mol

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(8) N. L. Allinger, M. A. Miller, F. A. VanCatledge, and J. A. Hirsch, *J. Am. Chem. Soc.*, **89**, 4345 (1967).

(9) B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964).

(10) N. L. Allinger and R. J. Curby, *J. Org. Chem.*, **26**, 933 (1961).

(11) E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961).

(12) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962).

(13) R. J. Ouellette and G. E. Booth, *J. Org. Chem.*, **31**, 587 (1966).

(14) N. L. Allinger and L. A. Freiberg, *ibid.*, **31**, 894 (1966).

(15) J. Sicher, M. Tichý, and F. Šipoš, *Tetrahedron Letters*, 1393 (1966).

(16) N. B. Chapman, J. Shorter, and K. J. Toyne, *J. Chem. Soc.*, 1077 (1964); N. B. Chapman, A. Ehsan, J. Shorter, and K. J. Toyne, *ibid.*, *Sect. B*, 570 (1967).

(17) (a) An unpublished value of 1.2 kcal/mol for COCl obtained by Dr. Rico Gerber in our laboratories is cited in ref 3. Dr. Gerber also undertook the preliminary studies of the thermal equilibration of the 4-*t*-butylcyclohexanecarboxylic acid in the molten state which prompted the present investigation. (b) A. Heymes and M. Dvolaitzky, *Bull. Soc. Chim. France*, 2819 (1966).

Table I. Conformational Thermodynamic Parameters for Compounds Ia–e

Group	Solvent	$-\Delta H°$, kcal/mol	$\Delta S°$, cal/deg mol	$-\Delta G°_{25}$, kcal/mol
COOH	Dodecane	1.64 ± 0.03	−0.85 ± 0.05	1.38 ± 0.04
	Aq diglyme[a]	1.56 ± 0.05	−0.68 ± 0.10	1.36 ± 0.08
	Aq diglyme[b]	1.71 ± 0.03	−0.87 ± 0.06	1.46 ± 0.05
COO^-K^+	$HOCH_2CH_2OH$	2.13 ± 0.06	−0.56 ± 0.13	1.96 ± 0.10
$COOCH_3$	Methanol[c]	1.12 ± 0.04	+0.50 ± 0.11	1.27 ± 0.08
$COOC_2H_5$	Ethanol[d]	1.09	+0.4 ± 0.1	1.21
	Ethanol[e]	1.10	+0.37	1.24 ± 0.10
COCl	Dodecane	1.39 ± 0.05	−0.32 ± 0.11	1.29 ± 0.09
$COCH_3$	Methanol[c]	1.17 ± 0.01	+1.16 ± 0.03	1.52 ± 0.02[f]

[a] Mole fraction of water 0.1. [b] Mole fraction of water 0.5. [c] Containing *ca.* 0.1*M* sodium methoxide. [d] Data from ref 13. [e] Data from ref 14. [f] Directly computed from K_{25}.

in different solvents) is slightly higher than the most recent values in the literature[9,15,16] (1.15–1.2 kcal/mol excluding one value obtained by the kinetic method[16]) but the discrepancy is probably of marginal significance. The present value for COO^-, 1.96 kcal/mol, is in good agreement with recorded[9,15] values of 1.8–1.9 kcal/mol.

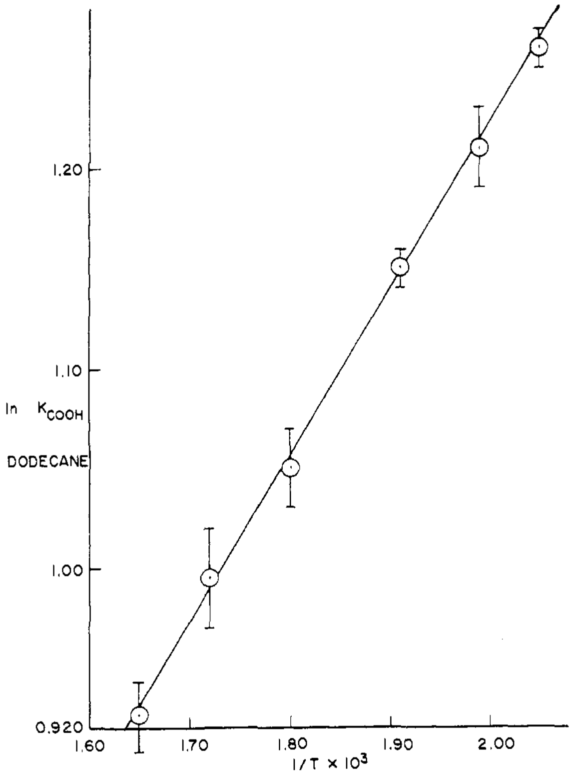

Figure 1.

The value for $COOCH_3$ (1.27 kcal/mol) is slightly and barely significantly lower than the COOH value and is somewhat higher than the value previously recommended[3,5] but it is in excellent agreement with independently determined[13,14] values for $COOC_2H_5$; the conformational enthalpy and entropy values for the two esters also agree very well.[18] The value for COCl, 1.29 kcal/mol, agrees closely with the values for COOH and COOR; the value for $COCH_3$, 1.52 kcal/mol, is significantly higher but agrees well with the value previously reported.[17b] It is interesting that the enhancement of $-\Delta G°_{COCH_3}$ over $-\Delta G°_{COOR}$ and $-\Delta G°_{COCl}$ is the result of a more positive conformational entropy (Table I) suggesting either that the $COCH_3$ group in the axial conformation is subject to greater rotational restrictions (*vis-à-vis* the equatorial $COCH_3$ group) than are COOR and COCl or that, in solvent alcohol, the difference in solvation favoring the equatorial isomer is greater for $COCH_3$ than for COOR.[19]

Perhaps the most interesting and surprising result obtained in the present investigation is the sizeable negative conformational entropy found for the COOH group. In general, one would assume, *a priori*, that an equatorial substituent would have a larger number of populated rotational conformations than an axial one and would therefore have the higher entropy.[20] Such is, in fact, found experimentally for $COOCH_3$, $COOC_2H_5$, and $COCH_3$ (Table I) but not for COOH, COO^-, and COCl, for which the equatorial conformation has the lower entropy. We first wanted to assure ourselves that the experimental finding of a lower conformational entropy for the equatorial isomer in these cases was really significant. The statistical errors indicated in Table I clearly suggest that it is. In order to apply a more stringent test in the case of COOH (in dodecane solution), we adjusted the plot shown in Figure 1 in the following way. First, the equilibrium constants at 214, 229, and 251° were increased by the amount of their respective standard deviations; the constants at 284, 310, and 332° were similarly decreased and a straight line was drawn through the six modified points. Then the procedure was reversed, the first three constants being diminished and the last three augmented by the amounts of their respective deviations. These extreme plots gave $\Delta S°$ values of −1.26 and −0.44 cal/deg mol, which values may be considered to represent the extreme confidence limits of the determination. Clearly, $\Delta S°$ cannot be positive for COOH. A corresponding treatment for COCl gave confidence limits of −0.98 to +0.34 cal/deg mol, indicating some marginal reservation about the negative entropy value for COCl.

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(18) After this manuscript was written, we learned that M. Tichý and J. Sicher (*Collection Czech. Chem. Commun.*, in press) had independently obtained the following thermodynamic parameters for $COOCH_3$: $-\Delta G°_{25}$ 1.27 ± 0.02 kcal/mol, $-\Delta H°$ 1.10 kcal/mol, $\Delta S°$ 0.5 cal/deg mol.

(19) The former reason (greater rotational restriction of the axial conformation of $COCH_3$ compared to COOR or COCl) appears much more likely, for we have found (unpublished observations with Dr. G. Neilson) that the conformational free energy of CHO, 0.56 kcal/mol in solvent methanol, is much smaller than that for $COCH_3$. Also it would appear that favoring of equatorial $COCH_3$ by solvation, while increasing $-\Delta G°$, should increase $-\Delta H°$ and decrease $\Delta S°$ (see discussion below). In fact, $-\Delta H°$ is constant and $\Delta S°$ is increased.

(20) *Cf.* ref 3, pp 60–62.

It appears to us that one can give two entirely different explanations for the negative conformational entropy of the COOH, COCl, and COO^- groups, one in terms of solvation and self-association, the other in terms of rotational conformations. The explanation in terms of solvation and association involves the assumption that the (more accessible) equatorial isomer is more strongly self-associated (or solvated) than the (more hindered) axial isomer. Since solvation and self-association lead to decreased enthalpy (through additional bonding) and also decreased entropy (through restriction of translational motion), one would then expect that the equatorial isomer should have lower enthalpy and entropy than it would have in the absence of such association and solvation. The data in Table I bear out this explanation: the COO^-, COOH, and COCl groups are more negative in both $\Delta H°$ and $\Delta S°$ than COOR and $COCH_3$.

There is very little doubt that the solvation explanation is the correct one for the COO^- group which is well known to be strongly hydrated. The situation for COOH and COCl is not so clear. If solvation played a large role for COOH, one would expect a much more negative conformational entropy for COOH in aqueous diglyme than in dodecane. However, the data (Table I) show little significant difference between the two solvents (see also Table II). One is forced to assume, then, that solvation (in the case of the aqueous diglyme solvent) and dimer formation of the acids (in the case of the dodecane solvent) fortuitously have the same effect. We tried to establish differential formation of dimers for the *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acids through osmometric determinations of molecular weights in hydrocarbon solvents (hexane and octane) but were unable to detect significant differences; both acids are strongly dimerized at the concentrations of the equilibration experiments. (However, the osmometric experiments are not fully significant, since they were carried out at temperatures considerably lower than were the equilibration runs.)[21] Solvation and association effects would not be expected to be very significant for the COCl group for which, however, the diminution of $\Delta H°$ and $\Delta S°$ (compared, say, to $COOCH_3$) is somewhat marginal.

An entirely different possible explanation of the data is in terms of rotational conformations of the COX groups. Figure 2 shows the rotational conformations of axial and equatorial COX. In both cases, assuming enhanced stability of C=O/single bond eclipsed over the corresponding staggered conformations,[22] one has two C=O/C and one C=O/H eclipsed conformers. In the case of the axial COX group, however, the C=O/H eclipsed conformation (a) will be very sparsely populated if at all because of the interference of the X group with the *syn*-axial hydrogens at C_3 and C_5 in the cyclohexane ring. Therefore the axial carboxyl group has effectively two (mirror image) C=O/C eclipsed conformations (b, c) available to it;[23] these conformations, being mirror images, must necessarily be equally populated and the conformational entropy of the axial COX group will then be $R \ln 2$ (the entropy of mixing) regardless of the substituent X.

In contrast, the equatorial COX group has three populated conformations, d, e, and f. Conformations e and f are enantiomeric and thus necessarily equally populated. The population of d, on the other hand, may vary with the nature of X. Three salient cases may be defined, with an infinite number of intermediate cases possible. (1) The C=O/C eclipsed conformations (e, f) are much more populated than the C=O/H eclipsed one (d). In this case the entropy of mixing is $R \ln 2$ and this will be the conformational entropy of the equatorial substituent; the difference in entropy between equatorial and axial group ($\Delta S°$) will then be zero. (2) The C=O/H eclipsed conformation (d) is much more stable than the other two. In that case, there is no entropy of mixing; the conformational entropy of the equatorial group will be zero, and the difference in conformational entropy between equatorial and axial substituent will be $-R \ln 2$ or -1.4 cal/deg mol (favoring the axial conformation). (3) The C=O/C and C=O/H eclipsed conformations are essentially equally stable and thus equally populated. In that case the conformational entropy will be equal to the entropy of mixing, $R \ln 3$ or 2.3 cal/deg mol, and the entropy favoring the equatorial isomer will be 2.3–1.4 or 0.9 cal/deg mol. Since, as already mentioned, intermediate situations are possible, the conformational entropy of the COX group may vary from -1.4 to $+0.9$ cal/deg mol. The experimental variation (Table I) is from -0.87 to $+1.16$ cal/deg mol and agrees well with the predicted if one assumes that there is no "pure" case of complete C=O/H eclipsing, but that there is always *some* C=O/C eclipsing in the equatorial conformation.

This explanation seems at first sight attractive because it can be made to cover the entire range of the experimental data. The argument implies that equatorial COOR and COR distribute themselves between both the C=O/C and C=O/H eclipsed conformations whereas equatorial COCl and especially equatorial COOH show a marked preference for the C=O/H eclipsed form. A corresponding suggestion had been made by Sicher and coworkers[15] and by Wepster and coworkers[24] on entirely different grounds. However, recent X-ray structural investigations[25] indicate that, at least in the crystalline state, equatorial COOH exists in the conformation in which C=O is eclipsed, or nearly eclipsed, with C—C.

Although the X-ray argument is not necessarily relevant to our studies (which were carried out in solution), it now appears[26] that propionic acid, similar to propionaldehyde,[20] exists predominantly in the conformation in which C=O is eclipsed with CH_3 even

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(21) We have learned that C. P. Rigau (Doctoral Thesis, Swiss Federal Institute of Technology, Zurich, Switzerland, 1965) has found that *trans*-4-*t*-butylcyclohexanecarboxylic acid is more associated in 0.023–0.028 *M* methylene chloride solution than the *cis* isomer. The association constants differ by a factor of about 1.8.

(22) There is much support for this assumption; see, for example, ref 3, pp 19–21, and G. J. Karabatsos and N. Hsi, *J. Am. Chem. Soc.*, **87**, 2864 (1965); S. S. Butcher and E. B. Wilson, *J. Chem. Phys.*, **40**, 1671 (1964).

(23) Others have postulated slightly different conformations in which the plane of the axial COX group is parallel to the plane defined by the *syn*-axial hydrogens at C_3 and C_5[24] and the plane of the equatorial COX is at right angles to the direction of the axial hydrogens.[15] Our work is equally compatible with these conformations, which, however, seem less likely on the basis of X-ray results.[25]

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

(25) J. D. Dunitz and P. Strickler, *Helv. Chim. Acta*, **49**, 2505 (1966); *Tetrahedron Letters*, 3933 (1966).

(26) O. L. Stiefvater, Abstracts, Molecular Structure and Spectroscopy Meeting, Columbus, Ohio, Sept 6–10, 1966.

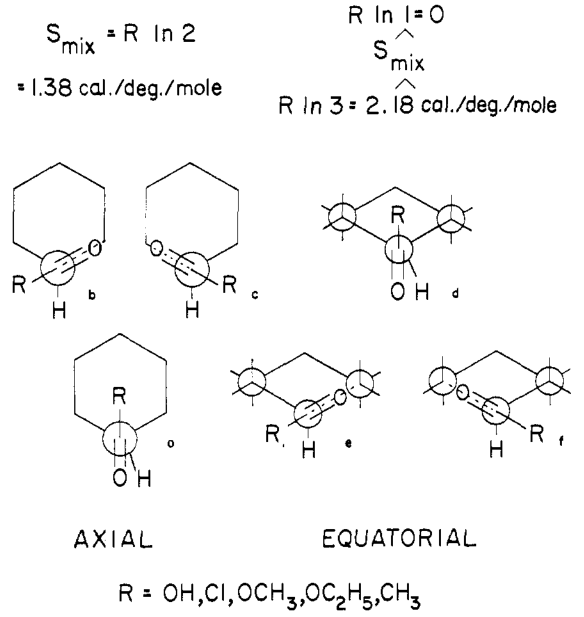

Figure 2. Rotational conformations of COR.

in the vapor state. Under the circumstances, and despite the supporting evidence from other quarters,[15,24] it appears unlikely that the conformational argument embodied in Figure 2 is valid. We are therefore, for the moment, more inclined to ascribe the negative conformational entropies for COOH and COCl as well as COO$^-$ to solvation–association phenomena. Studies in progress[27] involving solvent effects on conformation in other cyclohexyl derivatives may provide more definitive evidence in this regard.

Experimental Section

Materials. **4-*t*-Butylcyclohexanecarboxylic acid** (*cis–trans* mixture) was obtained by hydrogenating 62.0 g of 4-*t*-butylbenzoic acid in 150 ml of 95% ethanol over ruthenium (0.5 g of ruthenium oxide) at 50° and 1600 psi.[28] After 8 hr, hydrogen uptake ceased and the catalyst was filtered through Celite. The product contained 70% *cis* isomer and the pure *cis* isomer was isolated *via* the ammonium salt.[29] The *trans* isomer was enriched in the residual acid mixture by base-catalyzed isomerization and purified by crystallization.[30] The *cis* acid melted at 117–118° after two recrystallizations from *n*-hexane (lit.[30,31] 117.5–118°) and the *trans* acid, after three recrystallizations from benzene, melted at 172–173° (lit.[31] 174–175°). The *cis* isomer was also prepared from the crude acid through the thiourea clathrate.[32]

The methyl esters were prepared from the acids by treatment with ethereal diazomethane.[31] The *cis* ester boiled at 57–58° (0.7 mm), n^{20}D 1.4550 (lit.[30] bp 102–103° (9 mm), n^{20}D 1.4557); the *trans* ester boiled at 65–66° (0.8 mm), n^{20}D 1.4540 (lit.[30] bp 106–107° (10 mm), n^{20}D 1.4547). Both esters, prepared from the above-described acids, were pure within limits of detection by gas chromatography on a 9 ft × $^1/_8$ in. column of 20% Carbowax 20M on 42–60 Firebrick (column temperature 150°).

The acid chlorides were prepared by treatment of the pure acids in a slight excess of thionyl chloride at room temperature for 16 hr followed by removal of the excess thionyl chloride at reduced pressure (room temperature.)[29] Distillation gave the pure *cis*-chloride, bp 47–48° (0.05 mm), and the pure *trans*-chloride, bp 54–55° (0.1 mm) (lit.[29] bp 85° (1 mm)). Purity was established by converting the acid chlorides to the corresponding methyl esters by methanol–pyridine in the usual way and establishing purity of the methyl esters by gas chromatography. For purposes of analysis in the equilibrations, it was found more convenient to convert the acid chlorides to the *n*-butyl esters.

The *n*-butyl esters of the acids were prepared in bulk by treatment of the pure acid (2.0 g) with 1-butanol (8.10 g) in dry toluene (20 ml) containing a trace of *p*-toluenesulfonic acid. After the usual work-up, *n*-butyl *cis*-4-*t*-butylcyclohexanecarboxylate boiled at 70° (0.01 mm), n^{20}D 1.4538, and the *trans* ester boiled at 73° (0.03 mm), n^{20}D 1.4527.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found (*cis* ester): C, 74.99; H, 11.84. Found (*trans* ester): C, 74.87; H, 11.71.

4-*t*-Butylcyclohexyl Methyl Ketone. 4-*t*-Butylacetophenone was prepared from *t*-butylbenzene and acetyl chloride,[33] bp 72° (0.6 mm), n^{19}D 1.5208 (lit. bp 97–98° (0.8–0.9 mm),[34] n^{20}D 1.5210[35]). Thirty grams (0.17 mol) of the ketone was hydrogenated in 200 ml of cyclohexane over 10 g of 5% rhodium on alumina at room temperature and 60 psi. Hydrogenation stopped just short of the theoretical uptake of hydrogen (8 mol), so fresh catalyst (2 g) was added and hydrogenation continued for 4 hr. Work-up at this stage produced 31.4 g of a viscous oil which, according to gas chromatography and infrared spectrum, was largely (97.5%) 4-*t*-butylcyclohexylmethylcarbinol (*cis–trans* mixture). Part of the material (27.8 g, 0.15 mol) was oxidized by means of 22.4 g (0.085 mol) of sodium dichromate in 250 ml of water. The solution was stirred vigorously and 20.8 ml of concentrated sulfuric acid diluted in 50 ml of water was added slowly over 0.5 hr. The temperature of the solution rose to 50°. After addition of the acid the solution was stirred for an additional 3 hr and allowed to stand for 4 hr; then it was extracted three times with 100-ml portions of ether. The ether extracts were cleared with water, saturated aqueous sodium bicarbonate, and again water, dried over anhydrous $MgSO_4$, and concentrated to give a light yellow oil (26.5 g). Glpc analysis (same column as for the methyl ester) indicated 45% *cis* ketone 54% *trans* ketone, 1% unknown impurity. The ketones were separated by preparative gas chromatography on a 10 ft × $^3/_8$ in. column of 30% Carbowax 20M on 42–60 Firebrick at 180°. From 13 g of mixture was obtained 4.6 g of *cis* ketone (93% pure) and 5.9 g of *trans* ketone (97% pure). Further chromatography gave 99.5% pure ketone, *cis* bp 70° (1 mm), n^{30}D 1.4582 (compound solidifies at *ca.* 25°), and 99% pure *trans* ketone, bp 78° (0.6 mm), n^{30}D 1.4554, n^{20}D1. 4593.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.17. Found (*cis* ketone): C, 79.23; H, 12.10. Found (*trans* ketone): C, 79.13; H, 12.04.

Equilibrations. Samples to be equilibrated in general were not pure stereoisomers but mixtures rich in one or other of the two isomers; in all but two cases, however, equilibrium was approached from both sides. Solutions of the acids Ia in dodecane were prepared in volumetric flasks so that the concentration was known accurately. For the preparation of the aqueous diglyme solutions, the diglyme was first dried over magnesium sulfate, then distilled over lithium aluminum hydride, and then mixed with water by weight. For the equilibrations of the salts Ib, the acids were dissolved in a 0.8 *M* solution of potassium hydroxide in ethylene glycol, KOH being in excess. The acid chlorides Id were dissolved directly in dodecane. The esters Ic and methyl ketones Ie were dissolved in 0.07 *M* methanolic sodium methoxide (prepared by dissolving sodium in absolute methanol). About 0.25–1.0 ml of the appropriate solution was introduced in a 3-ml Pyrex ampoule; the dodecane solutions were evacuated whereas the basic solutions were degassed and evacuated (omission of the degassing lead to the formation of side products); the ampoules were then

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(27) Mr. E. Gilbert in our laboratories has studied $\Delta H°$ and $\Delta S°$ for OH (in cyclohexanol) as a function of solvent; the results are incompatible with a rotational–conformational explanation but entirely consistent with an explanation based on solvation phenomena. See also J. C. Celotti, J. Reisse, and G. Chiurdoglu, *Tetrahedron*, **22**, 2249 (1966).

(28) This reduction procedure was worked out in our laboratory by Dr. E. W. Della because of occasional difficulties, presumably due to catalyst poisoning, with the low-pressure reduction over platinum described in the literature.

(29) H. H. Lau and H. Hart, *J. Am. Chem. Soc.*, **81**, 4897 (1959). The aqueous ammonia used to prepare the ammonium salt also serves to coagulate some residual collodial ruthenium catalyst.

(30) M. Tichy, J. Jonaš, and J. Sicher, *Collection Czech. Chem. Commun.*, **24**, 3434 (1959).

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(32) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Koninkl. Ned. Akad. Wetenschap. Proc.*, **62B**, 147 (1959).

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sealed at Dry Ice temperature. For equilibrations carried out below or slightly above the boiling point of the solvent, the ampoules were lowered, by means of stainless steel wire, through the condenser of the vapor-Stat into the vapor space. The vapor-Stat consisted of a three-necked flask equipped with an air condenser (water condenser for low-boiling liquids), thermometer immersed in the vapor, and a nitrogen inlet tube through which a very slow stream of nitrogen was bubbled in the case of the high-boiling liquids to prevent bumping. Vapor-Stat liquids ranged from acetone (bp 56°) to *n*-eicosane (vapor temperature 332°). Temperatures of the vapors of the refluxing liquids were monitored at regular intervals and stayed within ±1°. The thermometers used were calibrated against a set of accurate Anschütz thermometers. Heating was supplied by a mantle, and the upper part of the flask was thermally insulated by means of fiber glass cloth and was enclosed in a wire cage in case of a possible explosion of the ampoules rupturing the flask. In the case of the aqueous diglyme solutions, the ampoules would not withstand the vapor pressures encountered at the highest temperatures used. Therefore a small stainless steel bomb was constructed which could be readily accommodated in the above apparatus and had space for two ampoules. After the ampoules were placed in the bomb, they were surrounded by the same solvent (aqueous diglyme) present inside the ampoule before the bomb was sealed, so that the pressures inside and outside the ampoules would be equalized. The proper functioning of the bomb as regards heat transfer was tested by carrying out an equilibration of the acid Ia in dodecane inside of it; the equilibrium constant thus obtained differed by only 0.3% from that obtained without use of the bomb. Heating times were chosen so that samples originally *cis* rich and originally *trans* rich came to the same equilibrium composition; they ranged from 47 to 264 hr, the longer times being required for equilibrations carried out near the minimum temperatures of the range (see Table II). The manner of quenching the ampoules depended on the temperatures reached. For the dodecane solutions of the acids, air cooling was considered adequate; the temperature dropped to *ca.* 60° in 130 sec. To assess the possibility of post-equilibration during the (rather short) cooling period, an ampoule equilibrated at 250° for 51 hr was transferred (within 5 sec) to a bath at 286° and was left there for 130 sec before being cooled as usual; the equilibrium constant measured in this case was 3.15 ± 0.03 as compared to 3.11 ± 0.03 for a sample similarly heated at 250° but quenched normally. Clearly, no appreciable post-equilibration takes place during a brief period of temperature change. In other cases, ampoules were quenched in cold water (temperature of *ca.* 25° reached in a maximum of 30 sec). The bomb was quenched by immersing it in ice water; it took 10 sec for the transfer and 30 sec for the bomb to cool. In the case of the ketones Ie where the lowest temperature run was carried out at room temperature, quenching was effected by chilling the ampoule in ice and quickly adding an excess (1 ml) of 2 *N* hydrochloric acid; the procedure took 30 sec.

Analyses. The dodecane solutions of the acids were treated with excess ethereal diazomethane, the ether and excess diazomethane boiled off, and the residue analyzed by glpc on a 9 ft × 1/8 in. column of 20% Carbowax 20M on 42-60 Firebrick at 150°, flow rate *ca.* 50-60 cc/min of He, retention time: *cis*, 18-20 min, *trans*, 24-27 min. The instrument used was an F & M Model 810-29 thermal conductivity detection instrument with a disk integrator and the areas were read from the integrator tracing. In some instances, areas were checked by manual integration with a planimeter. Area response corrections were applied in this case (and all others) by analyzing solutions of known composition of the esters and computing a response factor. The response factor for the methyl esters varied from 1.006 to 1.022, that for the *n*-butyl esters from 1.011 to 1.028, and that for the methyl ketones from 0.980 to 1.009. The aqueous diglyme solutions (N_{H_2O} 0.1) were treated similarly, but those with $N_{H_2O} = 0.5$ were twice extracted with ether, and the ether extracts were treated with diazomethane after clearing with water. By way of control, an ether solution of a mixture of acids was divided into two portions; one was analyzed as such and the other was treated with aqueous diglyme and worked up as above. Analyses were $K = 2.118 \pm 0.011$ for the untreated and 2.133 ± 0.004 for the treated solution; the two analyses are identical within their combined error limits.

The equilibrated solutions of the salts Ib in ethylene glycol were treated with 1 ml of 2 *N* hydrochloric acid per ampoule and the acids twice extracted with 10-ml portions of ether which were washed with two 10-ml portions of water. The ether layers were treated with excess diazomethane, dried over sodium sulfate, and then analyzed in the usual way. A check was carried out by analyzing an acid mixture in ether ($K = 3.131 \pm 0.016$) by the method described for the acid, then converting it to the salt by evaporating the ether and dissolving in 1 ml of KOH-ethylene glycol, and then analyzing as indicated for the salt which gave $K = 3.136 \pm 0.027$. Because of the rather high *trans*/*cis* ratios in equilibrated solutions of Ib, the *cis* peak was read at attenuation 4 and the *trans* peak at attenuation 8. Therefore the response ratio was determined in the same way, but its value, 1.014 ± 0.009, does not vary appreciably from the earlier reported one obtained at a constant attenuation.

The acid chlorides Id were treated with 1-butanol at room temperature to give the *n*-butyl esters which were analyzed by glpc (same column as above, but at 170°) directly. The accuracy of this procedure was checked by taking a mixture of acid chlorides, treating one aliquot as above, and hydrolyzing another aliquot with aqueous NaOH. Acidification, ether extraction, washing, and diazomethane treatment then gave the methyl esters which were analyzed. The composition (*trans*/*cis*) of the butyl esters was 2.336 ± 0.038 and that of the methyl esters 2.377 ± 0.063; it is concluded that the butyl ester method of analysis is reliable.

In the case of the methyl ester group Ic, the methanolic solution was acidified by addition of 1 ml of 2 *N* HCl and the mixture of esters was extracted with two 10-ml portions of ether which were cleared successively with water, 5% aqueous sodium bicarbonate, and water (10 ml each), dried over magnesium sulfate, concentrated somewhat, and analyzed. By way of control a methyl ester mixture of $K = 2.914 \pm 0.011$ was dissolved in methanol and put through the above isolation procedure; its analysis was then $K = 2.932 \pm 0.006$. An entirely analogous procedure was used for the methyl ketones; here a mixture of composition $K = 4.356 \pm 0.028$ after work-up gave $K = 4.333 \pm 0.016$. The retention time was 23-26 min for the *cis* ketone and 29-33 min for the *trans* ketone with the same column and under the same conditions described for the methyl ester. Here also the analysis and determination of response

Table II. Experimental Data (Equilibrium Constants)

Compound[a]	Temp, °C	Time,[b] hr	K = *trans*/*cis*
RCOOH in dodecane	214	143	3.529 ± 0.044
	229	98	3.374 ± 0.059[d]
	251	70	3.148 ± 0.042[e]
	284	48	2.853 ± 0.066
	310	50	2.706 ± 0.048
	332	50	2.525 ± 0.054
RCOOH in diglyme–$0.1H_2O$	215	140	3.562 ± 0.056
	228	28	3.383 ± 0.047
	249	70	3.205 ± 0.085
	283	70	2.958 ± 0.064
	311	50	2.703 ± 0.055
RCOOH in diglyme–$0.5H_2O$	229	226	3.604 ± 0.060
	251	73	3.369 ± 0.049
	284	73	3.027 ± 0.089
	312	48	2.835 ± 0.046
$RCOOCH_3$	78	144	6.382 ± 0.092
	99	122	5.874 ± 0.134
	118	149	5.527 ± 0.120
	157	203	4.742 ± 0.086
$RCOO^-K^+$	158	264	9.001 ± 0.194
	197	60	7.549 ± 0.149
	214	47	6.789 ± 0.115
	230	70	6.342 ± 0.116
	251	51	5.823 ± 0.086
RCOCl	186	190	3.916 ± 0.068
	196	216	3.782 ± 0.080
	212	190	3.547 ± 0.046
	229	74	3.438 ± 0.055
	249	50	3.252 ± 0.058
$RCOCH_3$	25	156	13.00 ± 0.27
	56	49, 108, 144[c]	10.73 ± 0.36
	78	168	9.689 ± 0.274
	96	51	8.819 ± 0.203
	118	53, 77[c]	8.109 ± 0.195

[a] R is 4-*t*-butylcyclohexyl. [b] Equilibration time. [c] Equilibrium reached from *trans*-rich side only; checked by equilibrating samples for different times. [d] Repetition gave a value of 3.327 ± 0.048. [e] Repetition gave values of 3.140 ± 0.044 and 3.131 ± 0.045.

ratio were carried out at an attenuation of 4 for the *cis* peak, 8 for the *trans* peak.

As mentioned earlier, at each temperature a *cis*-rich and a *trans*-rich sample was equilibrated; in a few cases more than one. Each equilibrated sample was analyzed at least three times. The equilibrium constants tabulated in Table II are therefore averages of at least six analytical determinations in each instance. In no case was a systematic difference noted between equilibrium mixtures obtained from the *cis* side and from the *trans* side. Standard deviations, $\Delta K'_X$, were computed for each raw analysis and similarly, deviations Δr were computed for each determination of response ratio (r). The deviations shown in Table II are $\Delta K_X = K_X(\Delta K'_X/K'_X + \Delta r/r)$ where K'_X is the raw area ratio uncorrected for response ratio.

The data for K_X shown in Table II were fed to a Univac 1107 computer with instructions to plot a least-squares plot of ln K_X *vs.* $1/(273.16 + t)$. The computer was then instructed to put out, in addition to the plot, $\Delta H°_X = Rm/1000$ where $R = 1.9872$ cal/deg mol and m is the slope of the least-squares plot. The computer was also instructed to compute the statistical slope error,[36] Δm, to put out $\Delta\Delta H° = R\Delta m/1000$, and to compute the standard entropy difference $\Delta S° = Rb$, where b is the intercept of the plot and the corresponding statistical error $\Delta\Delta S° = R\Delta b$, where Δb is the statistical intercept error. The resulting computer output for $\Delta H°$ and $\Delta S°$ is tabulated in Table I. $\Delta G°_{25}$ was calculated as $\Delta G°_{25} = \Delta H° - 298.16\Delta S°$ ($\Delta G°$ and $\Delta H°$ in cal/mol). The corresponding error was computed as $\Delta\Delta G° = \Delta\Delta H° + T\Delta\Delta S° + \Delta S°\Delta T$, the last term actually being negligible.

Acknowledgment. We are grateful to Professor Oliver G. Ludwig for his helpful advice with the computer program and error treatment and to Dr. R. J. L. Martin for his help and encouragement in the eary stages of this investigation. Acknowledgment is made to the Air Force Office of Scientific Research (Grant AF-AFOSR-772) and to the donors of the Petroleum Research Fund (Grant 266-A), administered by the American Chemical Society, for support of this research.

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Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Coupling Constants in Organometallic Compounds[1a]

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Received October 4, 1967

Abstract: High-resolution, natural-abundance ^{13}C nuclear magnetic resonance spectra have been obtained for the tetramethyl derivatives of group IV and the dimethyl derivatives of group IIb. The one-bond coupling constants between carbon and the spin $^1/_2$ metal atoms as well as the "through-metal" vicinal carbon–proton coupling constants are discussed in terms of the Fermi contact coupling mechanism.

Because of their simplicity and high symmetry, the tetramethyl derivatives of the group IV elements have been extensively studied by nuclear magnetic resonance spectroscopy. These studies have included determination of the proton chemical shifts,[2] ^{13}C chemical shifts,[2] one-bond, carbon–proton coupling constants,[2,3] and two-bond, metal–proton coupling constants.[3] Recently some carbon–metal coupling constants in compounds of this type have been determined by heteronuclear tickling experiments,[4] and a rather complete nmr investigation of dimethylmercury has been carried out.[5]

The ^{13}C spectra previously reported were obtained with rapid passage in the dispersion mode. Under these conditions line widths are such that, while the large, one-bond, carbon–proton coupling constants can be resolved, the noise level is normally too high to allow the observation of carbon–metal coupling, partly because the percentage of total metal with spin $^1/_2$ is low. Heteronuclear tickling experiments, while monitoring proton resonances, have made the observation of carbon–metal coupling possible, but difficulties in the interpretation of tickling experiments can lead to erroneous conclusions. The heteronuclear tickling technique not only failed to resolve the vicinal, carbon–proton coupling constants, but the stated error limits fail to include the actual values of these coupling constants.[4,5] In the present work, high-resolution, natural-abundance ^{13}C spectra were obtained in the absorption mode with slow passage conditions and time averaging and permitted the direct observation and measurement of carbon–metal couplings as well as of ^{13}C–X–C–H couplings which have not heretofore been reported.

Experimental Section

The compounds used in this study were obtained from commercial sources and used without further purification. The samples were placed in 10-mm precision-ground sample tubes with approximately 10% benzene for an internal proton lock signal. The samples were degassed and sealed under vacuum. High-resolution ^{13}C spectra were obtained using the Varian DFS-60 spectrometer.[6]

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