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NONPLANAR CYCLOBUTANE—II

THE METHYL 3-ISOPROPYLCYCLOBUTANECARBOXYLATE SYSTEM

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Abstract—NMR spectra and basic equilibration of *cis* and *trans* methyl 3-isopropylcyclobutanecarboxylate are reported. Treatment of the nonplanar cyclobutane system by analogy with cyclohexane is potentially possible, but limited by (1) greater dependence of ring puckering on substituents; and (2) intervention of planar conformers.

CONSIDERABLE physical evidence demanding a significantly nonplanar conformation for cyclobutane has been amassed,[2-6] including recent NMR studies on cyclobutane itself.[7] Detailed NMR study of several *gem*-difluorocyclobutanes has been interpreted in terms of nonplanar structures.[8] In prior years, however, the large body of chemical work on cyclobutanes, such as deamination[9] and solvolysis[10] for the most part did not take conformational phenomena into account. Until quite recently,[11] only scant attention was paid to these factors as they affect chemical reactivity, and as a result the conformational situation for cyclobutane derivatives has remained quite speculative as yet.

Unlike cyclohexane, in which a greater conformational rigidity enables a relatively clear definition of the well-known "chair" and "boat" conformers, with ensuing delineation of stereochemistry, cyclobutane is quite flexible; it exhibits a dynamic ring-bending equilibrium which has become known as "pseudorotation".[12] While in the unsubstituted ring all carbons are thus made equivalent, it is possible to describe this equilibrium by focusing attention on a pair of opposed atoms, 1 and 3, in the extremes of ring flexion represented below. Substituents may be either axial or equatorial; for lesser degrees of ring puckering, however, there will be deviation from

[1] Based in part on the dissertation submitted by R. A. Doughty to the Graduate School of the University of Miami in partial fulfillment of the requirements for the Ph.D. degree in chemistry.

[2] A. Almenningen, O. Bastiansen and P. N. Skancke, *Acta Chem. Scand.* **15**, 711 (1961).

[3] J. D. Dunitz and V. Schomaker, *J. Chem. Phys.* **20**, 1703 (1952).

[4] G. W. Rathjens, N. K. Freeman, W. D. Gwinn and K. S. Pitzer, *J. Am. Chem. Soc.* **75**, 5634 (1953).

[5] W. G. Rothschild and B. P. Dailey, *J. Chem. Phys.* **36**, 2931 (1962).

[6] R. C. Lord and I. Nakagawa, *J. Chem. Phys.* **41**, 2951 (1963).

[7] L. C. Snyder and S. Meiboom, *Chem. and Eng. News* **44**, No. 17, 51 (1966).

[8] J. B. Lambert and J. D. Roberts, *J. Am. Chem. Soc.* **87**, 3884, 3891 (1965).

[9] M. S. Silver, M. J. Caserio, H. E. Rice and J. D. Roberts, *J. Am. Chem. Soc.* **83**, 3671 (1961); and preceding papers in this series.

[10] J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.* **73**, 2509 (1951).

[11] N. L. Allinger and L. A. Tushaus, *J. Org. Chem.* **30**, 1945 (1965).

[12] J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, *J. Am. Chem. Soc.* **69**, 2483 (1947); J. B. Hendrickson, *Ibid.* **83**, 4537 (1961).

such well-proscribed conformations.[13] To the degree that such visualization approaches reality,[14] the consequences of replacing the appropriate hydrogen atoms with substituents should resemble the effects of such substituents in cyclohexanes. For example, a pair of *cis* 1,3 substituents would be predominantly diequatorial rather than axial. By the same token, a *cis* isomer would be more thermally stable than a *trans* isomer, which may have an axial substituent.[15] Thus, methyl *cis* 3-methylcyclobutanecarboxylate has been recently shown[11] to be more stable than the *trans* isomer, and to predominate under conditions of basic equilibrium.

In work begun some time ago, we reasoned that use of a relatively bulky group which would exercise a decided equatorial preference might cause a decrease in the flexibility of the cyclobutane ring system such that axial and equatorial conformers were more clearly delineated. Such reasoning is not novel, but parallels the well-established use of bulky groups to "hold" the conformation of the cyclohexanes;[16] however, the extent of the "holding" effect in this case was not predictable.[17] We have accordingly prepared a series of 3-isopropylcyclobutane derivatives as model compounds. In the course of this work, we have studied the behavior of *cis* and *trans* 3-isopropylcyclobutanecarboxylate esters, and in view of the recent appearance of data for the 3-methylcylcobutanecarboxylate esters, we wish to report our results and deductions at this time.

Methyl 3-isopropylcyclobutanecarboxylate was prepared in a conventional fashion from the base-catalyzed condensation of 2-isopropyl-1,3-dibromopropane and diethyl malonate, followed by hydrolysis of the diester, decarboxylation and Fisher esterification. VPC analysis revealed two peaks in ratios approaching 1:1 from several runs. The ratio was several times seen to be identical with the ratio of the two peaks obtained for the precursor acid. The two isomeric esters were separated by preparative vapor phase chromatography, and their NMR spectra obtained (Fig. 1). Peak one under the present conditions (Experimental) corresponds to the *cis* isomer (see below).

The Me protons of the isopropyl group appear as an unsymmetrical doublet centered at ca. 0·8 ppm, while the single sharp resonance of the methoxy Me appears at ca. 4·6 ppm, in both cases. The two spectra differ in the ring methylene region; the *cis* isomer exhibits a broader and less intense resonance from about 1·5 to 2·4 ppm,

[13] Unfortunately, close parallelism with cyclohexane does not appear to be tenable, as recent work has shown that for cyclobutanes containing a single halogen substituent, the "axial" conformer may be relatively planar; see Ref. 8; H. Kim and W. D. Gwinn, *J. Chem. Phys.* **44**, 865 (1966); W. G. Rothschild, *Ibid.* **45**, 1214 (1966). Thus it is possible for equatorial–axial conformer pairs to differ greatly in degrees of ring puckering.

[14] A comparison of the dihedral angle of 36° obtained by the investigators in Ref. 7 for the unsubstituted cyclobutane ring with that of ca. 54° for cyclohexane would initially support this analogy.

[15] Polar factors aside; see Ref. 11.

[16] S. Winstein and N. J. Holness, *J. Am. Chem. Soc.* 77, 5562 (1955).

[17] A successful holding group would be required to maintain a similar degree of ring puckering for both equatorial and axial conformers, and thus obviate not only the problem raised by ring bending equilibrium, but the question of possible planarity for the axial conformer which might otherwise be present; see Ref. 13.

while the *trans* isomer has a narrower and more intense resonance from ca. 1·7 to 2·4 ppm. These are clearly composite regions for all four methylene protons; the broader *cis* vs. *trans* region may be seen in the amplified and slower sweep signals. Thus, while the "axial" effect is considerably less dramatic than that for the alcohols and amines studied in another phase of this work,[18] a similar trend is evident. The dissimilarity may be ascribed to two major factors: (1) the lesser electronegativity and greater anisotropy of the carbomethoxy as compared to the amino and hydroxy groups; (2) lesser steric disparity between isopropyl and carbomethoxy as compared to isopropyl and amino or hydroxy. The present data do not serve to distinguish these factors adequately.

Equilibration of several samples of mixed ester of varying composition by prolonged reflux in methanolic sodium methoxide and assay of aliquots to the point of no further change revealed that peaks one and two exhibited a final ratio of 2·2 ± 0·05/1·0, irrespective of original ratio. Since, in the case of the 3-methylcyclobutanecarboxylates, the *cis* isomer was synthesized unequivocally and predominates at equilibrium,[11] there is no reason to doubt that the first peak in the present case is the *cis* isomer and the second peak the *trans*.

It may be instructive to compare the ratio of K_{eq}s for the methyl and isopropyl substituted esters, $1{\cdot}6/2{\cdot}2 = 0{\cdot}73_{338°K}$, with the corresponding ratio for the known 4-alkylcyclohexanecarboxylate esters,[19] $4{\cdot}8/5{\cdot}3 = 0{\cdot}91_{338°K}$, bearing in mind the different equilibration conditions, different relative substituent positions[20] and different solvents which would affect entropies to a greater or lesser degree. For the present equilibration, $-\Delta F = 0{\cdot}53$, and $\Delta F_{i\text{-}pr} - \Delta F_{CH_3} = 0{\cdot}21$; for the 4-alkylcyclohexanecarboxylates the same difference is 0·10 (1·11 − 1·01). As a first approximation, the group effect, while similar, appears to be more pronounced in the cyclobutane system.

In 1,3-disubstituted cyclobutanes, axial groups must engender more repulsive energy than axial cyclohexane substituents, since the transannular distance in cyclobutane is less than 2·2 Å[3] as compared to a 1,3-transannular distance of 2·5 Å in cyclohexane.[21] This small increment in distance is quite significant, since repulsive force rises abruptly by $1/r^{12}$.[22] Thus, while an axial group in cyclobutane does not have as many guache interactions as an axial cyclohexane group, this lack of comparable energy for axial destabilization may be counterbalanced by the shorter transannular distance. Such additional energy can be overcome by flexion toward the plane in cyclobutane, to different degrees for different groups. In the case of the isopropyl group, for example, being statistically axial, this cyclobutane deformation

[18] The NMR spectra of the isomeric 3-isopropylcylcobutanols and 3-isopropylcyclobutylamines have indicated that these compounds most probably exist as conformationally homogeneous systems with equatorial isopropyl and axial or equatorial amino and hydroxy, validating the effectivity of the holding group; I. Lillien and R. A. Doughty, *J. Am. Chem. Soc.* **89**, 155 (1967).

[19] Equilibrated in the same fashion; N. L. Allinger and L. A. Freiberg, *J. Org. Chem.* **31**, 894 (1966).

[20] The influence of the holding group (i.e. t-butyl) in cyclohexane, perhaps through subtle effects on ring deformability, appears to be a poorly-understood but significant cause for anamolous reactivity of 3- vs. 4-positioned substituents of analogous conformation; see for example Ref. 22, p. 77.

[21] From measurement of Dreiding model.

[22] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 449. Interscience, New York (1965).

should be more facile than deformation of the "chair" which may occur in cyclohexanes which are forced to accept axial isopropyl.[23] While it is unlikely that axial isopropyl is significant in the present compounds, other axial groups may have lesser but similar effects; however, the precise degree of axial relief which would be produced by even a slight degree of cyclobutane planarization is an unknown quantity. A very slight change in dihedral angle might be sufficient for average-sized or small groups, in terms of the converse of the repulsive-energy consideration above, and it is thus quite sound to refer to axial substituents in this system. In any event, such ring-deformation processes in cyclobutane and cyclohexane would obviously be of different energetic requirement. At the same time, the severer 1,3 diaxial interactions in the cyclobutane may cause the equatorial, bulky isopropyl group to be favored by an even greater entropy of mixing than in cyclohexane,[23] while the Me group entropies may be more alike. In cyclobutane, axial carbomethoxy is more rotationally hindered than axial Me, and more than it would be in cyclohexane, while in the case of axial isopropyl vs. axial carbomethoxy, the gain in entropy for the equatorial isopropyl group should more than offset the similar gain for carbomethoxy. All or part of the foregoing may account for the differences in $\Delta\Delta F$ for the two systems.

If the isopropyl group were as effective a holding group in the esters as it appears to be in the amines and alcohols,[18] this factor would be important in causing a larger $\Delta\Delta F(\text{i-}C_3H_7 - CH_3)$ than in the cyclohexanes. However, the much smaller *magnitude* of the present K_{eq} as compared to the 4-t-butyl- or 4-isopropylcyclohexanecarboxylate cases is quite significant; it tentatively militates against such a conclusion. Indeed, were conformational homogeneity prevalent in the present pair of isomers (the conditions of Footnote 17), one might reasonably expect, *a priori*, a much *larger* value of $\Delta\Delta F$ than is actually observed. On the other hand, were K_{eq} in the cyclobutanes to reflect a *cis* (diequatorial $\rightleftharpoons$ planar) $\rightleftharpoons$ *trans* (homoplanar) equilibrium[13, 24] rather than a *cis* (e,e) $\rightleftharpoons$ *trans* (a,e $\rightleftharpoons$ e,a) equilibrium, then the basis of comparison with cyclohexyl values would be largely vitiated.[25] Until this eventuality can be evaluated,[26] it is premature to draw more than the conclusion that the present results underscore the limitations of analogies drawn with cyclohexane. It may indeed be possible by extrapolation of methods established for cyclohexane to gain greater insight into the conformational properties of the nonplanar cyclobutane system; however, the restrictions imposed by the substituent-ring puckering interdependence may prove to be formidable.[27]

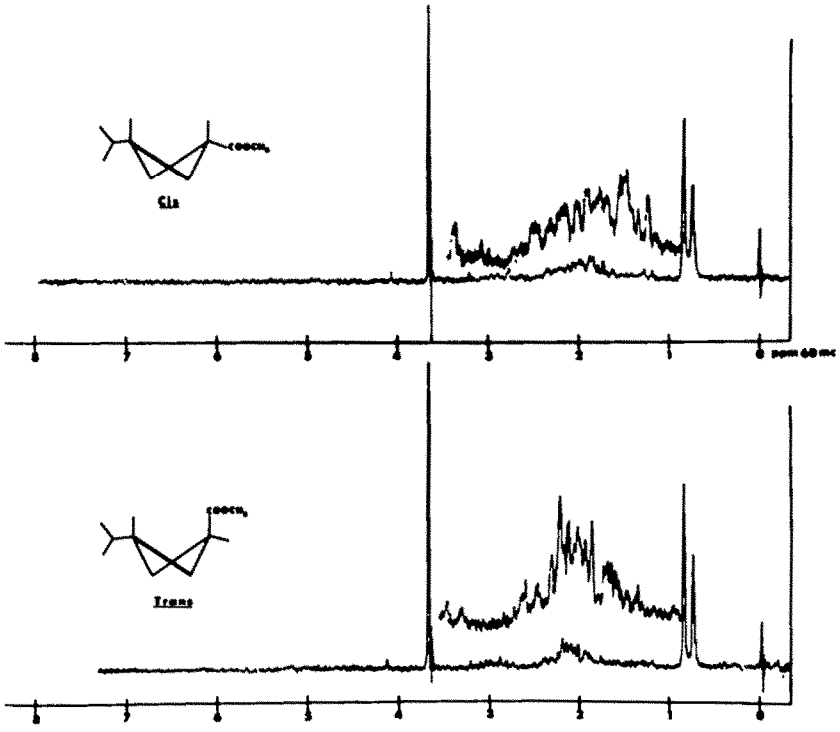
[23] N. L. Allinger and S.-E. Hu. *J. Org. Chem.* **27**, 3417 (1962).

[24] Only 1 kcal/mole separates the equatorial and planar conformers of bromocyclobutane; see W. G. Rothschild, Ref. 13. A generally similar energy range for the flexion of the present cyclobutane system would be far exceeded in the conditions of chemical equilibrium employed.

[25] It would be of no small interest in this regard to obtain K_{eq} for the 3-t-butylcyclobutanecarboxylate esters as a means of checking this possibility. Dr. Gary Lampman of Western Washington State College is independently examining this system (priv. comm.).

[26] Work is now in progress to obtain further data apropos of this possibility.

[27] The meaningfulness of the large body of data which has been accumulated involving the use of the t-butyl group as a holding group in the cyclohexanes in terms of axial vs. equatorial substituent reactivity is clouded by the largely ignored question of ring deformation; see Ref. 20; Ref. 22, pp. 50, 126, 345. It is therefore not surprising that in the more flexible cyclobutanes, such effects will prove to be more manifest.



EXPERIMENTAL

Bps and mps are uncorrected. Mps were taken with a Thomas–Hoover capillary apparatus. VPC was run on Aerograph A-90-P, A-700 or F & M 775 instruments; the ester separation was carried out on the 775. The NMR spectra of the esters were obtained from NMR Specialities, Inc., and were run on an A 60 instrument in $CDCl_3$ soln against reference TMS. Microanalyses were by Drs. Weiler and Strauss, Oxford, England.

Diethyl 3-isopropyl-1,1-cyclobutanedicarboxylate. In a 5 l. 3-necked flask equipped with mechanical stirrer, reflux condenser with $CaCl_2$ drying tube, and dropping funnel, were placed 2-isopropyl-1,3-dibromopropane[28] (660 g, 2·7 m) and diethyl malonate (480 g, 3·0 m). The soln was heated and stirred, and a previously-prepared soln of 124 g (5·4 g-atom) Na in 3 l. abs EtOH was added over a period of 3 hr. Stirring and reflux were continued overnight, after which a maximum possible quantity of EtOH was distilled away. Water (1·5 l.) was added, the upper organic layer separated, and the aqueous layer extracted twice with 500 ml portions ether. The combined organic layers were dried over Na_2SO_4 and the ether removed by distillation. Fractionation of the residual organic material yielded *diethyl 3-isopropyl-1,1-cyclobutanedicarboxylate* (509 g, 2·1 m, 78%) as a liquid of b.p. 117–125°$_{3\,mm}$, n_D^{20} 1·4375; reported[29] b.p. 115–117°$_{6\,mm}$, n_D^{20} 1·4374. VPC on several columns showed only one peak.

3-Isopropylcyclobutane-1,1-dicarboxylic acid. To an ice-cold soln of ethanolic KOH (454 g) was added slowly diethyl 3-isopropyl-1,1-cyclobutanedicarboxylate (383 g, 1·6 m).[30] The soln was stirred for 1 hr, the salt filtered, washed with abs EtOH, abs ether, and air-dried overnight. The dry solid was taken up in a minimum of water, acidified with conc HCl with cooling, and the resulting ppt removed. The filtrate was

[28] H. Pines, W. D. Huntsman and V. N. Ipatieff, *J. Am. Chem. Soc.* **75**, 2311 (1953).
[29] V. P. Golmov, *J. Gen. Chem. USSR* **22**, 1944 (1952).
[30] W. A. Nevill, D. S. Frank and R. D. Trepka, *J. Org. Chem.* **27**, 422 (1962).

evaporated nearly to dryness at 44–50° under aspirator suction, and the resulting mush extracted with ether. The ether was then filtered and dried over Na_2SO_4. Evaporation of the ether gave *3-isopropylcyclobutane-1,1-dicarboxylic acid* as a white crystalline solid of m.p. 161–162° (89·3 g, 0·48 m, 30%); reported[29] m.p. 168°.

3-Isopropylcyclobutanecarboxylic acid. The procedure of Cason and Allen[31] was used. 3-Isopropylcyclobutane-1,1-dicarboxylic acid (89·3 g, 0·48 m) was heated at atm press in the open at 180° for 3 hr. Distillation gave *3-isopropylcyclobutanecarboxylic acid* as a liquid of b.p. 100–103°$_{2.5\ mm}$. VPC on several columns revealed 2 peaks, occurring in slightly different ratios depending on the preparation, but approaching 1:1; retention times on a column of $\frac{3}{8}$" × 20' containing 5% Carbowax 20M on Chromosorb P at 125° and He flowrate of 60 cc/min were 102 and 112 min. A sample of composition 52% first peak (*cis*) and 48% second peak (*trans*) showed n_D^{20} 1·4410. (Found: C, 67·48; H, 9·80. $C_8H_{14}O_2$ requires: C, 67·61 H, 9·86%).

Methyl 3-isopropylcyclobutane carboxylate. 3-Isopropylcyclobutanecarboxylic acid (6·0 g, 0·04 m), abs MeOH (60 ml) and conc H_2SO_4 (2 ml) were refluxed with stirring for 5 hr. 150 ml water was added, the soln extracted with ether, the ether then extracted with $NaHCO_3$ aq followed by water washing and drying over Na_2SO_4. The ether was distilled away, and the residual liquid, *methyl 3-isopropylcyclobutanecarboxylate*, collected at 186–189°; redistillation through a packed column gave a liquid of b.p. 185–186°. VPC on several columns showed 2 peaks, occurring in slightly different ratios for different preparations, but approaching 1:1; retention times on a column of $\frac{1}{2}$" × 6' containing 20% ditridecyl phthalate on Chromosorb P at 122° and He flowrate of 40 cc/min were 52 and 57 min. Preparative separation was accomplished on a column of $\frac{1}{4}$" × 16' containing 10% Bentone-diisodecyl phthalate on Chromosorb 60/80 W at 100° and He flowrate of 900 ml/min; peak one was rechromatographed under the same conditions. Final purities of the 2 peaks were ca. 95% for peak one (*cis*) and 99% for peak two (*trans*) as used for NMR analysis. A sample of composition 52% first peak and 48% second peak (identical with precursor acid from which it was obtained) had n_D^{20} 1·4283. (Found: C, 68·98; H, 10·22. $C_9H_{16}O_2$ requires: C, 69·19; H, 10·33%).

The ester was equilibrated by reflux with methanolic MeONa; 3·2 g ester of approximately 1:1 composition was placed in a soln of 0·01 g Na in 25 ml anhyd MeOH and refluxed for periods up to 144 hr while protected from moisture by a $CaCl_2$ drying tube. The *cis/trans* ratio was determined by withdrawing aliquots and injecting them onto an appropriate column for VPC; an additional column of $\frac{1}{2}$" × 5' containing 5% SE-30 on Chromosorb 60/80 W at 65° and He flowrate of 40 cc/min gave retention times of 47 and 52 min. Peak areas at final equilibrium were in the ratio of 2·20 ± 0·05/1·0 (peak one/peak two). Areas were determined by cutting out and weighing as well as directly by trangulation.

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[31] J. Cason and C. F. Allen, *J. Org. Chem.* **14**, 1036 (1949).