Tetrahedron. Vol. 28, pp. 1529 to 1536. Pergamon Press 1972. Printed in Great Britain

CONFORMATIONAL ANALYSIS BY X-RAY CRYSTALLOGRAPHY—III†

GEOMETRY AND THE CONFORMATION OF *TRANS*-4-*t*-BUTYLCYCLOHEXANOL *PARA*BROMOBENZOATE

R. PARTHASARATHY and J. OHRT
Center for Crystallographic Research, Roswell Park Memorial Institute,
Buffalo, New York U.S.A.

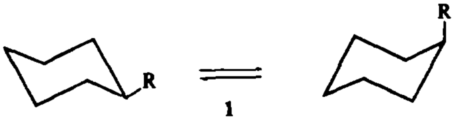
and

H. B. KAGAN and J. C. FIAUD
Laboratoire de Synthèse Asymétrique—Faculté des Sciences d'Orsay 91-Orsay, France

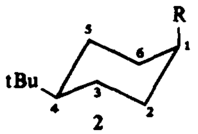
(*Received in the UK* 16 *July* 1971; *Accepted for publication* 3 *November* 1971)

Abstract—The conformation of *trans*-4-*t*-butyl-cyclohexanol*para*bromobenzoate has been studied by X-ray crystallographic methods. The main results of this study are: (i) there are indications for the existence of steric compression between the t-butyl group and the hydrogens axial on C_3 and C_5; (ii) contrary to the suggestion of various workers, no flattening is induced in the cyclohexane ring and no elongation of the c(tbu)—c(cyclohexane) bond; (iii) the steric strain seems to be minimized by a flattening of the $C_4(C_3C_7C_5)$ pyramid; (iv) the axial hydrogen on C_1 nearly eclipses the carbonyl oxygen, as found in the earlier studies of the acetates and esters of cyclohexanols.

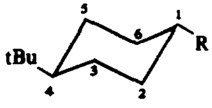
THE CONFORMATIONAL ANALYSIS of mobile cyclohexane systems has made rapid progress following the suggestion by Winstein and Holness,[2] to use the t-butyl group as a conformation holding group in the cyclohexane ring. By using the reluctance of the t-butyl group to occupy the axial position in the ring, both Winstein and Holness[2] and Eliel, *et al.*[3,4] evaluated conformational preferences of substituents R in the mobile cyclohexane (**1**) by comparison of rates of reaction of **1** with those of the "anancomeric"[5] systems (**2** and **3**).[6,7] Subsequently, the use of t-butyl as a holding group was extended to the evaluation of conformational preferences by equilibrium,[8] and NMR methods.[9] Recently, however, the use of t-butyl as a holding group has been subjected to criticism[10] leaving open to question some or all of the assumptions* underlying this method.



1



2



3

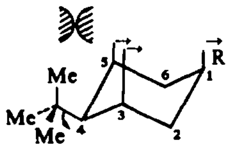
---

* The usual assumptions[7,11] are: the t-butyl group (i) has no effect on the reactivity of the substituent R, (ii) must not exert polar and steric effects at the 4-position, (iii) must not distort the ring in the ground or the transition state

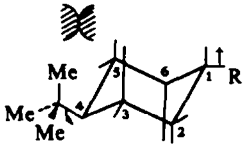
† For part II, see ref 1

The results of several investigators[10, 12, 13, 14] suggest that the reactivity is influenced by the presence of the t-butyl group. The examination of the mode of action of formation of complexes between ICl and cyclohexane carbonitriles with different R-groups has led Shah-Malak and Utley[15] to suggest that the cyclohexane ring is flattened in order to relieve the steric interactions of the axial hydrogens and the t-butyl group. Mazaleyrat and Welvart[16] have studied the *pK* of several 1-methyl-1-aminocyclohexanes and have concluded that, contrary to the assumptions alluded to earlier, the 4-t-butyl group has an influence on the *pK* of an amino group axial at C_1. The energy of compression of this group which inhibits solvation, is less decreased by a flattening of the cyclohexane ring at C_3, C_4 and C_5 when there is a t-butyl group at C_4.

The idea of distortions in substituted cyclohexanes is not new[7] and needs to be discussed only in the specific case of t-butylcyclohexanes. It was suggested at first by Cornubert[17] that steric interactions must arise between one of the methyl groups of t-butyl and the axial hydrogens at C_3 and C_5. This strain would probably find relief by a flattening of the ring. If there is an axial R-group on C_1 and also a t-butyl group on C_4 (as in 4), then there is no such possibility of a lateral displacement of the axial hydrogens on C_3 and C_5. Consequently, it is understandable that an axial R-group, by virtue of the buttressing effect, will find itself in a different environment depending on whether or not there is a t-butyl group at C_4. The effect will be less pronounced for an equatorial R. However, Utley *et al.*[18] showed recently that in the case of 3 (R = $-CHCl-C_6H_5$) the t-butyl group lowers the steric strain on R, presumably by ring flattening which decreases the interactions between R and the equatorial hydrogens on C_2 and C_6. The use of molecular models shows in addition the possibility of some distortions opposite to the flattening discussed above if there are sterically large equatorial substituents. These large groups can be repelled by the neighbouring axial hydrogens as shown in 5, thereby introducing some puckering in the ring. Altona and Sundaralingam[19] recently computed the preferred conformation of a t-butyl group in t-butylcyclohexane and proposed a conformation wherein there was not perfect staggering along the C_4—C(tbu) bond.



4



5

In view of the above situation, it seemed interesting to study the structure of *trans*-4-t-butyl cyclohexanol-*para*bromo benzoate (6) (hereafter referred to as PBTB) in order to obtain directly the conformation of the t-butylcyclohexane system.

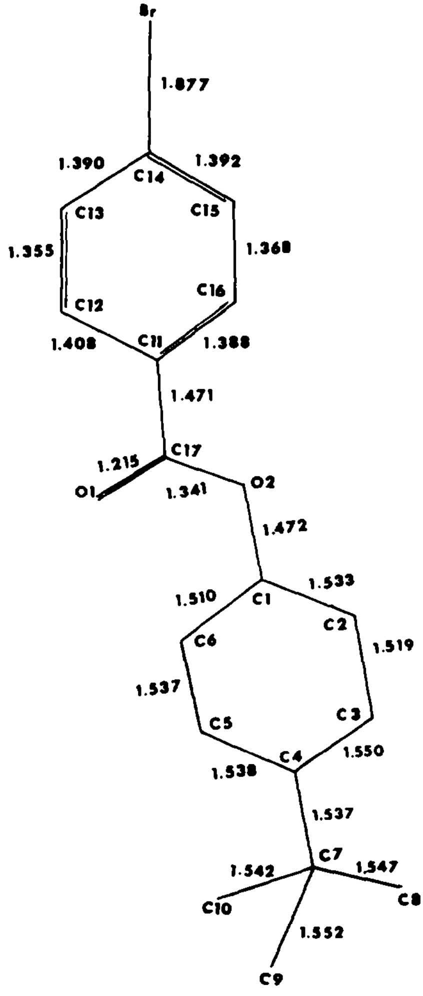
PBTB was prepared as described* and crystallized from MeOH at room temperature. The crystals are triclinic, space group P$\bar{1}$, with two molecules in the unit cell.

---

* Prepared by esterification of *trans*-4-t-butylcyclohexanol. F = 101°. Analysis: $C_{17}H_{23}O_2Br_2$ (339·3): (Calc. C, 60·17; H, 6·83. Found: C, 60·31; H, 6·90%).

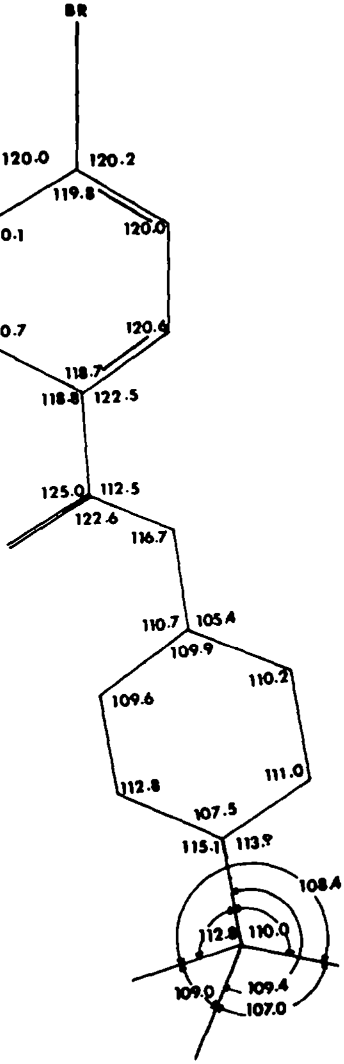
The cell constants at room temperature (22° ± 3°) are a = 9·813 (2) Å, b = 13·451 (3) Å, c = 6·564 (3) Å, α = 102·99 (03)°, β = 98·88 (03)° γ = 89·99 (03)°, ρ_{obs} = 1·34/cm^3, ρ_{calc} = 1·34 g/cm^3.

Using a GE-XRD-6 diffractometer equipped with a single crystal orienter and scintillation counter, three-dimensional intensity data involving 3100 independent reflections were measured to the limit $2\theta = 140°$ for the CuKα_1 (= 1·5405 Å) radiation. The stationary crystal-stationary counter technique was employed for measuring the intensities and Ni—Co balance filters were used for monochromatization. The crystal structure was solved by the heavy-atom method and refined by applying Fourier and least-squares methods to an R value of 0·058. The hydrogen atoms were located directly from electron-density difference maps and their positional and individual thermal parameters refined by least-squares methods. The details of the structure analysis will be reported elsewhere.

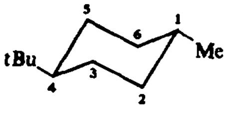


6. Bond distances in Å

The important structural and conformational features are discussed below and are illustrated in 6 and 7. This study seems to be one of the first crystallographic structural investigation on a cyclohexane system with a 4-t-butyl group.[20] The results are compared with the theoretical predictions by Altona and Sundaralingam[19] who used empirical valence force calculations on compound 8.



7. Bond angles in degrees



8

It is interesting to see how the steric strain introduced by the t-butyl group can be minimized by the system. The difficulty in such an analysis is the choice of a reference system for comparison. Evidently it cannot be the cyclohexane itself; as the standard, we took **9** whose detailed structure is known from X-ray analysis.[19,21] In Table 1 are reported the bond angles and the torsional angles of **9**, the predicted[19] data for **8** and our experimental data for PBTB **6**.

9

(a) It is quite evident by comparison of **6** and **9** that the t-butyl group does not cause any flattening of the ring in PBTB. In fact, PBTB (with a mean value of 58·3 (5)° for the torsion angle) appears slightly more puckered than **9** and much more puckered than what is predicted for **8** (predicted value 55°). It might be useful to compare the flattening of the rings by studying the distances of C_1 and C_4 from the least-squares plane through C_2, C_3, C_5, C_6. These distances for C_1 and C_4 are respectively 0·70 Å and −0·71 Å in PBTB (**6**) and 0·68 Å and −0·68 Å in **9**, indicating no flattening of the ring due to the t-butyl group.

TABLE 1

Bond angles	6*	9[21]	8 (Predicted[19])
6-1-2	109·9	111·1	110·3
1-2-3	109·6	110·4	112·4
1-6-5	110·2	110·4	111·1
2-3-4	112·8	110·4	113·0
6-5-4	110·0	110·4	112·9
3-4-5	107·5	111·1	108·7
Mean	110·2	110·6	111·4
Torsional angles			
6-1-2-3	57·9	57·2	54·5
2-1-6-5	60·1	57·2	55·8
1-2-3-4	58·1	56·9	54·3
1-6-5-4	60·2	56·9	57·7
2-3-4-5	56·4	57·5	52·7
3-4-5-6	57·1	57·5	54·8
Mean	58·3	57·2	55·0

* The average value of the standard deviations for the C—C bonds and C—Ĉ—C angles obtained directly from the inverse of the block diagonal matrix are respectively 0·007 Å and 0·5°

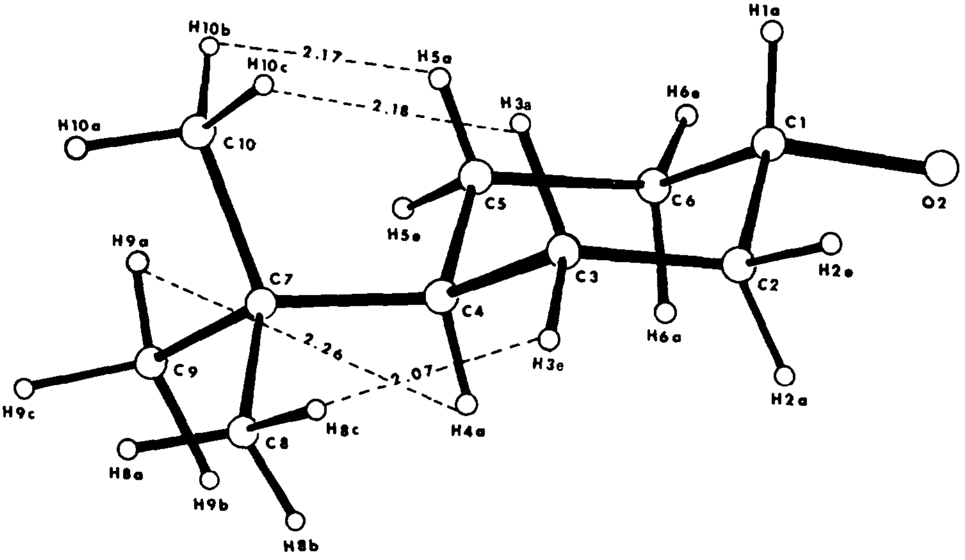
(b) The mean C—C bond in the ring is 1·531 (6) Å; the mean C—Ĉ—C bond angle in the ring is 110·2 (4)°.

(c) C_4—C_7 bond is 1·538 (7) Å compared to the calculated value of 1·570 Å.[19]

(d) No twist greater than 3° about the C_4—C_7 bond is observed in contrast to a calculated value of 17°.[19] The hydrogens of the homo-axial Me group are almost perfectly staggered about the C-methyl—C_4 bond with respect to the three carbons on C_4. The hydrogens on the homo equatorial Me groups are twisted considerably; up to 20° about the C-methyl—C_4 bonds. The thermal parameters of the t-butyl group are comparable to those of the other atoms in this structure and are not significantly larger than those observed for the other atoms.[19]

(e) The axial hydrogen on C_1 nearly eclipses the carbonyl oxygen; the torsion angle about the C_{17}—O_2 bond is −5·81°. This result is in close agreement with earlier studies of the acetates and esters of cyclohexanols.[1,22] The O_1—H_{1a} contact is 2·27 Å.

(f) The ester carbonyl C = 0 is approximately co-planar with the Ph group; it is at a distance of 0·024 Å from the least-squares plane through the benzene ring. This plane does not occupy a symmetric position with respect to the cyclohexane ring, though one would normally expect the plane to be symmetric, at least in an isolated molecule. The values of the torsion angle of C_2 and C_6 with respect to C_{17} about the O_2—C_1 bond are respectively, −153·4° and 87·9°. This asymmetry of the molecule probably arises due to the differing environments of the cyclohexane and benzene rings in the crystal; there was no C—C intermolecular contact less than 3·4 Å and C—H contact less than 3·1 Å.



10. Contact distances

The preceding structural and conformational features of PBTB (6) do not support the idea that any ring flattening or bond elongation[19] is caused by the t-butyl group. A careful study of the structural data might give answers to the following questions: Whether any steric strain in the system is introduced by the t-butyl group and by what means such strain is relieved.

The shortest H—H contacts between the t-butyl and the cyclohexane ring are listed in Table 2 and illustrated in **10**. The shortest contacts between the axial or equational hydrogens and those on the t-butyl group are: 2·07 Å between the equatorial hydrogen on C_3, and the hydrogen of the homo equatorial Me group: 2·18 Å between the axial hydrogen on C_3 and a hydrogen on the homo axial Me group, 2·17 Å between the axial hydrogen on C_5 and a hydrogen on the homo axial Me group. Other H—H contacts less than 2·4 Å are listed in Table 2.

TABLE 2. H—H CONTACTS LESS THAN 2·4 Å

H_{1a}—H_{2e}	2·37 Å	H_{4a}—H_{5}	2·26 Å
H_{1a}—H_{6e}	2·31 Å	H_{4a}—H_{9a}	2·26 Å
H_{3a}—H_{5a}	2·35 Å	H_{5a}—H_{10b}	2·17 Å
H_{3a}— H_{10c}	2·18 Å	H_{5e}—H_{6a}	2·31 Å
H_{3e}—H_{4a}	2·38 Å	H_{5e}—H_{9b}	2·35 Å
H_{3c}—H_{8c}	2·07 Å		

It should be remembered that the location of hydrogen atoms by X-ray diffraction is not as precise as can be obtained by neutron diffraction. Nevertheless, the contact distances obtained in this case, we believe, are a good starting point for discussing the sterical interactions. According to Ramachandran and Sasisekharan[23] the "normally allowed" and "extreme" H—H contacts have values 2·00 Å and 1·90 Å respectively. These distances were obtained from a survey of short contacts from a number of organic crystal structures. If we accept these distances, then all the H—H contacts fall within the allowed category and, consequently, any strain induced by the t-butyl group is minimal.

On the other hand, following Bondi,[24] if we use the usually accepted value of 1·20 Å for the Van der Wall radius of aliphatic hydrogens, then the shortest contacts alluded to earlier should cause the major strain. This strain seems to have been minimized mainly by a flattening of the C_4 ($C_3C_7C_5$) pyramid; the C_4—C_7 bond being pushed away from the $C_3C_4C_5$ plane ($C_3C_4C_7$ = 113·9°, $C_7C_4C_5$ = 115·1°).[19]

In conclusion, our results indicate the existence of steric compression between the t-butyl group and the hydrogens axial on C_3 and C_5, and the equatorial hydrogen on C_3. However, contrary to the suggestions of various workers, no flattening is induced in the cyclohexane *ring* and no elongation of the C(tbu)—C (cyclohexane) bond, at least in PBTB.

Acknowledgements—We are grateful to Drs Eliel and Welvart for many valuable discussions and to Dr D. Harker and Dr G. Tsoucaris for their keen interest in this work. Our thanks to Mrs Winiewicz for her excellent technical assistance. Partial financial assistance by NIH(GM-15787) is gratefully acknowledged.

REFERENCES

[1] R. Parthasarathy, J. Ohrt, A. Horeau, J. P. Vigneron and H. B. Kagan, *Tetrahedron* **26**, 4705 (1970)

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

[3] E. L. Eliel and C. A. Lukah, *Ibid.* **79**, 5986 (1957)

[4] E. L. Eliel and R. S. Ro, *Ibid.* **79**, 5995 (1957)

[5] M. Anteunis, D. Tavernier and F. Borremans, *Bull. Soc. Chim. Belg.* **75**, 396 (1966)

[6] E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill Book Co., Inc., New York (1962)

[7] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrisson, *Conformational Analysis*, Interscience Publishers, New York (1965)

[8] E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.* **79**, 5992 (1957)

[9] E. L. Eliel, *Chem. Ind.* (London), 568 (1959)

[10] H. Kwart and T. Takeshita, *J. Am. Chem. Soc.* **86**, 1161 (1964); H. R. Buys and E. L. Eliel, *Tetrahedron Letters* 2779 (1970)

[11] E. L. Eliel, *J. Chem. Educ.* **37**, 126 (1960)

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

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

[14] J. L. Mateos, C. Perez and H. Kwart, *Chem. Comm.* 125, (1967)

[15] F. Shah-Malak and J. H. Utley, *Ibid.* 69 (1967)

[16] J. P. Mazaleyrat and Z. Welvart, *Ibid.* 485 (1969)

[17] R. Cornubert, *Bull. Soc. Chim.* 996 (1956)

[18] J. P. Coleman, F. I. Shah-Malak, J. H. P. Utley, *J. Chem. Soc.* B 666 (1970)

[19] C. Altona and M. Sundaralingam, *Tetrahedron* **26**, 925 (1970)

[20] A.C.A. Meeting Abstracts, p. 55, Ottawa, Canada, March (1970)

[21] J. D. Dunitz and P. Strickler, *Helv. Chim. Acta* **49**, 2502 (1966)

[22] A. Mc.L. Mathieson, *Tetrahedron Letters* 4137 (1965)

[23] G. N. Ramachandran and V. Sasisekharan, *Adv. Prot. Chem.* **23**, 283 (1968)

[24] A. Bondi, *J. Phys. Chem.* **68**, 441 (1964)