P. L. Barili, G. Bellucci, G. Ingrosso, F. Marioni (*)

THE EFFECT OF A VICINAL *t*-BUTYL GROUP ON THE CONFORMATION AND THE KINETICS OF INTERCHANGE OF HALOGENS OF *trans*-2-CHLORO-1-BROMOCYCLOHEXANES (**)

Riassunto — *Effetto di un Gruppo* t-*Butilico Adiacente sulla Conformazione e sulle Cinetiche di Interscambio di Alogeni di* trans-2-*Cloro-1-bromocicloesani.* Sono stati misurati i parametri ^{1}H N.M.R. dei composti *r*-1-bromo-*t*-2-cloro- (1a) e *r*-1-cloro-*t*-2-bromo-*c*-3-*t*-butilcicloesano (1b) oltre alle costanti di velocità del primo ordine e ai parametri di attivazione per la loro interconversione termica in *r*-1-cloro-*t*-2-bromo-(2a) e *r*-1-bromo-*t*-2-cloro-*t*-3-*t*-butilcicloesano (2b). Tutti i risultati indicano per il composto (1b) un significativo contributo di un conformero *twist*, in cui l'angolo torsionale Br-C-C-Cl e la distanza tra l'atomo di bromo vicinale ed il gruppo *t*-butilico sono maggiori che nella forma triequatoriale.

Abstract — The ^{1}H N.M.R. parameters of *r*-1-bromo-*t*-2-cloro- (1a) and *r*-1-cloro-*t*-2-bromo-*c*-3-*t*-butylcyclohexane (1b) and the first order rate constants and activation parameters for their thermal rearrangement to *r*-1-cloro-*t*-2-bromo- (2a) and *r*-1-bromo-*t*-2-cloro-*t*-3-*t*-butylcyclohexane (2b) have been measured. All data indicate for compound (1b) a significant contribution of a twist conformer, in which the Br-C-C-Cl torsion angle and the distance between vicinal bromine and *t*-butyl group are higher than in the triequatorial form.

Key words — *trans*-2-chloro-1-bromocyclohexanes; conformational analysis; 1, 2-interchange of halogens; kinetics.

The effect of substituents adjacent to a *t*-butyl group on the conformation (Kellie and Riddel, 1974) and epimeric equilibrium of cyclohexane derivatives (Pasto and Rao, 1969; Aycard and Bodot, 1973) has received some attention. A contribution of non chair forms has been detected for compounds bearing adjacent *trans* oriented bromine and *t*-butyl (Barili, Bellucci, Ingrosso et Al., 1972; Bellucci et Al., 1978) and has been ascribed to a strong repulsive interaction between these two substituents. In order to compare the effects of a *gauche* chlorine- and bromine-*t-butyl* interac-

tion on both the conformations and the reactions of interchange of halogens (KIRK and HARTSHORN, 1968) of these compounds, we have now extended our previous investigations of *trans*-1,2-dibromocyclohexanes (BARILI, BELLUCCI, INGROSSO et Al., 1972; BARILI, BELLUCCI, BERTI et Al., 1972) to the four *t*-butyl substituted bromo chloro derivatives (1a-b) - (2a-b).

RESULTS

The 100 MHz ^{1}H N.M.R. spectra of the *trans* bromo chlorides (1a) and (1b) showed for the protons α to the halogen atoms line patterns very similar to those observed for the corresponding dibromo derivative (1c) (BARILI, BELLUCCI, INGROSSO et Al., 1972) and interpretable as the XY part of an ABXYC system with J_{AY}, J_{BY} and $J_{CX} = 0$ and the H_Y proton appearing in both compounds at higher field. The spectral parameters, obtained by computer simulation, are reported in Table 1 together with those of dibromide (1c) and of bromohydrin (1d), which are taken as models for 1, 2, 3-trisubstituted cyclohexane derivatives adopting, respectively, flexible twist-boat and frozen chair conformations (BARILI, BELLUCCI, INGROSSO et Al., 1972).
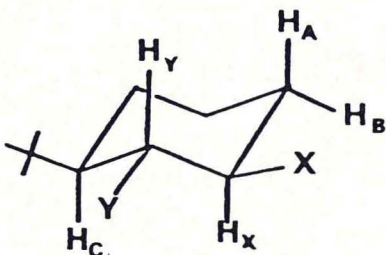
(1a): X = Br, Y = Cl
(1b): X = Cl, Y = Br
(1c): X = Br, Y = Br
(1d): X = Br, Y = OH
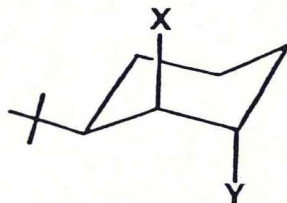
(2a): X = Br, Y = Cl
(2b): X = Cl, Y = Br

TABLE 1 - ^{1}H N.M.R. parameters (Hz) of dihalogenocyclohexanes [a]

Compound	J_{AX}	J_{BX}	J_{XY}	J_{CY}	Δ_{XY}
(1a)	10.3	4.8	8.9	9.5	22.9
(1b)	8.1	4.3	7.8	7.4	18.7
(1c) [b]	8.7	4.3	7.5	7.9	22.1
(1d)	11.6	4.7	9.4	9.3	43.5

[a] Solvent CCl_4, Temperature 25°C.
[b] Taken from (BARILI, BELLUCCI, INGROSSO et Al., 1972); Temperature 30°C.

In comparison with the chair compound (1d), the bromo chloride having bromine adjacent to the *t*-butyl group, (1b), exhibited a significant decrease in the coupling constants of the protons α to the halogen atoms. The values of J_{AX}, J_{XY} and J_{CY} were definitely smaller than those expected for axial-axial couplings, and very similar to those observed for the corresponding dibromo derivative (1c). As for the latter compound (BARILI, BELLUCCI, INGROSSO et Al., 1972), these observations suggest that a twist conformer of type (3b) (see Scheme), with H_X-C-C-H_Y, H_A-C-C-H_X and H_C-C-C-H_Y diedral angles smaller than in the triequatorial chair form, and therefore with higher Br-C-C-Cl torsion angle and *t*-butyl-bromine distance, give a significant contribution to the conformational equilibrium of bromo chloride (1b). Clearly, in both (1b) and (1c) the strong repulsive interaction between the *t*-butyl group and equatorial 2-bromine, in addition to the steric, dipole-dipole and lone pair orbital repulsion between equatorial halogens, (ZEFIROV et Al., 1976, and references cited therein) destabilizes the triequatorial chair conformation making a twist form of type (3) competitive. A conformation of the latter type has been detected by X-ray diffraction of a cyclohexane compound having the part structure of (1c) with a fourth substituent in place of H_A. (BELLUCCI et Al., 1976).

On the other hand, bromo chloride (1a) exhibited coupling constants higher than those of isomer (1b) and more similar to those of compound (1d), in which a hydroxyl group takes the place of chlorine of (1a) and can stabilize the triequatorial chair conformation by intramolecular hydrogen bonding to bromine. Since the repulsion terms associated with the vicinal halogen atoms should be identical for chair conformations of both (1a) and (1b), it can be

inferred that the presence of vicinal equatorial chlorine and t-butyl group is not sufficient to force a considerable population of compound (1a) in a non chair conformation.

Both bromo chlorides (1a) and (1b) were cleanly converted by heating into the respective diaxial partners (2a) and (2b). G.L.C. gave for the equilibrium composition of (1a) - (2a) and (1b) - (2b) at 165°C respectively 97 ± 1% of (2a) and 98 ± 1% of (2b).

The kinetic of the process was followed at four temperatures by a N.M.R. method starting from the pure isomer (1b) which could easily obtained by bromochlorination of 3-t-butylcyclohexene (BEL-LUCCI, INGROSSO et Al., 1974). The isomerization of the less easily available isomer (1a) (BELLUCCI, INGROSSO et Al., 1974) was instead followed with a G.L.C. method, requiring smaller amounts, at three temperatures. Clean first order kinetics were always observed. Table 2 shows the rate constants and activation parameters.

TABLE 2 - Rate constants and activation parameters for the 1,2-interchange reactions of bromo chloride (1a) and (1b) [a].

Reaction	T (°C)	$10^4 \, k_1$ (sec^{-1})	E_a	$\Delta H^{\neq}$	$\Delta S^{\neq}$
(1a) → (2a)	135.0	0.16 ± 0.005			
	150.2	0.80 ± 0.02		34.3±0.8 [b]	+2.9±1.8 [b]
	165.0	3.10 ± 0.05	35.1±0.7	34.3±0.7 [c]	+3.1±1.6 [c]
(1b) → (2b)	135.0	0.27 ± 0.01			
	150.0	1.08 ± 0.02		31.0±0.7 [b]	−4.1±1.6 [b]
	165.1	4.37 ± 0.05	31.8±0.4	31.0±0.4 [c]	−3.9±0.9 [c]
	179.5	12.40 ± 0.20			

[a] E_a and $\Delta H^{\neq}$ are expressed in kcal/mol, $\Delta S^{\neq}$ in cal/Kmol. Errors are quoted as standard deviations (*see Experimental*).

[b] Obtained as fitting parameters by a linear least-squares analysis of equation 2) (*see Experimental*). The correlation coefficient between the parameters was >0.999.

[c] Obtained as fitting parameters by a non linear least-squares analysis of equation 3) (*see Experimental*). The correlation coefficient between the parameters was > 0.999.

At all examined temperatures the rate of the reaction (1b) → (2b) was only slightly higher than that of (1a) → (2a), but the activation parameters showed a difference of 3.3 kcal/mol in activation

energy disfavouring the latter. The activation entropies were smaller in both cases, in agreement with an intramolecular process of 1,2-interchange, but more negative for the reaction of (1b).

DISCUSSION

The diequatorial-diaxial rearrangement of the present compounds is a case of a most general 1,2-interchange reaction of functional groups (KIRK and HARTSHORN, 1968) observed for steroid (GROB and WINSTEIN, 1952; BARTON and KING, 1958; KING and PEWS, 1965) as well as cyclohexane derivatives (BARILI, BELLUCCI, BERTI et Al., 1972, BELLUCCI, FERRETTI et Al., 1972) and can be visualized as shown in the Scheme.

(1)   (3)   (4)   (2)

a : X = Br, Y = Cl
b : X = Cl, Y = Br
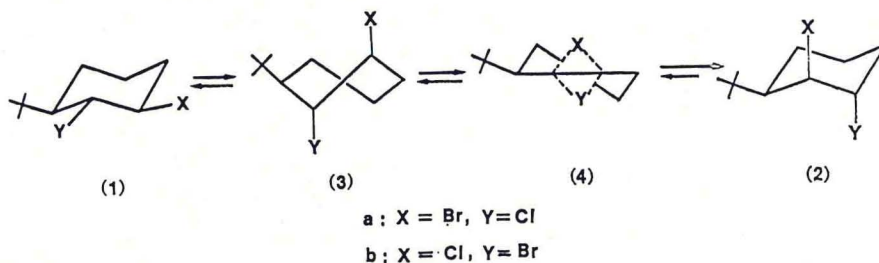
As far as the conformational aspects are concerned, it can be underlined that the starting diequatorial dihalide has to convert from a chair into a twist conformation in order that the halogen atoms have the *anti* coplanar orientation required to approach the transition state, which for bromo chloro compounds is expected (KIRK and HARTSHORN, 1968) to have some polarized bromonium-chloride type character not shown in (4). The driving force for these rearrangements is clearly the relief of the steric, electrostatic, and lone pair orbital repulsion (ZEFIROV et Al., 1976, and references cited therein) present in compound (1), the high increase in the equilibrium percentage of the diaxial dihalides relative to the conformational equilibrium of unsubstituted *trans*-2-chloro-1-bromo-cyclohexane (BUYS and HAVINGA, 1968) indicating a stronger *gauche* halogen-*t*-butyl interaction in the diequatorial (1) than in the diaxial forms (2). The preference for the axial position of substituents

adjacent to a *t*-butyl group had been observed in several cases, (PASTO and RAO, 1969; AYCARD and BODOT, 1973) but has not yet received an adequate explanation (BELLUCCI et Al., 1976).

The increase in activation energy observed for the rearrangement of both bromo chlorides (1a) and (1b) with respect to the corresponding reaction of dibromide (1c) ($E_a = 25.0$ kcal/mol) (BARILI, BELLUCCI, BERTI et Al., 1972) is in agreement with the trend observed for the activation energies for the racemization of *trans*-1, 2-dibromo- and *trans*-2-chloro-1-bromocyclohexane (BELLUCCI, MARSILI et Al., 1974), and for the rates of the diaxial-diequatorial rearrangement of steroid acetoxy-bromides and -chlorides (BARTON and KING, 1958), two reactions occurring through a mechanism similar to that of the present ones, and is due to the greater strength of the C-Cl with respect to the C-Br bond, as well as to the lower tendency of chlorine to nucleophilic participation in displacement reactions.

The differences in activation entalpy and entropy observed for isomer (1a) and (1b) are rather small, but beyond the experimental errors (see *Numerical treatment of the kinetic data* in the Experimental), and can be rationalized on the basis of the different conformational situations indicated by the N.M.R. spectra of these compounds. In fact the more negative value of the activation entropy for the reaction of the latter compound is consistent with the contribution of a flexible twist form of type (3) to its conformational equilibrium (but not that of isomer (1a)), the passage to the more rigid half chair transition state (4b) involving some loss of degrees of freedom (*). On the other hand, the lower value of the activation entalpy for the rearrangement of (1b) relative to that of (1a) could be a consequence of the increased ground state entalpy of (1b) due to the strain present in both the chair conformation, experiencing a severe bromine-*t*-butyl interaction, and the contributing twist form (3b) (**).

In conclusion, all data obtained in this work confirm the exis-

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(*) A twist conformation is expected to have higher entropy relative to a chair form, mainly because of the possibility of pseudolibration about the mean twist position (KELLIE and RIDDEL, 1974).

(**) The orientation of the *t*-butyl group with respect to bromine and chlorine is expected to have only a minor influence on the entalpy of the bridged half chair transition states (4a) and (4b), the steric halogen-*t*-butyl interactions being smaller than in the ground state chair conformations. Moreover, if a steric destabilizing interaction does exist, it should be higher in (4a), having the bigger bromine *syn* to the adjacent *t*-butyl group.

tence in cyclohexane derivatives of a *gauche* repulsive interaction between an equatorial halogen and an adjacent *t*-butyl group, which in the case of bromine is large enough to force a considerable population of compounds of type (1b) and (1c) in non chair conformations.

EXPERIMENTAL

Bromo chlorides (1a, b) - (2a, b) were prepared as already described (BELLUCCI, INGROSSO et Al., 1974). G.L.C. analyses were carried out with a Carlo Erba Fractovap instrument (column: 1% NPGS on silanized Chromosorb W, temp. 90°C, carrier gas N₂, flow rate 35 ml/min). The relative retention times of (1a) and (2a) were: 3.4:1; the relative retention times of (1b) and (2b) were: 2.7:1. N.M.R. spectra for the measurement of the coupling constants were taken from *c.a.* 25% (w/w) CCl₄ solutions with a JEOL PS-100 spectrometer, using TMS as internal standard. The theoretical spectra were calculated using a LEQUOR iterative program run on an IBM 370/168 computer. N.M.R. spectra for the determination of the (1):(2) ratios were obtained from neat liquids with a JEOL C-60 HL instrument.

Kinetic measurements.

A. *By N.M.R.* - Samples of *c.a.* 0.5 ml of (1b) were sealed under nitrogen in N.M.R. tubes which were immersed into a thermostatted bath at the temperatures reported in Table 2 (± 0.2°). The tubes were witdrawn at intervals and rapidly cooled in ice-water, the N.M.R. spectra were taken, and the tubes reimmersed into the bath. The operation was repeated until more than 90% of (1b) was converted into (2b). Analysis was based on the integration of the signals of the protons α to halogens of (1b) and (2b) at δ 3.8 ∼ 4.4 and δ ∼ 4.5 respectively and was reproducible within ± 1%. At least eight measurements were made for each kinetic run. Some darkening occurred at the higher temperatures, but N.M.R., I.R. and G.L.C. analysis did not reveal the formation of appreciable amounts of side-products, nor was the kinetic adversely affected.

B. *By G.L.C.* - Samples of (1a) (*c.a.* 50 mg) were sealed into Pyrex microtubes under nitrogen and immersed into the thermostatted bath at the indicated temperatures. At due time the tubes were withdrawn, rapidly cooled and opened and the content sub-

jected to G.L.C. analysis under the above mentioned conditions. The reaction was followed until ~80% conversion and at least eight different measurements were made at each temperature.

The product distributions at equilibrium for both couples (1a) - (2a) and (1b) - (2b) were determined by G.L.C., by continuing heating of the sample until three consecutive determinations gave a constant (1):(2) ratio.

Numerical treatment of the kinetic data. - All the kinetic runs exhibited a satisfactory dependence on the first-order rate law. The rate constants were calculated by the least-squares method and errors given in Table 2 are standard deviations. The ΔH^{+} and ΔS^{+} values were first obtained as fitting parameters by a linear least-squares analysis of equation 2), where $y = \ln k - \ln T - 23.775$, and $x = 1/T$ are the experimental variables, deriving from equation 1) relating the rate constant with absolute temperature, activation entalpy and entropy (GLASSTONE et Al., 1941).

$$k = \frac{kT}{h} e^{-\frac{\Delta H^{+}}{RT}} e^{\frac{\Delta S^{+}}{R}} \qquad 1)$$

$$y = -\frac{\Delta H^{+}}{R} x + \frac{\Delta S^{+}}{R} \qquad 2)$$

The activation parameters so obtained were then used as starting values for a non linear least-squares fitting of all experimental terns of values of concentration, time and temperature (used for the determination of the individual rate constants) to equation 3), where $c(t, T)$ is the mole fraction of compound (1) at time t and temperature T. It is apparent from equation 3) that only two fitting

$$\frac{c(t, T)}{c(0, T)} = e^{-\left(\frac{kT}{h} e^{-\frac{\Delta H^{+}}{RT}} e^{\frac{\Delta S^{+}}{R}} \right) t} \qquad 3)$$

parameters (*i.e.* $\Delta H^{\neq}$ and $\Delta S^{\neq}$) are needed to fit all experimental kinetic data obtained at different temperatures for a given compound. In comparison with the traditional Arrhenius plots, which in the present cases would be based on only three or four least-squares estimates of kinetic constants for as many temperatures, this method has the advantage of giving a more realistic estimate of the number of degrees of freedom of the system, to be used in statistical significance tests. The $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values and their standard deviations, obtained with the former (fitting of equation 2)) and the latter method (fitting of equation 3)), are reported in Table 2. Both methods gave identical or very similar values of the activation parameters, but the latter gave lower standard deviations, with a significance level $>99.5\%$ according to the Fisher and Behrens test (HAMILTON, 1964), so assuring that the differences in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ observed for the rearrangements of isomer (1a) and (1b), although small, are fully significant (BARD, 1974).

The activation energies were obtained by equation 4), where T is the average temperature of the examined range.

$$E_a = \Delta H^{\neq} + RT \qquad\qquad 4)$$

All calculations were carried out both with an IBM 370/168 computer and a HP 2114 B laboratory minicomputer using BASIC programs.

REFERENCES

BARD Y. (1974) - Non Linear Parameter Estimate. Academic Press, New York.

BARILI P. L., BELLUCCI G., BERTI G., MARIONI F., MARSILI A., MORELLI I. (1972) - Thermal Equilibration of Substituted *trans*-1,2-Dibromocyclohexanes. *J. Chem. Soc. Perkin II*, 58-62.

BARILI P. L., BELLUCCI G., INGROSSO G., MARIONI F., MORELLI I. (1972) - Conformational Analysis of Dibromocyclohexanes by Nuclear Magnetic Resonance Spectroscopy. Evidence for the Participation of a Twist Form to the Conformational Equilibrium of *r*-1, *t*-2-Dibromo-*c*-3-*t*-butylcyclohexane. *Tetrahedron*, **28**, 4583-4589.

BARTON D. H. R., KING J. F. (1958) - The Generalised Diaxial→Diequatorial Rearrangement. *J. Chem. Soc.*, 4398-4402.

BELLUCCI G., BERTI G., COLAPIETRO M., SPAGNA R., ZAMBONELLI L. (1976) - Crystal and Molecular Structure of *cis*-2,*trans*-3-Dibromo-*cis*-4-*t*-butylcyclohexyl p-Nitroben-

zoate: a Case of Non-Chair Conformation of a Saturated Monocyclic Cyclohexane Derivative. *J. Chem. Soc. Perkin II*, 1213-1218.

BELLUCCI G., FERRETTI M., INGROSSO G., MARIONI F., MARSILI A., MORELLI I. (1972) - Reagent Dependence of the Steric Course of Bromohydrin and Acetoxybromide Formation. A Case of Facile 1,2-Interchange in a Couple of Diastereoisomeric Bromohydrins. *Tetrahedron Letters*, 3527-3530.

BELLUCCI G., INGROSSO G., MARIONI F., MASTRORILLI E., MORELLI I. (1974) - Evidence for Different Addition Mechanisms in the Bromochlorination of 3-*tert*-Butylcyclohexene with Bromine Chloride and which Monopyridinebromine(I) Chloride. *J. Org. Chem.*, **39**, 2562-2565.

BELLUCCI G., INGROSSO G., MASTRORILLI E. (1978) - The Influence of a *t*-Butyl Group on the Conformational Equilibrium and the Hydrogen Bromide Catalyzed Isomerization of 2-Bromocyclohexanones. *Tetrahedron*, **34**, 387-390.

BUYS H. R., HAVINGA E. (1968) - The Conformation of Non-Aromatic Ring Compounds, Part XLIX. Relationship between the Conformational Equilibria in Halogenated Open-Chain and Six-Membered Carbocyclic Compounds. *Tetrahedron Letters*, 3759-3762.

GLASSTONE S., LAIDLER J. J., EYRING H. (1941) - The Theory of Rate Processes. McGraw-Hill ed., New York.

GROB C. A., WINSTEIN S. (1952) - Mechanismus der Mutarotation von 5,6-Dibromcholestan. *Helv. Chim. Acta*, **35**, 782-802.

HAMILTON W. C. (1964) - Statistic in Physical Sciences. Ronald ed., New York.

KELLIE G. M., RIDDEL F. G. (1974) - Non-Chair Conformations of Six-Membered Rings. *Top. Stereochem.*, **8**, 225-269.

KING J. F., PEWS R. G. (1965) - Reaction Mechanism Studies, (III). Solvent Effects and the Nature of the Transition State in the Diaxial→Diequatorial Rearrangement. *Canad. J. Chem.*, **43**, 847-861.

KIRK D. N., HARTSHORN M. P. (1968) - Steroid Reaction Mechanisms. Elsevier ed., Amsterdam.

PASTO D. J., RAO R. D. (1969) - Conformational Analysis of the 2,5-Di-*t*-butylcyclohexanol System. Evaluation of the Steric Effect of the *t*-Butyl Group in Cyclohexane Chair and Twist-Boat Conformations. *J. Am. Chem. Soc.*, **91**, 2790-2792; AYCARD J. P., BODOT H. (1973) - Intramolecular Interactions. XIV. Gauche Interactions with the *tert*-Butyl Group (Cyclohexane and Cyclohexene Series). *Canad. J. Chem.*, **51**, 741-747.

ZEFIROV N. S., GURVICH L. G., SHASHKOV A. S., KRIMER M. Z., VOROB'EVA E. A. (1976) - Stereochemical Studies. XX. Conformations of 1,2-*trans*-Disubstituted Cyclohexanes. *Tetrahedron*, **32**, 1211-1219.