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THE STERIC COURSE OF IODINE HALOGENIDE ADDITION TO 1-METHYL-4-t-BUTYLCYCLOHEXENE: INFLUENCE OF IODINATING SPECIES

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Abstract—The addition of ICl and IBr to 1-methyl-4-t-butylcyclohexene has been investigated in chloroform and carbon tetrachloride and the distribution of the produced trans-iodohalogenides has been determined by NMR spectroscopy. The stereoselectivity of the addition was found to be determined by both the reversible electrophilic first step and the nucleophilic second step. The higher stereoselectivity of the addition of IBr is interpreted on the basis of the higher softness of bromide ion with respect to chloride ion.

The mechanism of the electrophilic addition of halogens and of pseudohalogenic species of the type X^+Y^- (X = halogen) to alkenes may be summarized in a general way as in Scheme 1.[1]

$$S + XY \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SX^{+} + Y^{-} \xrightarrow{k_2} SXY$$

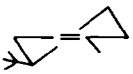
Scheme 1.

It has been accepted[2] for a long time that these reactions occur through an irreversible and rate-determining electrophilic step followed by a fast nucleophilic step that leads to the reaction adducts ($k_2 \gg k_1, k_{-1}$), the stereoselectivity of the reaction being determined by the first step. However, to rationalize a number of results collected[3–11] in the past few years it has been assumed that in some cases a change in the rate-determining step of the reaction occurs, both regio- and stereoselectivity being instead affected by the second step. This possibility has been inferred from the analysis of the reaction product ratios of some additions induced by Br^+ [3,6,9–11] and I^+ [4,5,7,8] to cyclic alkenes substituted in such a way as to give two diastereoisomeric halonium ions which can undergo nucleophilic attack at different rate depending on steric and/or electronic factors and thus lead to stereoisomerically different products.

In pursuing in our research on synthetic applications of electrophilic addition[8,12] to cyclic trisubstituted alkenes, we decided to study the reaction of interhalogens ICl and IBr with the aim of throwing some light on the factors affecting the rate constants of reaction steps in Scheme 1, and therefore the steric course of the reaction.

In this paper we report the results of the addition of ICl and IBr to 1 - methyl - 4 - tert - butylcyclohexene **1** in CCl_4 and $CHCl_3$. Compound **1** has previously been used as a suitable substrate of other electrophilic additions[3,4,7,13] since it undergoes electrophilic attack (see Scheme 2) to the two sides of the molecule at not very different rate to give diastereoisomeric iodonium ions **6** and **7**. These latter are then attacked by nucleophile Y^- at different rate. In fact, anti halonium ion **6** reacts with the nucleophile faster than syn halonium ion **7** since it undergoes the favoured axial attack at a tertiary site which has a carbocationic character higher than the secondary site involved in the corresponding axial attack to **7**. This latter reaction is further slowed by the shielding of the 4-H which is tilted[14] toward the centre of the ring by ~15°. It must be pointed out in addition that the carbocationic character of the tertiary site of **7** also allows to a lesser extent the equatorial attack to this site. Therefore, the dependence of the **3**/(**4** + **5**) ratio on the nucleophilic species Y^- may be used to obtain information on the relative contribution of the single reaction steps in determining the reaction rate. This approximate approach may usefully substitute the more rigorous kinetic study because of difficulty in collecting kinetic data owing to both complexity of the reaction pattern and rather high rate of these reactions.

For comparison purposes, the reaction of 1-methylcyclohexene **2** with ICl and IBr has been examined, too.



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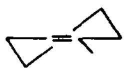

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RESULTS

The reactions carried out occurred in every case in the trans-addition mode affording mixtures of the trans-iodohalogenides shown in Scheme 3. The products were not isolated because structural changes would have occurred in the normal purification procedures. The analysis of the reaction mixtures was achieved by 270 MHz ^{1}H-NMR spectroscopy. The signals attributed to the single iodohalogenides are listed in Table 1 and the distribution of the io-

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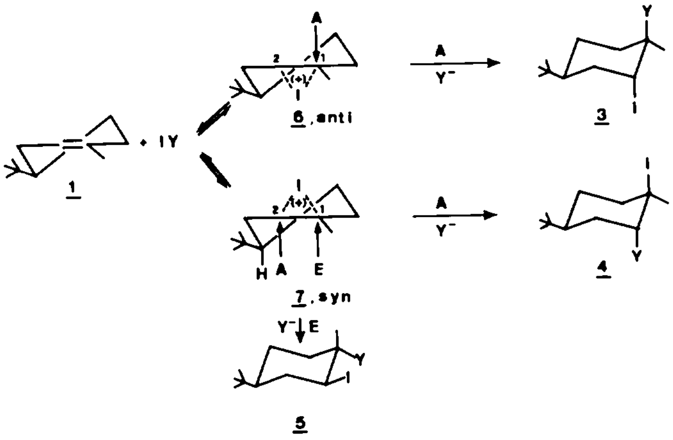
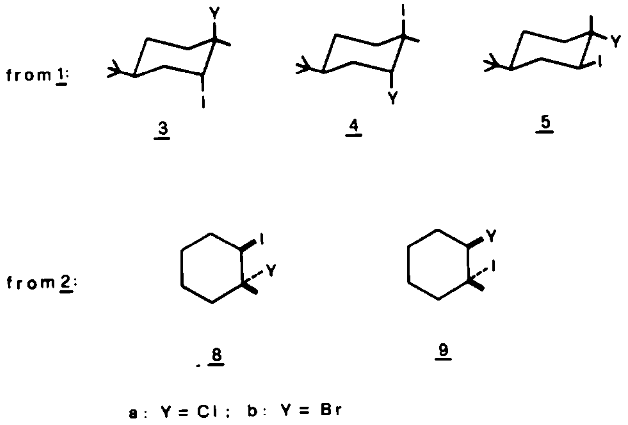


Scheme 2.



Scheme 3.

Table 1. ¹H-NMR (270 MHz) chemical shifts of (1) CH_3 and of (2) C*H*hal protons of the addition products

Compound	$\delta_{(1)CH_3}$	$\delta_{(2)CH\text{hal}}$
3a	1.833 s	4.825 m, $W_{\frac{1}{2}}$ = 6.5 Hz
3b	2.029 s	5.049 m, $W_{\frac{1}{2}}$ = 7.5 Hz
4a	2.224 s	4.700 m, $W_{\frac{1}{2}}$ = 7.5 Hz
4b	2.247 s	4.949 m, $W_{\frac{1}{2}}$ = 7.5 Hz
5a	1.727 s	4.550 dd, $J_{2,3_{eq}}+J_{2,3_{ax}}$ = 17.5 Hz
5b	1.925 s	4.698 dd, $J_{2,3_{eq}}+J_{2,3_{ax}}$ = 17.5 Hz
8a	1.800 s	4.676 m, $W_{\frac{1}{2}}$ = 10.5 Hz
8b	2.018 s	4.926 m, $W_{\frac{1}{2}}$ = 10.5 Hz
9a	2.160 s	4.578 m, $W_{\frac{1}{2}}$ = 10 Hz
9b	2.231 s	4.845 m, $W_{\frac{1}{2}}$ = 9.5 Hz

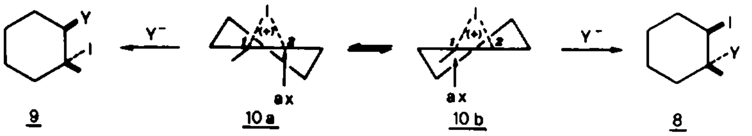
dohalogenides in the reaction mixtures from the addition of ICl and IBr to **1** and **2** is reported in Tables 2 and 3, respectively. The attribution of the NMR signals is based on the fact[15] that the signals of the groups geminal to iodine appear at a lower field than the signals of the equivalent groups geminal to bromine or chlorine, orientation remaining unchanged, and on the fact[16] that the width of the signal of an axial proton is larger than the width of the signal of an equatorial proton. The distribution of the iodohalogen-derivatives in the product mixtures was calculated from the integration of the signals dis-

Table 2. Product distribution, stereoselectivity and regioselectivity of iodohalogenation of 1 - methyl - 4 - tert - butylcyclohexene **1**

XY species	solvent	distribution of iodo halogenides, %			stereoselectivity of the electrophilic attack anti/syn ratio	regioselectivity of the nucleophilic attack C_1/C_2 ratio	
		3	4	5	3/(4+5)	anti	syn 5/4
ICl	CCl_4	52	40	8	1.08	attack to C_1 only	0.20
ICl	$CHCl_3$	48	45	7	0.92		0.15
IBr	CCl_4	58	36	6	1.38		0.17
IBr	$CHCl_3$	59	31	10	1.44		0.32

Table 3. Product distribution and regioselectivity of iodohalogenation of 1-methylcyclohexene **1**

XY species	solvent	distribution of iodo halogenides, %		regioselectivity of the nucleophilic attack C_1/C_2 ratio
		8	9	8/9
ICl	CCl_4	84	16	5.25
ICl	$CHCl_3$	80	20	4.0
IBr	CCl_4	80	20	4.0
IBr	$CHCl_3$	74	26	2.85



Scheme 4.

played by the protons geminal to halogen atoms. The values reported in Tables 2 and 3 are average values from three runs (average error ± 2%).

The possibility that equatorial derivative **5** might be formed by isomerization of **4** rather than di-equatorial opening of halonium ion **7** can be excluded since isomerization is inhibited by both mild reaction conditions (T = 0°) and presence of the methyl group.[17]

Control experiments performed with the presence of a radical inhibitor (2,6 - di - tert - butyl - p - cresol) did not give any change of the product distribution.

DISCUSSION

The use of product distribution as an indication of the influence of the nucleophilic step on the reaction rate of ICl and IBr addition to **1** requires the knowledge of the rate ratio of the electrophilic attack to the two sides of the molecule. This ratio may be assumed to be comparable to the ratio anti/syn = 0.6 between the two epoxides yielded[4] by epoxidation of **1**, which must be considered an irreversible electrophilic reaction.

Now, we have found for **1** that the anti/syn ratio is not only higher but depends on the nature of the mixed halogen. Thus the conclusion must be drawn that for these reactions the condition $k_2 \gg k_1, k_{-1}$ is not verified, as it has previously been found in methoxybromination[3] and in acetoxyiodination[8] of the same substrate.

To determine the influence of the attacking species on the nucleophilic step, we have carried out the same reactions on 1-methylcyclohexene **2**, since for this substrate it may be assumed that the product distribution is not dependent on the electrophilic step. In fact, iodonium ion **10** derived from **2** consists of two conformers which are interconverted at a rate that is very likely much higher than that of the nucleophilic attack. Thus both undergo antiperiplanar opening, **10a** by attack at the C-2 site (secondary) and **10b** by attack to the C-1 site (tertiary). The data reported in

Table 3 show that the expected preference for the attack to the tertiary site is higher in the case of Cl^- than in the case of Br^-.

This trend can also be expected in the case of the reactions of **1**.[18] Thus the stereoselectivity of the reactions of **1** with ICl should be higher than that of the reactions with IBr if a fast-preequilibrium first step occurred, given the reasonable hypothesis that the concentration ratio between iodonium ions **6** and **7** is equal in both additions. As a matter of fact, stereoselectivity is found to be higher (Table 2) in the case of the addition of IBr than in the case of the addition of ICl. Thus, the conclusion must be drawn that in the additions to **1** the electrophilic step is actually reversible but does not constitute a fast preequilibrium, i.e. the condition $k_2 \ll k_1, k_{-1}$ is not verified. Thus the lower stereoselectivity of ICl as compared to that of IBr may be rationalized by assuming that in the case of the addition of IBr the reversion/evolution ratio of the iodonium ions is higher than in the case of the addition of ICl and therefore stereoselectivity is more affected by the nucleophilic step, i.e. by the fact that the tertiary site of **6** is attacked faster than the secondary site of **7**.

A tentative rationalization of this behaviour may be found via the HSAB principle.[19] Iodonium ions **6** and **7**, which in the low polarity solvents we used are very probably ion-paired species, may be considered to behave as ambident electrophiles, where, because of its higher polarizability, the positive iodine constitutes a softer attack site than the partially electron deficient carbon atoms C-1 and C-2. Since Br^- is softer than Cl^-,[20] the former should display a higher preference than the latter in attacking the halogen instead of the carbon sites.[21] Thus the reversion of the halonium ion to alkene as compared to its evolution to the addition products would be faster in the case of IBr than in the case of ICl. The well known[22] reversibility of the addition of I_2 to alkenes may be considered to support this point of view since it may be ascribed to the still greater softness of I^- with respect to Br^- which consequently causes a still more favoured reversion of the iodonium ions.

In addition, since in iodonium ions **6**, **7** and **10** C-2 is softer than C-1 owing to its lower carbocationic character[23] the softer Br^- should attack C-2 more competitively than the harder Cl^-. The found regioselectivity ratios of the opening of **10**, where axial attacks are compared, appear consistent with this expectation (Table 3, last column). This is not the case of the regioselectivity ratios of the opening of **7**. Indeed, in this case one of the attacks is equatorially directed and this introduces a complication factor.[24]

We are currently extending this work to an investigation into the effect of solvent on addition reactions of the type referred to above. The results collected to date also seem to be rationalizable by an application of the HSAB principle. This study will shortly be reported.

EXPERIMENTAL

NMR spectra were recorded with a Bruker WH 270 Fourier transform spectrometer from 10% w/v $CDCl_3$ solutions using TMS as internal standard.

1-Methyl-4-t-butylcyclohexene, prepared[25] from a cis–trans mixture of 1 - methyl - 4 - t - butylcyclohexanol by dehydration with p-TsOH, and commercial (Fluka AG) 1-methylcyclohexene were redistilled and their purity was checked by GLC (1 m steel column, 4 mm id, packed with 15% DC-550 on silanized Chromosorb W, 80–100 mesh; column 120°, injector and detector 250°; N_2 flow: 20 ml/min) shortly before use. Chloroform (C. Erba RPE, > 99%) and carbon tetrachloride (C. Erba RPE, > 99.5%) were filtered through a column of aluminum oxide ("basic", Fluka AG) before use. Commercial (Fluka AG) ICl (95%) and IBr (98%) were used without further purification as 0.15 M solutions in chloroform or carbon tetrachloride. The purity was measured by iodometric titration with sodium thiosulphate. 2,6 - di - t - butyl - p - cresol was purchased from Merck.

Reaction conditions. 0.95 Mmol interhalogen (as a 0.15 M soln in the appropriate solvent) were added dropwise within 2 min to a stirred soln of 1 mmol of alkene in the same solvent (3.5 mL) at 0° in the dark. After the addition was complete, the reaction mixture was stirred for 3 min, washed with 5 N $Na_2S_2O_3$ and water, dried over Na_2SO_4 and evaporated in vacuo at room temp. The reaction product mixtures consisted of unreacted alkene and iodohalogenides and were analyzed by NMR spectroscopy. Iodohalogenide distribution is reported in Tables 2 and 3.

Three runs were carried out for every condition. A fourth run was also carried out in the presence of 2,6 - di - t - butyl - p - cresol (0.2 mmoles) added to alkene.

REFERENCES AND NOTES

[1] G. H. Schmid and D. G. Garratt, *The Chemistry of Double-Bonded Functional Groups* (Edited by S. Patai), Part 2 (suppl. A), Interscience, New York, p. 725 (1977).

[2] R. C. Fahey, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 3, p. 237. Interscience, New York (1968).

[3] D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.* **93**, 6909 (1971).

[4] P. L. Barili, G. Bellucci, B. Macchia, F. Macchia and G. Parmigiani, *Gazz. Chim. Ital.* **101**, 300 (1971).

[5] C. Freppel and J. C. Richer, *Tetrahedron Letters* 2331 (1972).

[6] M. Parrilli, G. Barone, M. Adinolfi and L. Mangoni, *Gazz. Chim. Ital.* **103**, 1265 (1973).

[7] M. Parrilli, M. Adinolfi, V. Dovinola and L. Mangoni, *Ibid.* **104**, 819 (1974).

[8] M. Parrilli, G. Barone, M. Adinolfi and L. Mangoni, *Ibid.* **104**, 835 (1974).

[9] P. L. Barili, G. Bellucci, F. Mariani, I. Morelli and V. Scartani, *J. Org. Chem.* **37**, 4353 (1972).

[10] G. Bellucci, G. Ingrosso, F. Maroni, E. Mastrorilli and I. Morelli, *Ibid.* **39**, 2562 (1974).

[11] G. Bellucci, G. Berti, M. Ferretti, G. Ingrosso and E. Mastrorilli, *Ibid.* **43**, 472 (1978).

[12] L. Mangoni, M. Adinolfi, G. Barone and M. Parrilli, *Gazz. Chim. Ital.* **75**, 377 (1975); M. Parrilli, G. Barone, M. Adinolfi and L. Mangoni, *Tetrahedron Letters* 207 (1976).

[13] M. Parrilli, V. Dovinola and L. Mangoni, *Gazz. Chim. Ital.* **104**, 625 (1974).

[14] C. Altona and M. Sundaralingam, *Tetrahedron* **24**, 925 (1970).

[15] L. M. Jackman and S. Sternhell, *Application of Nuclear Magnetic Resonance in Organic Chemistry*, 2nd Ed., Chap. 3-2. Pergamon Press, Oxford (1969).

[16] Ref. 15, Chap. 4-2.

[17] M. Adinolfi, M. Parrilli, G. Barone, G. Laonigro and L. Mangoni, *Gazz. Chim. Ital.* **107**, 263 (1977).

[18] The hindrance difference between attack on the two conformers of **10** is not the same as that between the two modes of axial attack on **6** and **7** because of the tilting of the H-4 which hinders the attack to **7**. But this tilting may be thought to exert only a slight effect as inferred from an examination of the diequatorial/diaxial product ratio in the addition of bromine to 4 - t - butylcyclohexene.[9]

[19] R. G. Pearson, *J. Am. Chem. Soc.* **85**, 3555 (1963).

[20] Tse-Lok-Ho, *Hard and Soft Acids and Bases: Principles in Organic Chemistry*, p. 6. Academic Press, New York (1977).

[21] Accordingly, soft species I^- and Br^- are found to be halogenophilic, as shown by their preferential catalytic effect on dehalogenation with respect to substitution and dehydrohalogenation (Ref. 20, p. 57; E. Baciocchi and C. Lillocci, *J. Chem. Soc. Perkin II* 38 (1973)).

[22] P. B. D. De la Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, p. 113. Elsevier, Amsterdam (1966).

[23] J. E. Dubois, M. H. Durand, G. Manvier and J. Chretins, *Tetrahedron Letters*. 3911 (1973).

[24] Actually, in other analogous additions in chloroform a surprisingly higher tendency than in carbon tetrachloride of halonium ions to be opened diequatorially has been observed.[10]

[25] A. Lebel and G. G. Ecke, *J. Org. Chem.* **30**, 4316 (1965).