[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Stereochemistry of the Non-radical Halogen Exchange between Active *sec*-Octyl Iodide and Chlorine[1]

BY ELIAS J. COREY AND WILLIAM J. WECHTER

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The reaction of optically active *sec*-octyl iodide with chlorine or iodine monochloride affords both inverted and non-inverted *sec*-octyl chloride, with inversion invariably predominating. The amount of inversion is greater with iodine monochloride than with chlorine and is greater in polar solvents than in non-polar solvents. The results of this study are consistent with a termolecular mechanism which has been proposed previously for this type of reaction on the basis of kinetic studies.

One of the most unusual of all displacement reactions at a saturated carbon atom is that in which an alkyl bromide or iodide is transformed by treatment with molecular chlorine into the corresponding alkyl chloride.[2-5]

$$RX + Cl_2 \longrightarrow RCl + XCl$$
$$X = I, Br$$

Although the reaction has little preparative value, it is of special interest theoretically and, as a consequence, has recently attracted considerable attention.[6-11]

In addition to these reactions in which alkyl chlorides are formed, similar exchanges are known of bromine for iodine and radioiodine for iodine. There appear to be at least three mechanisms by which halogen exchange of this type can occur. (1) a non-radical process involving reaction between a molecule of halogen and an alkyl halide or alkyl halide–halogen complex[6,7]; (2) a thermal or photochemical exchange with atomic halogen which proceeds *via* free radical intermediates[8,11]; (3) an exchange unique to allylic halides which involves halogen molecules participating in displacement by a cyclic process.[11,12]

At low temperatures and in the absence of light the formation of an alkyl chloride from an iodide with chlorine occurs without appreciable intervention of the atom-radical mechanism (2) which requires much more drastic conditions. It is this low temperature reaction, herein called the "normal exchange" reaction, which is least understood and which forms the subject of the present paper.

The normal halogen exchange has been studied kinetically by Andrews and Keefer[6,7] who have concluded that the reaction between iodine monochloride and isopropyl iodide involves attack of iodine monochloride on a 1:1 iodine monochloride–isopropyl iodide complex.[13] We have investigated the stereochemistry of normal halogen exchange at an asymmetric carbon in order to gain further information concerning this process.

Results

The reaction chosen for study was the transformation of optically active *sec*-octyl iodide to *sec*-octyl chloride by means of chlorine and also iodine monochloride. The conversions were carried out by mixing the reactants in solvent at *ca.* −70° (Dry Ice–acetone bath) in the absence of direct light and allowing the usually rapid reaction to proceed at low temperatures. The *sec*-octyl chloride was purified by suitable washing and fractional distillation through a semi-micro column and was usually obtained in a yield of 30–50%. From the optical rotation of the chloride isolated $[\alpha^{Cl}]_D$, the rotation of the starting iodide $[\alpha^{I}]_D$ and the rotations of optically pure *sec*-octyl iodide $[\alpha_0{}^{I}]_D$ and *sec*-octyl chloride $[\alpha_0{}^{Cl}]_D$ the quantity k_i/k_r, the ratio of the rate of inversion to retention, was calculated for each run. The relationships used are

$$\frac{k_i}{k_r} = \frac{X}{1 - X};\; X = {}^1/_2 \left[\frac{[\alpha^{Cl}]_D[\alpha_0{}^{I}]_D}{[\alpha_0{}^{Cl}]_D[\alpha^{I}]_D} + 1\right]$$

where X is the fraction of chloride molecules formed with inversion.

Before carrying out the exchange experiments it was first determined that the rotation of active *sec*-octyl iodide is not changed by treatment with iodine under the reaction conditions and that the rotation of active *sec*-octyl chloride is unaffected by treatment with chlorine. Furthermore, it was shown that the halides are optically stable under the conditions involved in the purification steps including washing with concentrated sulfuric acid. These observations rule out the possibility of racemization of the starting material or product and permit the assumption that changes in configuration at the asymmetric carbon atom take place only during the exchange reaction.

Although the rotation of optically pure *sec*-octyl chloride was known with a high degree of certainty[14] ($[\alpha]_D$ 36.14°), the rotation of *sec*-octyl iodide was not and had to be established. In our experience the best recorded preparation of optically active *sec*-octyl iodide is that of Berlack and

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[1] Taken from the A.B. thesis of William J. Wechter, University of Illinois, June, 1953.

[2] A. Geunther, *Ann.*, **123**, 124 (1861).

[3] C. Friedel, *ibid.*, **135**, 206 (1865).

[4] J. Thiele and W. Peter, *Ber.*, **38**, 2842 (1905).

[5] C. Willgerodt, "Die organischen Verbindungen mit Mehrwertigen Jod," F. Enke, Stuttgart, 1914.

[6] R. M. Keefer and L. J. Andrews, THIS JOURNAL, **75**, 543 (1953).

[7] R. M. Keefer and L. J. Andrews, *ibid.*, **76**, 253 (1954).

[8] R. A. Ogg, Jr., and M. Polanyi, *Trans. Faraday Soc.*, **31**, 482 (1935).

[9] J. H. Sullivan and N. Davidson, *J. Chem. Phys.*, **19**, 143 (1951).

[10] R. M. Noyes, THIS JOURNAL, **70**, 2614 (1948).

[11] D. J. Sibbett and R. M. Noyes, *ibid.*, **75**, 761, 763, 767 (1953).

[12] This reaction appears analogous to the hydrogen–halogen exchange observed in the low temperature halogenation of olefins such as isobutylene, R. T. Arnold and W. W. Lee, *ibid.*, **75**, 5396 (1953); W. Reeve and D. H. Chambers, *ibid.*, **73**, 4499 (1951).

[13] Recent work (R. M. Keefer and L. J. Andrews, *ibid.*, **74**, 1891 (1952)) indicates that 1:1 alkyl iodide–halogen complexes occur in solution at room temperature as well as at low temperatures (ref. 3). Equilibrium constants for the formation of several of these complexes have been measured.

[14] H. Brauns, *Rec. trav. chim.*, **65**, 799 (1946).

Gerrard[15] using phosphorus triiodide–pyridine as the reagent. The iodide obtained by this method is free of structural isomers, and is essentially optically pure. However, because of the occurrence of some racemization by interaction of active iodide with pyridinium iodide the *sec*-octyl iodide produced is of variable rotation depending on the length of the preparative run and also the temperature. By working carefully iodide of rotation $[\alpha]^{30}_D$ +52.7° was obtained. That this was essentially optically pure was shown by its conversion with a fifty-fold excess of potassium thiocyanate in methanol to *sec*-octyl thiocyanate of rotation −67.0°. The rotation of optically pure thiocyanate, made from active (+)*sec*-octyl tosylate is −67.68° (corrected for optical purity of the sample of alcohol from which the tosylate was derived).[16]

The values of k_i/k_r for runs with chlorine in different solvents are listed in Table I; the results of similar runs with iodine monochloride are given in Table II.

TABLE I

REACTION OF OPTICALLY ACTIVE *sec*-OCTYL IODIDE WITH EXCESS CHLORINE AT *ca.* −70°

Run	Medium	k_i/k_r
4	Methylene chloride	1.5
2	Methylene chloride[a]	1.9
7	Methylene chloride[b]	2.3
5	Methylene chloride–ether (1:1)	1.5
20	Pentane	1.6
6	Ethyl acetate	2.3
21	Methylene chloride–pyridine[b]	5.0
13	Methylene chloride–methanol (3:1)	5.8
14	Methylene chloride–methanol (3:1)–hydrogen chloride (4 *M*)	10.25
8	Methylene chloride–hydrogen chloride (14 *M*)	1.5

[a] Run made with slow addition of chlorine. [b] Run made at 0°.

TABLE II

REACTION OF OPTICALLY ACTIVE *sec*-OCTYL IODIDE WITH EXCESS IODINE MONOCHLORIDE AT *ca.* −70°

Run	Medium	k_i/k_r
19	Methylene chloride	2.1
15	Methylene chloride–iodine (sat.)[a]	2.2
16	Methylene chloride–methanol (3:1)	6.5

[a] Slow addition of iodine monochloride.

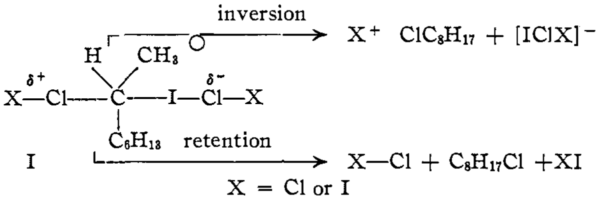
In no case was a stereospecific substitution observed and in no case was a preponderance of retention over inversion obtained. The amount of inversion is somewhat greater when iodine monochloride is the reagent than when chlorine is used. For this reason in those runs in which chlorine was used a large excess was employed and was added all at once. Slow addition of chlorine afforded more inversion than immediate addition. The amount of inversion also changes with the solvent used and can be correlated roughly with polarity and/or basicity.

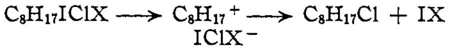
In the runs made in methanol as solvent some methyl *sec*-octyl ether (between 20 and 40%) was formed along with *sec*-octyl chloride. This was detected from the infrared spectrum of the distilled but unfractionated reaction product by comparison with the infrared spectra of the pure ether and the pure chloride.

The presence of hydrogen chloride had little effect on the stereochemical outcome of the reaction in methylene chloride solution, but caused much more inversion in methanol solution.

Discussion

If the most important process by which normal halogen exchange takes place is a termolecular one as is indicated by kinetic studies,[6,7] it follows from the present work that the termolecular complex should be represented by I and must be capable of decomposing to give either inverted or non-inverted chloride. Our results are consistent with this termolecular mechanism, but do not, when taken alone rigorously exclude other mechanisms, *e.g.*, the ionization of the alkyl iodide–halogen complex to give a carbonium ion–trihalide ion-pair intermediate





$$C_8H_{17}IClX \longrightarrow \underset{IClX^-}{C_8H_{17}^+} \longrightarrow C_8H_{17}Cl + IX$$

However, several of our observations seem to be in better agreement with the termolecular process than with mechanisms involving a carbonium ion or ion-pair intermediate. The increase in the ratio k_i/k_r in going from chlorine to iodine monochloride as the reagent is only to be expected from the termolecular mechanism because the chlorine atom of iodine monochloride should be considerably more nucleophilic than a chlorine atom in molecular chlorine. Such an effect would not be predicted for the reaction *via* the carbonium ion.

The formation of inverted chloride from I involves further separation of charge and generation of Cl^+ or I^+ and ICl_2^- or I_2Cl^- ions, whereas the formation of non-inverted chloride does not. Solvents which can solvate these ions should afford more inversion than the non-polar solvents. Such an effect was observed as is indicated from the runs using ethyl acetate, pyridine and methanol as solvents. If a carbonium ion mechanism were operative to an appreciable extent the value of k_i/k_r would be expected to approach unity in the more polar solvents in which the ion should be formed more readily and should be more nearly racemized.

Apparently methanol and molecular chlorine are roughly comparable in nucleophilicity since both *sec*-octyl chloride and methyl *sec*-octyl ether are formed in the solvent methanol. Chloride ion in methanol appears to be more nucleophilic than chlorine (Table I, runs 13, 14), whereas molecular hydrogen chloride appears to be much less nucleophilic than chlorine (Table I, runs 4, 8).

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[15] M. C. Berlack and W. Gerrard, *J. Chem. Soc.*, 2309 (1949).

[16] J. Kenyon, H. Phillips and V. P. Pitman, *ibid.*, 1072 (1935).

It is not possible at present to assign unequivocally an order of electrophilicity on halogen or nucleophilicity on carbon to all the halogens and interhalogen compounds. It can be concluded from the relative stability of active *sec*-octyl iodide in the presence of iodine, as well as from runs made with iodine monochloride in the presence of iodine that iodine is much less nucleophilic on carbon than iodine monochloride which is more nucleophilic than molecular chlorine. The optical stability of active *sec*-octyl chloride in the presence of chlorine is probably due to the lack of complex formation between the chloride and chlorine.

Experimental

Materials.—*d*,**1-2-Octanol** was resolved by the customary procedure[17] and purified by fractional distillation, b.p. 88–89° (23 mm.), $n^{21.5}\text{D}$ 1.4250 (lit.[18] $n^{20}\text{D}$ 1.4244), $[\alpha]^{25}\text{D}$ ± 8.99 to $\pm 9.9°$ (ethanol) (lit.[16] $[\alpha]^{20}\text{D}$ 9.9°).

sec-**Octyl iodide** was prepared by the method of Berlack and Gerrard,[15] $n^{20}\text{D}$ 1.4880, $[\alpha]^{30}\text{D}$ ± 23.7 to $\pm 52.7°$ (carbon tetrachloride), b.p. 49–50° (1.4 mm.) [lit.[15,19] $[\alpha]^{18}\text{D}$ $\pm 56.8°$, b.p. 98–100° (18 mm.), $n^{25}\text{D}$ 1.4263].

sec-**Octyl chloride** was made according to the procedure of McKenzie and Tudhope,[20] b.p. 62° (14 mm.), $n^{19.3}\text{D}$ 1.4270, $[\alpha]^{25}\text{D}$ $\pm 24.2°$ (ether) [lit. b.p. 79 ($\sim$16 mm.).[21] $[\alpha]^{20}\text{D}$ (max.) $\pm 36.14°$[14]]. The chloride exhibited characteristic absorption in the infrared at 690 cm.$^{-1}$ (strong, sharp, C–Cl stretching).

Methyl *sec*-**octyl ether** was prepared by the reaction of methyl iodide with potassium *sec*-octoxide in refluxing ether. It was purified by filtration through a column of activated alumina (in pentane) and subsequent distillation, b.p. 57.5° (13 mm.), $n^{20}\text{D}$ 1.4083 [lit.[21] b.p. 76–77° (44 mm.), $n^{25}\text{D}$ 1.4212]. The ether showed characteristic C–O stretching absorption in the infrared at 1090–1100 cm.$^{-1}$ and no trace of alcoholic hydroxyl.

(−)*sec*-**Octyl Thiocyanate.**—A solution of one gram (0.00415 mole) of (+)*sec*-octyl iodide ($[\alpha]^{34}\text{D}$ +52.7°) and 20 g. of potassium thiocyanate in 150 ml. of methanol was heated to reflux overnight. The solvent was removed under reduced pressure and the residue was treated with water and extracted with pentane–methylene chloride (40:1). The pentane solution was concentrated and the residue was fractionally distilled through a semi-micro column to give 42% (−)*sec*-octyl thiocyanate, b.p. 119–120° (18 mm.). $n^{22}\text{D}$ 1.4630, $[\alpha]^{34}\text{D}$ −60.8° (ethanol) [lit.[16] b.p. 119–120° (20 mm.), $n^{17}\text{D}$ 1.4651, $[\alpha]^{20}_{5893}$ −64.68° (ethanol) for a sample obtained *via* the tosylate from *sec*-octyl alcohol, $[\alpha]^{20}_{5893}$ +9.48°].

General Procedure for Exchange Reactions.—To a solution of active *sec*-octyl iodide in the solvent or solvent mixture, chilled under anhydrous conditions in a Dry Ice–acetone bath, was added rapidly a cold solution of excess chlorine (or iodine monochloride) in the particular solvent (final concn. ~10 *M*). After storage in the dark at cooling-bath temperature for 5–15 minutes, the reaction mixture was allowed to warm to about 0° and then washed successively with 10% aqueous sodium bisulfite and water. The solution of the chloride was then diluted with pentane, washed successively with concentrated sulfuric acid and water, dried and distilled fractionally to obtain a sample of pure chloride for the determination of optical rotation. In some cases the product was first isolated without washing with sulfuric acid by total distillation for infrared analysis. The yield of chloride, b.p. 60–62° (14 mm.), $n^{20}\text{D}$ 1.4280–1.4310, varied from 30 to 50% depending on the efficiency of the isolation. The crude chloride obtained from the exchange runs using methanol as solvent without a sulfuric acid washing contained methyl *sec*-octyl ether as an impurity as determined from the infrared spectrum. The pure chloride could be obtained by removal of the ether using a sulfuric acid wash.

URBANA, ILLINOIS

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[17] "Organic Syntheses," Coll. Vol. I. John Wiley and Sons, Inc., New York, N. Y., 1943, p. 418.

[18] J. W. Brühl, *Ann.*, **203**, 29 (1880).

[19] P. A. Levene and A. Rothen, *J. Biol. Chem.*, **115**, 415 (1936).

[20] A. McKenzie and T. M. A. Tudhope, *ibid.*, **62**, 561 (1924–1925).

[21] J. Kenyon and R. A. McNicol, *J. Chem. Soc.*, **123**, 14 (1923).

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Phosphate Anhydrides of Amino Acids

BY A. KATCHALSKY AND M. PAECHT

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A method for the synthesis of free phosphate anhydrides of leucine, aspartic and glutamic acid is described. The silver salt of carbobenzyloxy amino acid is condensed with dibenzyl chlorophosphate and the carbobenzyloxy and benzyl groups are split off by a stream of dry hydrogen bromide. The free phosphate anhydrides of these amino acids are obtained as heavy oils of 70–90% purity. The substances are extremely hygroscopic and reactive. They react spontaneously with alcohols to give esters; with amines, to give amides; and with hydroxylamine, to give hydroxamic acids suitable for analytical determination. In aqueous solution at room temperature, the phosphate anhydride of leucine polymerizes spontaneously to produce polypeptides of 3–20 amino acids.

Introduction

For the past twenty years reactive intermediates in the biosynthesis of proteins have been sought[1] which would condense, under conditions found in the living cell, to form polypeptides and proteins.

Lipmann has suggested[2] that these intermediates are the mixed anhydrides of phosphoric and amino acids. Several attempts have therefore been made to synthesize such compounds, which could serve as models for the reactive substances that enable the peptide bond formation. Hitherto, however, the compounds have proved very unstable and could not, therefore, be isolated. Some of the more stable derivatives of the phosphate anhydrides have been prepared by Chantrenne.[3]

The phosphate anhydrides of glycine and alanine were synthesized in this laboratory[4] as follows.

The silver salt of N-carbobenzyloxy amino acid was coupled with dibenzyl chlorophosphate[5] and the product treated with anhydrous hydrogen bromide, analogous to the method of Ben-Ishai and

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[1] (a) H. Borsook and J. W. Dubnoff, *J. Biol. Chem.*, **168**, 397 (1947); (b) P. P. Cohen and R. W. McGilvery, *ibid.*, **171**, 121 (1949); (c) G. V. Schulz, *Naturwissenschaften*, **37**, 196 (1950); (d) H. Waelsch, *Advances in Enzymol.*, **13**, 275 (1952).

[2] F. Lipmann, *Advances in Enzymol.*, **1**, 154 (1941).

[3] (a) H. Chantrenne, *Nature*, **160**, 603 (1947); (b) H. Chantrenne, *Biochim. Biophys. Acta*, **2**, 286 (1948); (c) H. Chantrenne, *Nature*, **164**, 576 (1949).

[4] A. Katchalsky and M. Paecht, *Bull. Res. Counc. of Israel*, **2**, 312 (1952).

[5] F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).