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STEREOCHEMISTRY OF NUCLEOPHILIC DISPLACEMENT REACTIONS AT THE THIOPHOSPHORYL CENTRE. CHLORIDE-CHLORIDE EXCHANGE AT THE ASYMMETRIC PHOSPHORUS ATOM IN O-ETHYL ETHYLPHOSPHONOCHLORIDOTHIONATE

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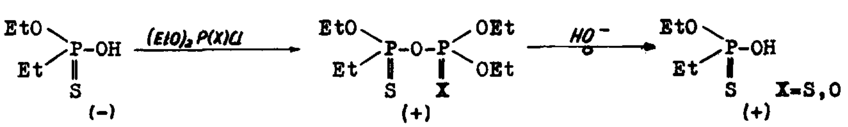
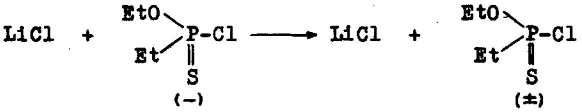
Recent investigations /1-4/ on the stereochemistry of nucleophilic substitution at the thiophosphoryl centre gave a strong support to the view that bimolecular substitution by anions involves inversion of configuration. In a previous work /4,5/ from this Laboratory the inversion mechanism was demonstrated by transformation of one enantiomer of O-ethyl ethylphosphonothioic acid into another by a series of two reactions of which only one broke a bond at the asymmetric phosphorus atom.



Inversion must have occurred during the nucleophilic attack of the hydroxyl anion upon the thiophosphoryl group of the corresponding thiopyrophosphonate system.

In order to extend the previous results to other leaving groups and nucleophiles a study of chloride-chloride exchange at the thiophosphoryl centre was undertaken. A suitable model for such studies, O-ethyl ethylphosphonochloridothionate, has recently been obtained by stereospecific synthesis from O-ethyl ethylphosphonothioic acid by action of phosphorus pentachloride /2,3/. Direct proof of inversion at the thiophosphoryl centre was now provided by the demonstration that the rate of exchange between radioactive chloride anion and the O-ethyl ethylphosphonochloridothionate is equal to the rate of inversion, e.g. to half the rate of racemisation. This method, successfully applied in carbon chemistry /6,7/, has been recently extended to phosphorus /8/ and silicone /9/.

Racemisation of (-)O-Ethyl ethylphosphonochloridothionate



The rate of racemisation of O-ethyl ethylphosphonochloridothionate, $[\alpha]_D^{25}$ -63.8°, /0.2 M/ by lithium chloride /0.02 M/ in acetone[*] was measured with a photoelectric Perkin-Elmer 141 polarimeter /sensitivity ±0.001°/[†] at 25° and 30°C. Readings were taken every 10 min. The pseudo-unimolecular rate constant was calculated from the equation $k_{rac.} = /\ln \frac{\alpha_0}{\alpha_t}/t$ /where α_0 and α_t are the optical rotations at t=0 and time t, respectively/ by assuming that each displacement involves stereochemical inversion. The rate constans were obtained graphically. The results are summarised in table I.

TABLE I

Rate-constant data for racemisation of Et/EtO/P/S/Cl, /0.2 M/ in acetone with lithium chloride /0.02 M/

Temp. °C	$k_{rac.}$ sec. $^{-1}$	$k_{rac.}$ $l \cdot sec.^{-1} \cdot mole^{-1}$	$k_{inv.}$ $l \cdot sec.^{-1} \cdot mole^{-1}$
25	$3.6 \cdot 10^{-5}$	$1.8 \cdot 10^{-3}$	$9.0 \cdot 10^{-4}$
30	$5.8 \cdot 10^{-5}$	$2.9 \cdot 10^{-3}$	$1.4 \cdot 10^{-3}$
30	$5.3 \cdot 10^{-5}$	$2.6 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$

Isotopic exchange

The radioactive lithium chloride was prepared from ^{36}Cl-labelled hydrochloric acid and lithium hydroxide, and the crystalline product was heated at 130°C for 3 hours. The isotopic exchange experiments were carried out with a reacting mixture of Li^{36}Cl /0.02 M/ and O-ethyl ethylphosphonochloridothionate /0.2 M/ in acetone kept in a closed glass vessel in a thermostat /± 0.1°C/. In order to separate the two reactants, 2 ml aliquots of the mixture were shaken with a mixture of 3 ml carbon tetrachloride and 13 ml water. In independent experiments it was shown that this procedure enables complete and fast separation of lithium chloride and the O-ethyl ethylphosphonochloridothionate. The ^{36}Cl-activity was counted with a glass thin-wall Geiger-Mueller counter, the results being corrected for the different densities of organic and inorganic fractions. Values of the rate constant for the exchange reaction were calculated from $k_{ex.} = \ln 2/(a+b)\, t_{1/2}$, where a and b are the concentrations of lithium chloride and organic chloride. The half-time of the exchange, $t_{1/2}$, was determined graphically from the function ln/1-F/ versus time, where F is the ratio of the organic phase after time t to that after the establishment of equilibrium. In table II the corresponding values of the rate constants are listed, each value being the mean from two or three determinations. The activation energy of radiohalogen exchange calculated from the date in table II is 13.5 Kcal/mole.

TABLE II

Rate-constant data for radiochlorine exchange between Et/EtO/P/S/Cl /0.2 M/ and Li^{36}Cl /0.02 M/ in acetone.

Temp. °C	$k_{ex.}$ $l \cdot sec.^{-1} \cdot mole^{-1}$
20	$6.2 \cdot 10^{-4}$
30	$1.3 \cdot 10^{-3}$
40	$2.8 \cdot 10^{-3}$

The equality of the rate constants $k_{inv.}$ and $k_{ex.}$ proves that this reaction proceeds stereospecifically with inversion of configuration. This result is a direct consequence of the stereochemistry of the transition state involved. The transition state /or intermediate/ is assumed to be of a form a trigonal bipyramid. Such a transition state has been postulated for other nucleophilic substitution reactions at phosphorus which proceed with inversion of configuration /10/. Although the question as to whether the entering and leaving groups occupy axial or basal positions is not fully settled /8,11,12/, the former suggestion seems preferable on general chemical grounds /13/.

The results of Hudson and Green /8/ and ours on the exchange reactions at the phosphoryl and thiophosphoryl centres are indicative of inversion as being the rule for the bimolecular mechanism of S_N2-P substitution.

REFERENCES

/1/. M. Green, R.F. Hudson, J. Chem. Soc., 1963, 3883.

/2/. J. Michalski, M. Mikołajczyk, Chem. and Ind., 1964, 661.

/3/. J. Michalski, M. Mikołajczyk, Chem. Comm., 1965, 35.

/4/. J. Michalski, M. Mikołajczyk, J. Omelańczuk, Tetrahedron Letters, 1965, 1779.

/5/. J. Michalski, M. Mikołajczyk, B. Młotkowska, unpublished results concerning alkaline hydrolysis of thiopyrophosphonate, X=O.

/6/. E.D. Hughes, F. Juliusburger, S. Masterman, B. Topley, J. Weiss, J. Chem. Soc., 1935, 1525; 1936, 1173.

/7/. W.A. Cowdrey, E.D. Hughes, T.P. Nevell, C.E. Wilson, J. Chem. Soc., **1938**, 209.

/8/. M. Green, R.F. Hudson, J. Chem. Soc., **1963**, 541.

/9/. L.H. Sommer, F.O. Stark, K.W. Michael, J. Am. Chem. Soc., **86**, 5683(1964).

/10/. R.F. Hudson, M. Green, Angew. Chem., **75**, 47(1963).

/11/. P.C. Haake, F.H. Westheimer, J. Am. Chem. Soc., **83**, 1102(1961).

/12/. N.K. Hamer, J. Chem. Soc., **1965**, 2731.

/13/. R.S. Drago, V.A. Mode, J.G. Kay, D.L. Lydy, J. Am. Chem. Soc., **87**, 5010(1965).

*/ Commercially pure acetone was refluxed with potassium permanganate. It was then distilled and dried over calcium sulphate. Further purification involved the formation and subsequent decomposition of acetone-sodium iodide complex. Resulting acetone was fractionated through a column.

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