Unexpected Opposite Stereochemistries and Different Mechanisms of Nucleophilic Substitution Reactions of Homochiral *tert*-Butylphenylthiophosphinoyl Chloride and Bromide

Jan Omelańczuk and Marian Mikolajczyk*

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź Sienkiewicza 112, Poland

Reactions of ethylmercapto (ethylsulfanyl) anion with homochiral (+)-(*S*)-*tert*-butylphenylphosphinochloridothionate **2** and (−)-(*S*)-*tert*-butylphenylphosphinobromidothionate **3** proceed with inversion and retention at phosphorus, respectively, as a consequence of different reaction mechanisms; the stereoretentive reaction with bromide **3**, in contrast to the direct nucleophilic substitution at phosphorus in chloride **2**, is a two-step process involving in the first step nucleophilic attack of EtS^- at the electropositive bromine atom.

In the majority of cases, nucleophilic substitution reactions at the chiral tetracoordinate phosphorus atom[1] are accompanied by inversion of configuration. It is customary to consider that such reactions occur synchronously by an S_N2-P mechanism involving a transition state, or stepwise by an addition–elimination (A–E) mechanism involving a trigonal bipyramidal phosphorane intermediate, with the entering nucleophile and departing leaving group in apical positions, that decomposes before any ligand reorganization (pseudorotation) takes place. On the other hand, the retention of configuration at phosphorus observed in some of these reactions, often in five-membered cyclic systems, is rationalized in terms of an A–E mechanism and formation of a phosphorane intermediate, having the apical–equatorial arrangement of the nucleophile and leaving group, that undergoes a single pseudorotation followed by decomposition of a newly formed phosphorane intermediate.

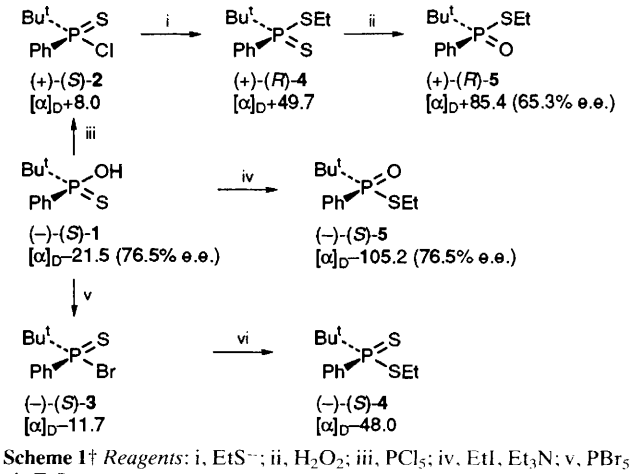
Here we report that two closely related homochiral phosphorus halogenides, *tert*-butylphenylphosphinochloridothionate **2** and *tert*-butylphenylphosphinobromidothionate **3**, react with the ethylmercapto (ethylsulfanyl) anion with inversion and retention of configuration at phosphorus, respectively, and that this contrasting stereochemical outcome is due to completely different mechanisms operating in these two very similar reactions.

Both chiral halogenides (+)-**2** and (−)-**3** were obtained from a common precursor, (−)-(*S*)-*tert*-butylphenylphosphinothioic acid **1**,[2] *via* reaction with phosphorus pentachloride and phosphorus pentabromide, respectively. Unexpectedly, the reaction of sodium ethanethiolate with (+)-**2** and (−)-**3**, which we believed to have the same chirality at phosphorus, gave the enantiomeric (+)- and (−)-*S*-ethyl *tert*-butylphenylphosphinodithioates **4**. Therefore, in order to elucidate the stereochemical course of the reaction with the mercapto anion, it was necessary to establish firmly the configuration of both substrates. At first, the absolute configuration *R* was assigned to (+)-**4**, based on its stereoretentive oxidation by hydrogen peroxide[3] to (+)-*S*-ethyl *tert*-butylphenylphosphinothiolate **5**. The latter has *R* chirality at phosphorus because ethylation of (−)-(*S*)-**1**, a reaction which does not affect any bond attached to the chiral phosphorus atom, afforded the thioloester (−)-(*S*)-**5**. All the reactions discussed above are summarized in Scheme 1.

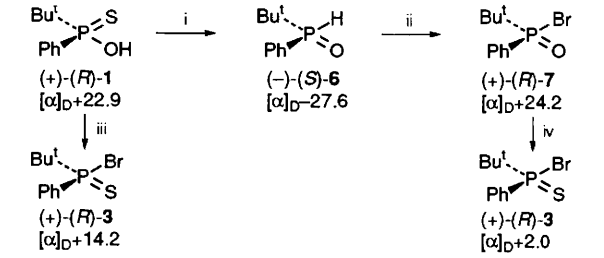
Since the reaction of chiral phosphorus monothioacids with phosphorus pentachloride is known to occur with inversion of configuration at phosphorus,[4] and in the reaction sequence **1** → **2** → **4** → **5** forming antipodal diligostatic cycle[5] there is one ligand metathesis, it is most reasonable to assume that the reaction of (+)-**2** with ethanethiolate occurs with inversion of configuration.

In the next step, the configurational relationship between (−)-**1** and (−)-**3** was determined. A reasonable assumption that bromination of the thioacid **1** proceeds with inversion‡ was unequivocally confirmed by chemical correlation, shown in Scheme 2. All the reactions presented there, *i.e.* reduction of (+)-(*R*)-**1** with Raney nickel,[6] bromination of the anion of (−)-*tert*-butylphenylphosphine oxide **6**[7] and the P=O → P=S exchange[8] of (+)-*tert*-butylphenylphosphinobromidate **7**,§ occur with retention at phosphorus. Therefore, taking into account one ligand metathesis in this cycle, one can conclude that (+)-bromide **3** has *R* configuration and is formed from **1** and PBr_5 with inversion. Consequently, the reaction of (−)-**3** with ethanethiolate should occur with retention.

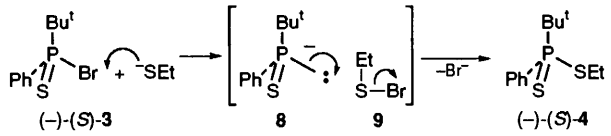
There is no doubt that inversion in the reaction of (+)-**2** with EtS^- is due to a direct nucleophilic substitution at phosphorus. Although the unexpected retention observed in the reaction with (−)-**3** may be due to the operation of an A–E mechanism, analysis of the structural features of both reactants and some additonal experiments incline us to propose a different reaction mechanism in this case. Since direct nucleophilic attack at phosphorus is hindered by the bulky *tert*-butyl group, and bromine is a highly polarizable (soft) atom that acts in some reactions as a so-called 'electropositive halogen',[12] the nucleophilic attack of the soft mercapto anion can be directed towards bromine and not phosphorus.¶ Such a reaction should result in the formation of two very reactive intermediates, *tert*-butylphenylphosphine sulfide anion **8** and ethylsulfenyl bromide **9**, which in the second, fast step should give the dithiophosphinate **4**. The stereochemical outcome of this two-step reaction sequence should be retention at phosphorus, as shown in Scheme 3.



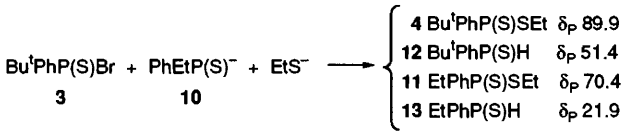
Scheme 1† *Reagents*: i, EtS^-; ii, H_2O_2; iii, PCl_5; iv, EtI, Et_3N; v, PBr_5; vi, EtS^-



Scheme 2 *Reagents*: i, Raney Ni; ii, BuLi, then Br_2; iii, PBr_5; iv, B_2S_3, toluene



Scheme 3



Scheme 4

A convincing argument in support of the above proposed reaction mechanism‖ was provided by the experiment in which the reaction of bromide **3** with EtS^- was carried out in the presence of equimolar amounts of ethylphenylphosphine sulfide anion **10** (Scheme 4). The reaction products were identified using ^{31}P NMR and MS. Interestingly, *S*-ethyl ethylphenylphosphinodithioate **11** was formed as a major product and was isolated from the reaction mixture in a pure state by preparative TLC. The formation of **11** may be best explained by competitive reaction of the anion **10** with ethyl sulfenyl bromide **9** that is generated from **3** and thiolate anion.

In summary, we have demonstrated that a combination of steric hindrance at phosphorus and the presence of polarizable halogens bonded to phosphorus causes a dramatic change in stereochemistry and mechanism of nucleophilic substitution reaction at the phosphorus centre.

Received, 23rd May 1994; Com. 4/03081H

Footnotes

† Enantiomerically pure (+)-(*R*)-**1**, $[\alpha]_D$ +28.1 was obtained by Harger.[2]

‡ In earlier studies we have demonstrated that the reaction of chiral *O*-ethyl ethylphosphonothioic acid with triphenylphosphine dibromide occurs with inversion.[10]

§ This reaction represents an example of the P=O→P=S exchange in a chiral phosphoryl halide. However, the low rotation value of (+)-(*R*)-**3** obtained indicates that substantial racemization accompanies the exchange, probably due to the instability of both halogenides under reaction conditions.[9]

¶ Recently, Kawashima, Iwanaga and Okazaki[11] reported a similar observation that *Se*–benzyl *tert*-butylphenylphosphinoselenoate underwent nucleophilic attack by phenyllithium not at phosphorus but at selenium.

‖ The considerable difference in reactivity between chloride **2** and bromide **3** towards EtS^- is probably also due to different reaction mechanisms. Thus, the reaction of **2** with EtS^- must be heated under reflux for 30 h in DME for completion, while the same reaction with **3** is completed within 3 h (^{31}P NMR assay).

References

1 For review, see: C. R. Hall and T. D. Inch, *Tetrahedron*, 1980, **36**, 2059.
2 M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 2*, 1978, 326; 1980, 1505.
3 N. J. De'ath, D. J. Smith and S. Trippett, *J. Chem. Soc., Chem. Commun.*, 1971, 714.
4 M. Michalski and M. Mikołajczyk, *Chem. Ind.*, 1964, 661; *Tetrahedron*, 1966, **22**, 3055; M. Mikołajczyk and M. Leitloff, *Russ. Chem. Rev.*, 1975, **44**, 670; Z. Skrzypczyński and J. Michalski, *J. Org. Chem.*, 1988, **53**, 4549.
5 D. C. Garwood and D. J. Cram, *J. Am. Chem. Soc.*, 1970, **92**, 4575.
6 L. P. Reiff and H. S. Aaron, *J. Am. Chem. Soc.*, 1970, **92**, 5275; J. Michalski and Z. Skrzypczyński, *J. Organomet. Chem.*, 1975, **97**, C31.
7 B. Krawiecka and E. Wojna-Tadeusiak, *J. Chem. Soc., Perkin Trans. 2*, 1990, 301.
8 J. Omelańczuk and M. Mikołajczyk, *Tetrahedron*, 1971, **27**, 5587; B. E. Maryanoff, R. Tang and K. Mislow, *J. Chem. Soc., Chem. Commun.*, 1973, 273.
9 Z. Skrzypczyński, Łódź, 1977, Ph.D. Thesis.
10 J. Michalski, M. Mikołajczyk and B. Pliszka-Krawiecka, *Angew. Chem.*, 1966, **78**, 716.
11 T.Kawashima, M. Iwanaga and R. Okazaki, *Chem. Lett.*, 1993, 1531.
12 B. Miller, *Topics in Phosphorus Chemistry*, Wiley Interscience, New York, 1965, vol. 2, p. 133.