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Dynamic Cross-Exchange in Halophosphonium Species: First Direct Observation of Stereochemical Inversion in the Course of an S_N2 Process.**

Kirill Nikitin, Elizabeth V. Jennings, Sulaiman Al Sulaimi, Yannick Ortin, Declan G. Gilheany**

Abstract: The complex fluxional interconversions between, otherwise very similar, phosphonium bromides and chlorides $R_3PX^+X^-$ (R = Alk, Ar, X = Cl or Br) was studied by NMR techniques. Their energy barriers are typically ca. 11 kcal/mol but rise rapidly as bulky groups are attached to phosphorus, revealing the importance of steric factors. In contrast, electronic effects, as measured by Hammett analysis, are modest (ρ 1.46) but still clearly indicate negative charge flow towards phosphorus in the transition state. Most significantly, detailed analysis of the exchange pathways unequivocally, and for the first time in any such process, shows that nucleophilic attack of the nucleophilic anion on the tetrahedral centre results in inversion of configuration.

The study of reactivity at tetrahedral centres is ubiquitous in chemistry, not only because this geometry allows for strong bonds and efficient use of space but also because of its potential for asymmetry. Thus modern asymmetric synthesis makes extensive use of stereospecific reactions, especially at carbon, boron, silicon and phosphorus.[1,2] A crucial feature of most of these reactions is the *act of inversion* at the stereogenic centre. However, in all the time since the discovery of Walden inversion, this central event has not been directly observed and, typically, inversion has been inferred from the final product configuration.

Phosphorus chemistry provides an ideal platform to study the issue of inversion because, just as carbon chemistry relies on Walden inversion, syntheses of *P*-stereogenic compounds[3] depend heavily on stereospecific inversions at phosphorus after an initial stereoselective reaction.[4,5,6] However, unlike carbon, the phosphorus intermediates may be easier to study. This was certainly the case in our *P*-stereogenic synthesis[7] utilising the dynamic kinetic resolution[8] of rapidly interconverting *P*-halophosphonium halides (Figure 1a). Since the fully degenerate process was difficult to study, we used[9] the corresponding diastereomeric pseudo-degenerate exchange (Figure 1b) of *model* species to quantify (by NMR) the rates and energy barriers. However, the more general dynamics of e.g. common *P*-stereogenic DKR intermediates (Figure 1a: $R^1/R^2/R^3$ = Ph/Me/^{o}Tol) or simple symmetrical analogues (R^1-R^3 = Ph) could not be studied in this way, which prompted us to seek a different methodology for the systematic study of the electronic and steric effects.

We had previously observed[9] that, separately, the interconverting dichloro- and dibromo-diastereomers (Figure 1b) had very similar NMR behaviour. Therefore we sought to lift degeneracy by simply mixing the chloro- and bromo-species (Figure 1c). As we show below, this *nearly degenerate* cross-exchange system enabled us to create a unified scale of reactivity based on sterics[10] and electronics. Most significantly, we were able to observe *inversion* of tetrahedral configuration directly for the first time.[11] This also validated our (and others) previous computational predictions[9, 12] of Walden-type inversion in the course of nucleophilic attack at tetrahedral phosphorus.

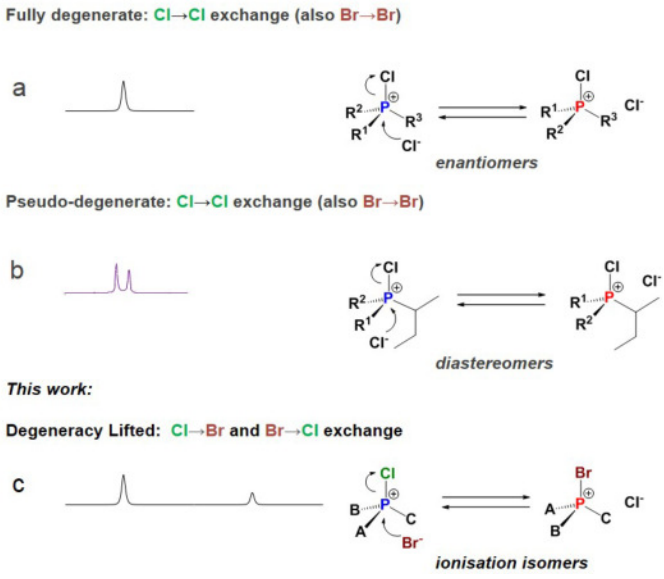

Figure. 1. ^{31}P NMR observations of halide exchange: a) single peak due to full degeneracy; b) two close signals in the presence of a chiral *s*-Bu group[9]; c) in this work degeneracy has been lifted as both P-Cl and P-Br species are present.

The halophosphonium salts in this study (XPS **1-17**, Scheme 1, X = Cl or Br) were generated from the corresponding phosphine oxides by treatment with oxalyl dihalides.[13] We have previously shown that, in the solid state, such salts have the free anion positioned to perform a nucleophilic attack on the phosphonium cation.[13, 14] Individual XPS were fully characterised by NMR spectroscopy and in all cases the ^{31}P signals of the bromides were observed 20-30 ppm upfield from the chlorides (see ESI). Variable temperature NMR spectra were recorded using equimolar amounts of both halides in dichloromethane (DCM) or chloroform. Figure 2 shows the ^{31}P NMR of a 1:1 mixture of halides [**1**-Cl]$^+$Br$^-$ and [**1**-Br]$^+$Cl$^-$ where the interconversion of the species is slow on the NMR timescale below *ca.* -20 °C.[15] The coalescence (T_c = 0 °C) in this case corresponds to an average activation barrier of 11.1 kcal/mol.[16] Scheme 1 shows the results of similar experiments for XPS **2-17**.

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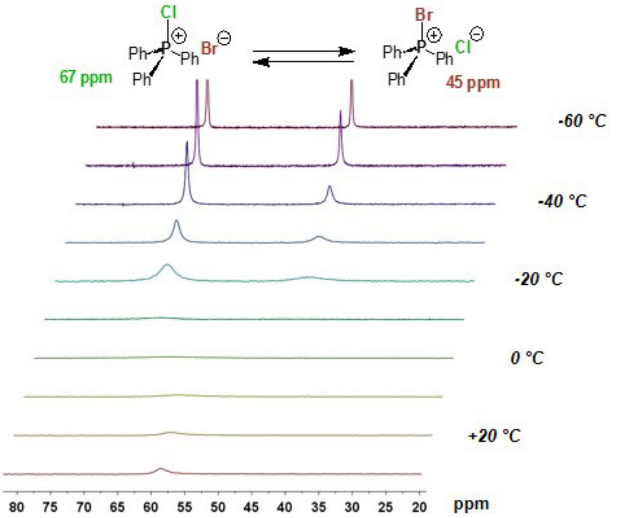
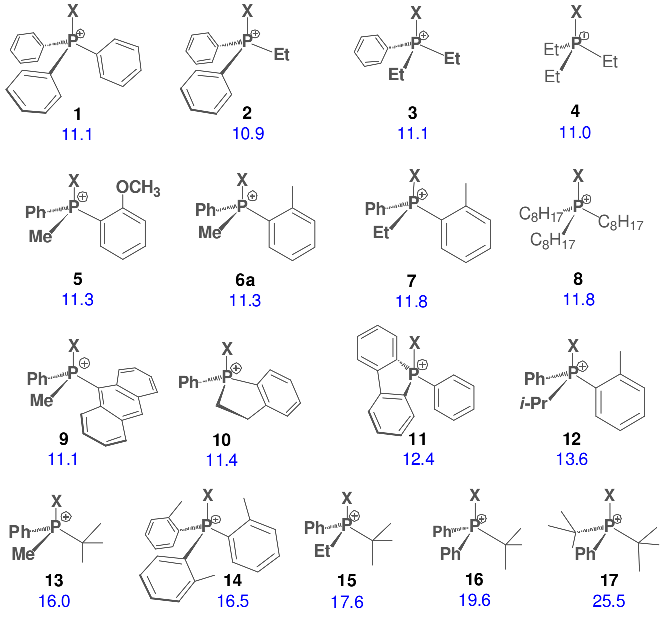


Figure 2. Coalescence of ^{31}P NMR signals of triphenylphosphonium halides $[\mathbf{1}\text{-Cl}]^+Br^-$ and $[\mathbf{1}\text{-Br}]^+Cl^-$ due to pseudo-degenerate exchange (DCM, 202 MHz).

Generally, XPS with primary aliphatic or aromatic groups, have average barriers of 10-12 kcal/mol in excellent agreement with our diastereomeric self-exchange systems in the absence of branched alkyl groups.[9] The fact that the reactivity of cyclic cation **10** is not significantly different from its close acyclic analogues **6a** and **7** is consistent with our earlier report of the similarity in the stereoselectivity in their respective DKR processes.[17] However the introduction of the conformationally more strained dibenzophosphole moiety imposes a pronounced (~1 kcal/mol) rise in the activation energy in **11**. The unusually high activation barrier for the tri-*o*-tolyl cation **14** is in stark contrast to the relatively minor effect of an individual *o*-tolyl group (compare **2** and **7**). This cooperative effect could be attributed to the limited access to the *P*-centre on the side *opposite* to the leaving group X blocked by one of the *o*-tolyl groups (conformation of ion-pairs **14**, see ESI). This indicates, but does not prove, predominant back-side attack with inversion of the *P*-configuration.

The consistency of the earlier self-exchange and the present cross-exchange results also extends to branched substrates. Thus, the reactivity of diaryl-isopropyl system **12** (cross-exchange barrier 13.6 kcal/mol) is close to the *arithmetic average* of Cl/Cl and Br/Br self-exchange in comparable *sec*-butylphenyltolylphosphonium (13 kcal/mol) and *sec*-butyl-*iso*-propylphenylphosphonium (13.7 kcal/mol) salts.[9] This indicates that the cross-exchange pentacoordinate transition state (TS) can be energetically interpolated between the corresponding self-exchange processes and stresses the parallel with carbon S_N2 reactions - a very similar interpolation in carbon chemistry was documented for self- and cross-Finkelstein reactions by Ingold and co-workers.[10c,d] Therefore, the relatively slow exchange in *iso*-Pr compound **12** and, especially, *t*-Bu derivatives **13, 15** and **16** can readily be attributed to the steric effect of bulky groups mimicking other S_N2 processes. Accordingly, introduction of one *t*-Bu (**13**) adds 5 kcal/mol, while the second *t*-Bu (**17**) adds another ca. 10 kcal/mol to the barrier.

There is, nevertheless, a caveat to be associated with these cross-exchange measurements: the degree of speciation between homo- and hetero-halogenated ion pairs is not known.[18] For example, in system $\mathbf{1}X_2$ (Figure 2) equilibration of $[\mathbf{1}\text{-Cl}]^+Br^-$ and $[\mathbf{1}\text{-Br}]^+Cl^-$ is observable by DNMR but the competing degenerate exchange in both $[\mathbf{1}\text{-Cl}]^+Cl^-$ and $[\mathbf{1}\text{-Br}]^+Br^-$ is hidden. Purely statistically, with equal speciation, the observed nominal cross-exchange rate constant would be about one half of its true value for the individual mixed halides. However the fact (*vide supra*) that the cross-exchange results are comparable to the self-exchange values shows that the "hidden" homo-halogenated species are not dominant and the observed cross-exchange barriers can simply be treated as very reasonable estimates.



Scheme 1. *P*-halophosphonium salts (XPS, X = Cl, Br) **1-17** arranged in approximate ascending order of their free energy barriers of activation for pseudo-degenerate exchange (in blue, average of the forward and reverse barriers, ±0.5 kcal/mol).

Turning now to electronic effects, we have shown previously by calculation that the attack of halide anion follows a pronounced associative pathway (strongly curved-in on the More-O-Ferrall-Jencks diagram).[9] To explore this experimentally, we employed a series of *P*-stereogenic XPS **6a-h** (Figure 3). In our earlier studies this series had shown very little effect of the substituent on the stereoselectivity of our DKR process.[7a,e]

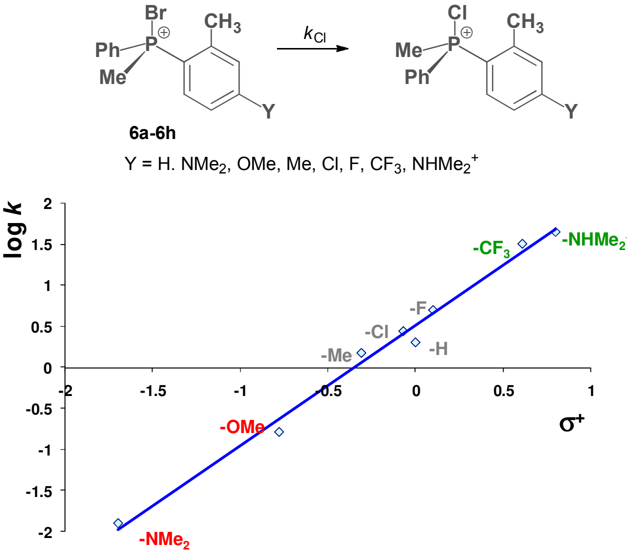


Figure 3. Experimental Hammett plot of the exchange rate constants (k_{Cl}) in series **6** (error bar ± 0.05 log units; R^2 0.989) corresponding to ρ = 1.46, determined by 2D ^{31}P EXSY NMR.

When series **6** was studied at -50 ˚C by ^{31}P two-dimensional EXSY spectroscopy using the non-equal exchange approximation (see ESI for details),[19] electron-donating groups (EDG) were found to slow the exchange while electron-withdrawing groups (EWG) accelerated it. Interestingly it was the σ^{+} parameter[20] that demonstrated best linearity with a small *positive* reaction parameter (Figure 3, $\rho = 1.46 \pm 0.15$). This somewhat uncommon combination reflects the diminution of positive charge on phosphorus in the TS during the substitution process.[21]

The above observations show that the XPS cross-exchange has all the standard characteristics of an S_N2 mechanism. However, in common with all other studies of this type, the inversion of the reaction centre is not directly seen. Thus in Figure 3, we have intentionally indicated stereospecific halide-ion attack with *inversion* of the *P*-configuration but this is not yet proven – the rapid interconversion of the phosphonium species could be accompanied by either inversion or retention at the *P*-centre, or both. Just as in our recently reported[19] phenomenon of two independent and geometrically orthogonal stereomutations at a single asymmetric phosphonium centre, one cannot rule out a concomitant retention process via equatorial nucleophilic attack or via a pseudorotation-type stereomutation. We realized that cross-exchange techniques provide the only way to directly probe the stereochemistry of halide-ion attack on the *P*-centre by *combining the two degeneracy-lifting methods* together (Figure 1b with 1c).

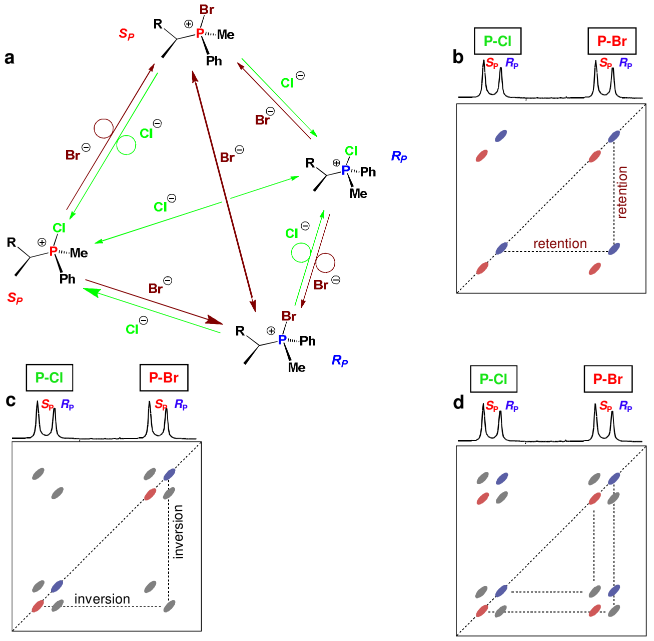
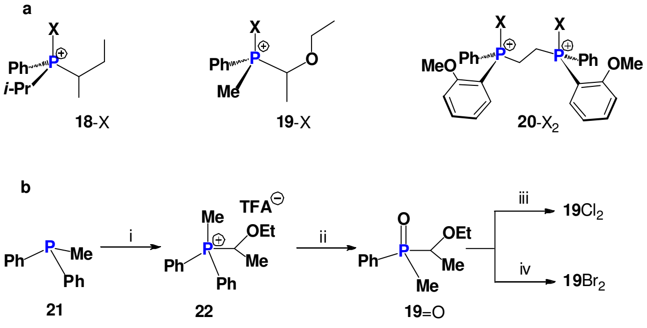


Figure 4. Halide exchange pathways in a generic diastereomeric mixed-halogen XPS: a) tetrahedron representation: single arrows - Walden-type inversion of the *P*-configuration with change of the halogen; double arrows - inversion *without* change of halogen; curled arrows – putative retention pathway with change of the halogen; b) expected 2D ^{31}P EXSY signature of exclusive retention; c) of exclusive inversion; d) of the mixed case.

Figure 4a shows pseudo-degenerate cross-exchange in a generic diastereomeric system. This situation allows essentially independent self- and cross-exchange of four XPS (not counting their enantiomers). Crucially, in 2D EXSY experiments, cross-exchange where the *P*-configuration is retained (curled pseudorotation arrows) can be distinguished from cross-exchange with inversion (equilibrium single arrows) or self-exchange with inversion (double "↔" arrows) as shown in the idealised diagrams in Figures 4b-d. Specifically, attack of bromide anion on R_{P}-chlorophosphonium cation with retention of configuration leads to R_{P}-bromophosphonium cation giving rise to a blue cross-peak as shown in Figure 4b. Likewise, Br ion attack on S_{P}-chlorophosphonium with retention of configuration leads to S_{P}-bromophosphonium (red peak). Conversely, an attack of bromide anion on S_{P}-chlorophosphonium cation with *inversion* of configuration leads to R_{P}-bromophosphonium cation giving rise to a cross-peak as shown in Figure 4c in grey. Should, however, both retention and inversion of the *P*-configuration happen at an appreciable rate, all coloured and grey cross-peaks, would be observed (Figure 4d).

We tested diastereomeric systems **18** and **19** (Scheme 2a). System **18** proved unsatisfactory[22] but the introduction (Scheme 2b) of the α–alkoxyalkyl group in **19** enabled better ^{31}P NMR peak separation (ca. 4 ppm) and slightly lower average barrier (11.4 ± 0.2 kcal/mol). Both **19**Cl_2 and **19**Br_2 are unstable at r.t. and were handled at -20 ˚C.



Scheme 2. a) diastereomeric *P*-stereogenic systems studied; b) synthesis of **19**X_2: i) ethylvinyl ether/TFA; ii) alkaline hydrolysis; iii) oxalyl chloride or iv) oxalyl bromide, -20 ˚C, DCM.

When a mixture of **19**Br_2 and **19**Cl_2 was examined by ^{31}P NMR at -60 ˚C four well-resolved resonances of individual chloro- and bromo-species were observed at 87, 82, 72, 68 ppm corresponding to S_{P}-**19**-Cl, R_{P}-**19**-Cl**,** S_{P}-**19**-Br, R_{P}-**19**-Br. The 2D EXSY spectrum recorded with short mixing time (T_m = 20 ms) displayed four main diagonal peaks and a set of cross-peaks (Figure 5). The peaks at 68/72 and 72/68 ppm clearly correspond to bromide self-exchange S_{P}-**19**-Br → R_{P}-**19**-Br (Figure 4a, double "↔" arrows).

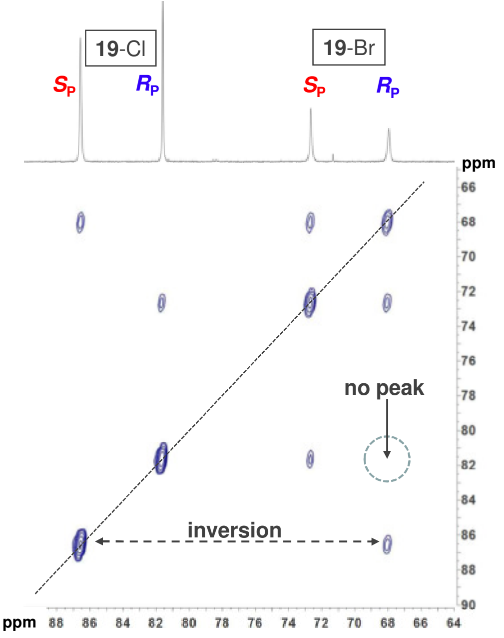


Figure 5. Dynamic inversion of the *P*-configuration observed in the **19**-Br/Cl exchange system by EXSY (DCM, -60ºC, *Tm* = 20 ms), clearly showing correspondence to Figure 4c and strongly predominant inversion on this time-scale.

Significantly, four remaining peaks (86/68, 82/72, 68/86, 72/82 ppm) aligned in the same fashion as Figure 4c correspond to cross-exchange between bromo- and chloro-species with inversion of the *P*-configuration S_{P}-**19**-Cl → R_{P}-**19-**Br and S_{P}-**19**-Br → R_{P}-**19**-Cl. Crucially, no cross-peaks were observed in the main-diagonal fashion of Figure 4b, corresponding to retention of *P*-configuration. Therefore we have unequivocally established strongly predominant[23] inversion of the *P*-configuration in the course of nucleophilic exchange processes in halophosphonium species. Stereospecific inversion at the *P*-centre is in excellent agreement with our recent findings on the fluxional dynamics of tetrahedral phosphonium salts.[9,19] To the best of our knowledge, obtaining of such stereochemical information from an inseparable mixture of rapidly interconverting reacting species is the first example of a dynamic exchange experiment of this type. We note that attribution of the lower-field ^{31}P NMR peaks to the S_{P}-isomers of **19**-Cl and **19**-Br as shown is consistent with computed chemical shifts.[24] Should one of those assignments be incorrect, the observed 2D EXSY pattern would mean that self-exchange leads to inversion while cross-exchange leads to retention – an entirely irrational situation. Work is underway on detailed analysis of self- and cross-exchange processes in more complex double *P*-stereogenic systems, for example DiPAMP halides (**20**-X_2 Scheme 2a).

To conclude, by introducing two different halogens in the dynamic exchange of XPS species we were able to extend the measurement of reaction activation barrier to essentially any phosphonium structure and construct a reactivity scale for the process. Notably, for XPS containing ordinary hydrocarbon groups, the barriers are around 11 kcal/mol, rising rapidly with increased steric bulk in agreement with our earlier findings.[9] Secondly, we have used, to our knowledge for the first time for a fast nucleophilic reaction, low temperature exchange experiments on the millisecond scale to build an informative Hammett plot. Both findings enable us to predict the reactivity of a wide variety of XPS and are not, in principle, limited to the halogen exchange process. Finally, by rigorously analysing the dynamic pattern of multiple pathway exchange systems, we successfully established the stereochemistry of the exchange process. In excellent agreement with computations strongly favouring the di-axial orientation of halogens in the transition state, the attack of nucleophilic halide anion results in an inversion of the *P*-configuration. This latter result is significant for Main Group element chemistry in general as it underlines the deep similarity between carbon and non-carbon chemistry.

Experimental Section

Experimental procedures for dynamic measurements and characterisation of individual compounds are given in the Electronic Supporting Information section.

Acknowledgements

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[23] No retention was observed within detection limit, 5% relative, of this measurement. Second-generation "retention" peaks are observed in experiments with longer mixing times (T_m = 50 ms or greater). As their intensity is time-lagged, this behaviour is attributed to a sequential process e.g. S_P-**19**Br → R_P-**19**Cl → S_P-**19**Cl.

[24] Chemical shifts computed (SPARTAN 10, carbon *S*-configuration fixed) for the S_P-isomers were consistently higher than for the R_P-isomers.