A Phosphorus Nuclear Magnetic Resonance Spectroscopic Study of the Conversion of Hydroxy Groups into Iodo Groups in Carbohydrates using the Iodine–Triphenylphosphine–Imidazole Reagent

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^{31}P N.m.r. spectroscopic studies on the mechanism of the reaction between 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and the reagent system iodine–triphenylphosphine–imidazole are presented. Three different solvents were tested, toluene–acetonitrile (2:1), acetonitrile, and pyridine. A mechanism is proposed, which is largely consistent with that previously suggested. Imidazole may be replaced by triethylamine, and the reaction also proceeds in pyridine without imidazole or triethylamine. Some features of the equilibrium between triphenyldi-iodophosphorane and iodotriphenylphosphonium iodide (formed from iodine and triphenylphosphine) are also discussed.

Deoxyiodo sugars are of value in carbohydrate chemistry.[1] They are biologically interesting, *e.g.* in *X*-ray urology,[2] as well as being useful intermediates in the synthesis of deoxy sugars, which are involved in a host of biointeractions. The conversion of hydroxy groups into iodo groups has therefore attracted considerable attention. Significant progress has been made in the last few years. This includes the use of tetraiodomethane together with triphenylphosphine to give substitution at C-6 in hexopyranosides,[3] the use of various reagents based upon triphenyl phosphite,[4–6] triphenylphosphine and diethyl azodicarboxylate[7] (Mitsunobu reaction), as well as displacements of the trifluoromethanesulphonyl group[8] and imidazolylsulphonates[9] by iodide ion.

We have previously described the conversion of hydroxy groups into iodo groups in carbohydrates using the iodine–triphenylphosphine–imidazole and the tri-iodoimidazole–triphenylphosphine–imidazole reagents; a reaction which proceeds with inversion of configuration at secondary positions. Noteworthy features include selective substitution in pyranosides with several hydroxy groups, facile substitution at the normally difficulty accessible 2-position in hexopyranosides, and the simultaneous introduction of deoxyiodo and alkenic functions in pyranosides.[10]

Although a mechanism has been proposed for this reaction,[10,11] mechanistic studies have so far not been carried out. We now report the results of ^{31}P n.m.r. spectroscopic studies on the reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**) with iodine–triphenylphosphine–imidazole.

Results and Discussion

The reagent system I_2–Ph_3P–Im has been successfully used with toluene–acetonitrile (2:1) as the solvent.[10] The first experiments were therefore carried out in this mixture (the solvent originally used, toluene, is not suitable for n.m.r. studies since this gives a heterogenous reaction).

The reaction was performed in an n.m.r. tube with sequential addition of 1 equivalent of triphenylphosphine, 1 equivalent of iodine, 2 equivalents of imidazole, and 1 equivalent of the pyranose (**1**). ^{31}P N.m.r. spectra were recorded after each addition. As shown in the Figure, triphenylphosphine produced a signal at −5.0 p.p.m. [spectrum (a)]. The signal disappeared completely in less than 2 min when iodine was added and two new peaks appeared [spectrum (b)] at 38.8 and −19.9 p.p.m. These signals are assigned to a slow equilibrium between triphenyliodophosphonium iodide (**2a**) and triphenyldi-iodophosphorane (**2b**) respectively. After the addition of imidazole to this mixture, the spectrum changed in less than 2 min to (c). This contains one major peak at 39.8 p.p.m. and two minor ones (at 27.9 p.p.m. and −11.6 p.p.m.). We suggest that the major peak is due to the phosphonium salt (**3a**), previously suggested as an intermediate. The weak signal at 27.9 p.p.m. is given by triphenylphosphine oxide, produced from (**3a**) and moisture, and the other at −11.6 p.p.m. could possibly arise from a pentavalent compound such as (**3b**) which exists in equilibrium with (**3a**).

Addition of compound (**1**) resulted in spectrum (d) (within 2 min), which shows signals at 27.9 (Ph_3P=O) and 63.0 p.p.m. The latter, most likely, arises from phosphonium salt (**4**), which has been suggested as the final intermediate before conversion into products[10,11] [the iodopyranose (**5**) and Ph_3-P=O]. Undecoupled ^{31}P n.m.r. spectra did not provide additional information about the proposed structure, since all the signals appeared as broad, unresolved multiplets. However, the structure was substantiated by the ^{13}C n.m.r. spectrum which showed a doublet at 67.7 p.p.m. (C-6, $^2J_{CP}$ 6.1 Hz). With time, the ^{31}P peak at 63.0 p.p.m. ascribed to the phosphonium iodide (**4**) slowly disappeared (during several hours at 70 °C) and the signal from triphenylphosphine oxide (27.9 p.p.m.) increased, until all of compound (**4**) had been converted into products and only one resonance line (27.9 p.p.m.) was observed [spectrum (e)].

After this first study we turned to the use of two other solvents, acetonitrile and pyridine. The reaction followed essentially the same path, as with toluene–acetonitrile, in both solvents. The chemical shifts were essentially the same (see the Table). The rates of all steps in pyridine were comparable to the corresponding rates in toluene–acetonitrile (2:1), but in acetonitrile the final step was somewhat slower. One difference observed was the equilibrium between compounds (**2a**) and (**2b**). In the more polar solvent, acetonitrile, only the salt (**2a**) seemed to be present (signal at 46.1 p.p.m.) but in pyridine only the pentavalent compound (**2b**) could be detected (at −21.0 p.p.m.).

Next, the role of imidazole in this reaction was examined. Imidazole, together with the iodide (**2**), would appear to give the intermediate (**3a**), and possibly (**3b**). One question arising was whether the pyranose (**1**) can react directly with (**2**) to form compound (**4**), or whether intermediate formation of the phosphorane (**3**) is necessary for such a transformation.

When the reaction was carried out in pyridine, without imidazole, compound (**1**) did indeed react rapidly with (**2**) to form (**4**), but in toluene–acetonitrile (2:1), in the absence of imidazole, (**1**) failed to react with (**2**) even after an hour. If,

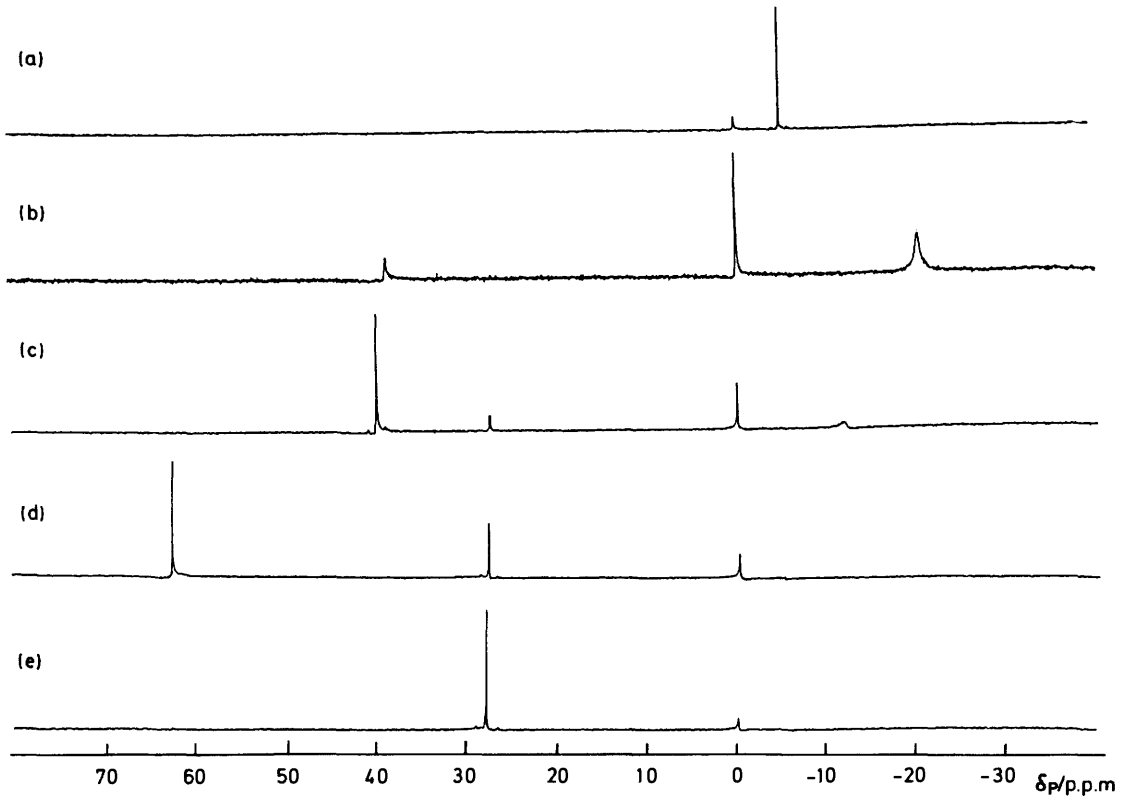
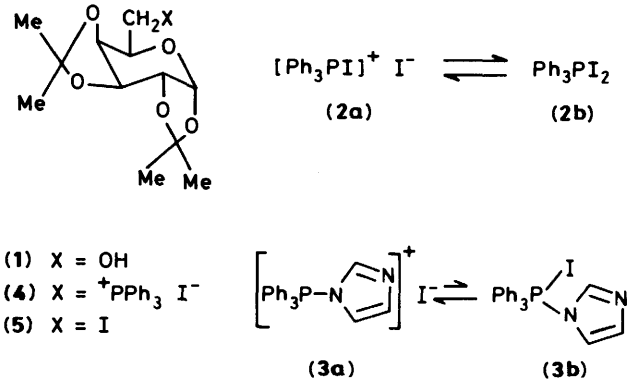


Figure. ^{31}P N.m.r. spectra of the reaction between (**1a**) and I_2–Ph_3P–imidazole in toluene–acetonitrile (2:1): (a) Ph_3P, (b) $Ph_3P + I_2$, (c) $Ph_3P + I_2$ + imidazole, (d) $Ph_3P + I_2$ + imidazole + (**1a**), (e) after completion of reaction. The signal at 0 p.p.m. is from the reference: 2% H_3PO_4 in D_2O (inner tube)

Table. ^{31}P N.m.r. chemical shifts of important intermediates involved in the reaction. (Values reported in p.p.m. from 2% H_3PO_4 in D_2O)

	Solvent, Temp. (°C)		
Compound	Toluene–acetonitrile (2:1) 70	Acetonitrile 70	Pyridine 40
Ph_3P	−5.0	−5.5	−6.0
Ph_3PI_2	−19.9		−21.0
$[Ph_3PI]^+I^-$	+38.8	+46.1	
$[Ph_3PIm]^+I^-$	+39.8	+40.6	+39.5
$[Ph_3POR]^+I^-$	+63.0	+63.5	+62.7
$Ph_3P{=}O$	+27.9	+28.7	+25.3



Scheme 1.

however, triethylamine (2 equiv.) was added, the reaction proceeded as smoothly as with imidazole.

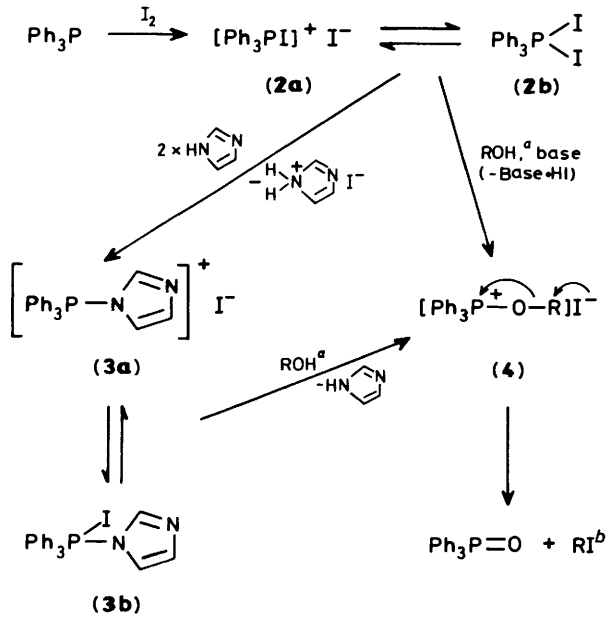
From these results we conclude that, in the reaction investigated, the role of imidazole is mainly to facilitate, as a base and as scavenger of hydrogen iodide, the formation of the phosphonium salt (**4**). We could not determine, using ^{31}P n.m.r. spectroscopy, the main reaction pathway for the formation of (**4**), since the reaction of (**1**) with (**3**) or (**2**) to give (**4**) was found to be complete before the first spectrum could be recorded. As compounds (**2**) and (**3**) are both reactive towards the pyranose (**1**) it is considered likely that the reaction takes place both *via* (**3**) and directly from (**2**), when (**4**) is formed.

We therefore propose the mechanism to be that shown in Scheme 2, with the rate being determined by the last, product-forming, step which takes place with inversion of configuration.[10] Furthermore, the reaction is faster in less polar solvents such as toluene–acetonitrile (2:1) and pyridine than in the more polar acetonitrile. These observations indicate an S_N2-like transition state. In agreement with this, the addition of tetrabutylammonium iodide increased the overall rate of reaction (t.l.c. examination). Also, the use of triethylamine instead of imidazole enhanced the overall reaction rate. This can be explained in terms of a counter ion effect: the concentration of free iodide ions should be higher when triethylamine is used as an acid scavenger, since triethylammonium hydrogen iodide should be more dissociated in the reaction medium than the corresponding imidazolium salt.

It is known that phenylhalogenophosphoranes in solution can exist as an equilibrating mixture of the phosphorane

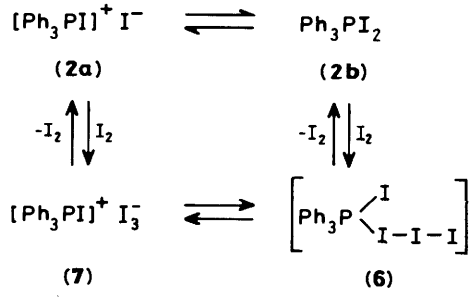
and the phosphonium salt.[12] We suggest that we have an equilibrating mixture between iodotriphenylphosphonium iodide (**2a**) and di-iodotriphenylphosphorane (**2b**) and that the equilibrium is slow on the n.m.r. time-scale, so that both (**2a**) and (**2b**) are observed in the ^{31}P n.m.r. spectrum. When we tried to record spectra at various temperatures (15—80 °C), extensive precipitation occurred when the temperature was lowered. However, it was noticeable that the ratio of (**2b**) to (**2a**) was higher at higher temperatures. The fact that some precipitation occurred even at 70 °C indicates that the broadening of signals in spectrum (b) is due to partial insolubility rather than to exchange. However, the equilibrium was still slow, on the n.m.r. time-scale, near the boiling point of acetonitrile. In order to speed up the equilibrium, we added various amounts of tetrabutylammonium iodide (QI). N.m.r. spectra of the resulting reaction mixtures indicated that the equilibrium was reached more rapidly, since broadening of the signals, which also moved closer together, was observed, as well as a small change in composition in favour of compound (**2b**). When 3 equiv. of QI was added, all the precipitate dissolved, but the signals showed even more broadening. When this mixture was cooled to 30 °C, both signals became much sharper and shifted apart. The equilibrium at the lower temperature shifted towards (**2a**). When 1 equivalent of aluminium trichloride was added to (**2**) in toluene–acetonitrile (2:1), extensive precipitation occurred and the spectrum changed from that in spectrum (b) to one with a single broad peak (presumably from $[Ph_3PI]^+[AlCl_3I]^-$) with the same chemical shift as the signal we earlier assumed to have arisen from compound (**2a**), a further indication that the signal at 38.8 p.p.m. is given by this compound.

We also recorded spectra of Ph_3P in toluene–acetonitrile (2:1) with various amounts of iodine added. Two equivalents of iodine gave two broad peaks at 2.7 and 7.4 p.p.m., 3 equivalents gave one peak at 8.3 p.p.m. (sharp, but with broadening near the baseline), and 4 equivalents produced one single sharp signal at 10.0 p.p.m. These results indicate that increasing amounts of iodine raise the rate of equilibration between phosphorane and phosphonium salt, and that the equilibrium is also shifted towards the latter. It is also likely that the tri-iodide [both as the phosphorane (**6**) and phosphonium salt (**7**)] is involved so that the equilibrium, when an excess of iodine is used, becomes that shown in Scheme 3, analogous to the study of the reaction between triphenylphosphine and chlorine.[5]



Scheme 2. [a] ROH = (**1**). [b] RI = (**5**)

The results largely confirm the previously proposed pathway for the conversion of hydroxy functions into iodo functions using iodine–triphenylphosphine–imidazole.[10,11] If an excess of iodine is used it is likely that the equilibrium shown in Scheme 3 is also involved.



Scheme 3.

It would seem that the nucleophilic properties of imidazole are not important in this reaction, and that imidazole in homogeneous systems probably only plays the role of a general base and of an acid scavenger. It thus can be replaced by other bases such as triethylamine or pyridine. In the absence of hydroxy-containing compounds imidazole reacts with compound (**2**) to form the intermediate (**3**), but we could not prove, using ^{31}P n.m.r. spectroscopy, that the reaction proceeds *via* this intermediate, since the intermediate (**2**) in the presence of base is at least as reactive as (**3**). The rate-limiting step proceeds *via* an S_N2-type mechanism. A base, as *e.g.* imidazole, triethylamine, or pyridine, is an indispensable component of the reagent system. The possibility of choosing different bases and/or basic solvents, *e.g.* pyridine, should make iodine–triphenylphosphine–base a versatile reagent system in carbohydrate as well as in general organic synthesis.

Experimental

Materials.—Triphenylphosphine and iodine were commercial grade (Merck). Imidazole was dried by distilling water off azeotropically with toluene (twice) and was then stored in a desiccator under reduced pressure. Triethylamine was stored over calcium hydride. Acetonitrile (p.a.) was distilled from calcium hydride and stored over molecular sieves (3 Å). Toluene (p.a.) was stored over sodium wire. Pyridine (p.a.) was distilled from phosphorus pentaoxide and stored over molecular sieves (4 Å).

Methods.—All ^{31}P n.m.r. spectra were recorded in 12 mm tubes with a Varian Associates XL-100 FT spectrometer operating at 40.48 MHz. Chemical shifts are reported relative to 2% phosphoric acid in D_2O (inner tube). In all n.m.r. experiments the concentrations of Ph_3P and I_2 were the same (0.6 mmol in 3 ml solvent which is close to concentrations used in synthesis).

The equivalents of other compounds, added to the n.m.r. tube, were varied as stated earlier in the text. All reactions involving (**1**) were checked at completion of the n.m.r. experiment using t.l.c. on Merck silica gel plates [toluene–ethyl acetate (5:1)]. In all experiments the same compound (**5**) was the sole product detected.

Some additional t.l.c. experiments were performed in which all starting material was mixed from the beginning (to mimic real synthesis). Merck silica gel plates were used and the samples were checked in two different solvent systems [toluene–ethyl acetate (5:1), and benzene–diethyl ether (9:1)]. In all reactions triphenylphosphine (0.2 mmol), iodine (0.19 mmol), and the pyranose (**1**) (0.095 mmol) were dissolved in the solvent (0.6 ml), together with other compounds as stated below.

In toluene–acetonitrile (2:1 v/v): imidazole (2 equiv.); *or* Et_3N (2 equiv.); *or* Et_3N (2 equiv.) + imidazole (2 equiv.); *or* imidazole (2 equiv.) + tetrabutylammonium iodide (1 equiv.).

In acetonitrile: imidazole (2 equiv.); *or* Et_3N (2 equiv.); *or* Et_3N (2 equiv.) + imidazole (2 equiv.).

In pyridine: imidazole (2 equiv.); *or* Et_3N (2 equiv.); *or* Et_3N (2 equiv.) + imidazole (2 equiv.); *or* tetrabutylammonium iodide (1 equiv.) (equivalents calculated from triphenylphosphine).

In pyridine: imidazole (2 equiv.); *or* Et_3N (2 equiv.); *or* Et_3N ation were in agreement with results obtained using ^{31}P n.m.r. spectroscopy. In addition we observed that tetrabutylammonium iodide enhanced the overall rate as did triethylamine. The reactions in acetonitrile were somewhat slower than the corresponding reactions in the other two solvents. Furthermore, the presence of triethylamine increased the rate of formation of the product (**5**). However, when *only* Et_3N was used, the solutions became dark. This, however, did not seem to affect the transformation of (**1**) to (**5**). When both Et_3N and imidazole were used, the solution was only slightly coloured.

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