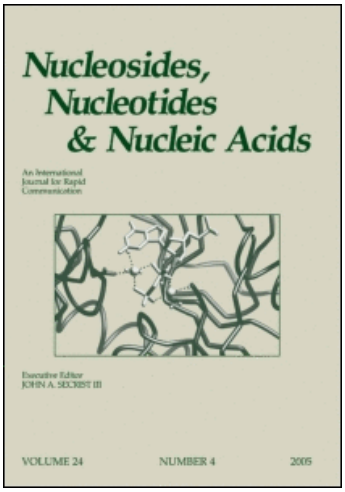


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Iodine and Iodine Catalysed Phosphorylation of Nucleosides by Phosphorodiester Derivatives

Roger Strömberg[a]; Jacek Stawinski[a]
[a] Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm., Stockholm, Sweden

To cite this Article Strömberg, Roger and Stawinski, Jacek(1987) 'Iodine and Iodine Catalysed Phosphorylation of Nucleosides by Phosphorodiester Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 6: 5, 815 — 820
To link to this Article: DOI: 10.1080/15257778708073428
URL: http://dx.doi.org/10.1080/15257778708073428

NUCLEOSIDES & NUCLEOTIDES, 6(5), 815-820 (1987)

IODIDE AND IODINE CATALYSED PHOSPHORYLATION OF NUCLEOSIDES BY PHOSPHORODIESTER DERIVATIVES

Roger Strömberg and Jacek Stawinski*

Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, 106 91 Stockholm, Sweden.

Abstract

Sodium iodide was found to catalyse the phosphorylation of nucleosides by phosphorodiester derivatives such as chlorophosphates, pyrophosphates and triazolides. A similar catalytic effect, but on phosphorochloridates only, was also exerted by iodine.

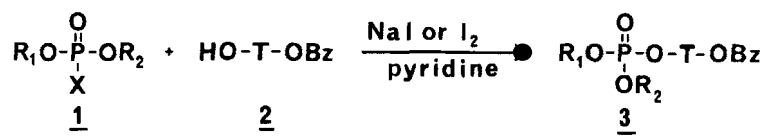
The phosphorylation reaction occupies a prominent position in natural products chemistry, because of its importance in the synthesis of biologically active compounds such as nucleotides[1,2], oligonucleotides[1,2], phospholipids[2,3], nucleopeptides[4].

Using monofunctional phosphorylating reagents, e.g. diesters of phosphorochloridic acid and their derivatives, several valuable phosphorus-containing intermediates have been synthesized[1,3]. The phosphorylation reaction with phosphorochloridates is usually carried out in pyridine in the presence of nucleophilic catalysts. However, until now, mainly two types of nitrogen-based nucleophilic catalysts, namely 1-alkyl derivatives of imidazole[1,5] and 4-dimethylaminopyridine[6,7] have been employed.

Searching for another type of catalyst, suitable for the preparation of phosphorotriesters, we investigated the phosphorylation of partially protected nucleosides by diesters of phosphorochloridic acid or other phosphorodiester derivatives, in the presence of sodium iodide. We reasoned that pyridine mediated exchange of halogen in the phosphorylating agent should result in the formation of a rather reactive species,

namely diesters of phosphorochloridic acid, and in this way, accelerate the phosphorylation of nucleosides[8].

Indeed, when 3'-O-benzoylthymidine 2 was reacted with diethyl phosphorochloridate 1a (2 equiv.) in pyridine in the presence of sodium iodide (2 equiv.), phosphorylation was over in a few seconds, compared to 75 min for the analogous reaction without a catalyst (Table 1, entry 1 and 4). A similar catalytic effect was also observed for the other types of phosphorylating reagents, e.g. diphenyl phosphorochloridate 1b, tetraphenyl pyrophosphate 1c, o-chlorophenyl-2,2,2-trichloroethyl phosphorochloridate 1d and diphenyl phosphoro-1,2,4-triazolide 1e (see Table 1).



1a, $R_1=R_2$=ethyl, X=Cl

1b, $R_1=R_2$=phenyl, X=Cl

1c, $R_1=R_2$=phenyl, X= -O-P(O)(OPh)

1d, R_1=o-chlorophenyl, R_2=2,2,2-trichloroethyl, X=Cl

1e, $R_1=R_2$=phenyl, X= 1,2,4-triazole-yl-1

Attempted phosphorylation of nucleoside 2 with stoichiometric amounts of 1a and NaI, failed to drive the reaction to completion. This is probably due to decomposition of phosphorylating reagent 1a under the reaction conditions. Indeed, when 1a (2 equiv.) and NaI (2 equiv.) were kept in pyridine for 5 min before the addition of nucleoside, phosphorylation was fast but only went to ca 20% completion. Such a phenomenon was not observed for the other phosphorylating reagents 1b-e[9] investigated.

A slightly yellow coloration of the reaction mixtures, invariably observed upon the addition of phosphorylating reagent to a pyridine solution of nucleoside and sodium iodide, would suggest the formation of traces of iodine. To investigate if iodine itself could act as a catalyst,

Table 1. Influence of various catalysts on the phosphorylation reaction of 3'-O-benzoylthymidine by the phosphorylating reagents 1a-e*.

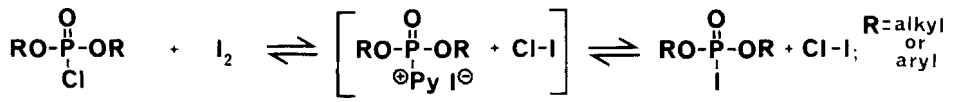
No	Phosphorylating agent (equiv.)	Catalyst (equiv.)	Time to completion	Solvent
1.	1a (2)	-	75 min	pyridine
2.	1a (2)	MeIm (2)	4 min	pyridine
3.	1a (2)	NaI (1)	6 min	pyridine
4.	1a (2)	NaI (2)	10-15 sec	pyridine
5.	1a (2)	I_2 (0.2)	10 min	pyridine
6.	1a (2)	I_2 (1)	2 min	pyridine
7.	1a (2)	I_2 (2)	10-15 sec	pyridine
8.	1a (1.1)	I_2 (2)	2 min	pyridine
9.**	1a (2)	MeIm (2)	3 min	acetonitrile
10.**	1a (1.1)	NaI (1) + Py (2)	4 min	acetonitrile
11.**	1a (2)	NaI (2) + Py (2)	1.5 min	acetonitrile
12.**	1a (1.1)	I_2 (1) + Py (2)	5 min	acetonitrile
13.**	1a (2)	I_2 (1) + Py (2)	1.5 min	acetonitrile
14.	1b (2)	-	20 min	pyridine
15.	1b (2)	MeIm (2)	2 min	pyridine
16.	1b (2)	NaI (1)	3 min	pyridine
17.	1b (2)	NaI (2)	5-10 sec	pyridine
18.	1b (2)	I_2 (1)	10-15 sec	pyridine
19.	1c (2)	-	4 h	pyridine
20.	1c (2)	MeIm (2)	2.5 h	pyridine
21.	1c (2)	NaI (2)	25 min	pyridine
22.	1d (2)	-	50 min	pyridine
23.	1d (2)	MeIm (2)	3 min	pyridine
24.	1d (2)	NaI (1)	3 min	pyridine
25.	1d (2)	NaI (2)	10-15 sec	pyridine
26.	1d (1.1)	I_2 (1)	1.5 min	pyridine
27.	1e (2)	-	90 min	pyridine
28.	1e (2)	MeIm (2)	10 min	pyridine
29.	1e (2)	NaI (2)	10 min	pyridine

* Reaction conditions: 3'-O-benzoylthymidine (0.05 mmole) and catalyst (0.2-2 equiv.) were dissolved in pyridine (0.2 ml) or in acetonitrile (0.2 ml) and the appropriate phosphorylating reagent 1a-e (1.1-2 equiv.) was added. Progress of the reactions was checked by TLC (silica gel, $CHCl_3$-MeOH 9:1, v/v). In all cases, reactions were over after the time specified in the Table, and 3 was present as the sole nucleotidic material.

** To ensure homogenous conditions for the phosphorylation, 3'-O-3-N--dibenzoylthymidine was used as a nucleosidic material.

phosphorylation was carried out in the presence of various amounts of iodine. As can be seen from Table 1 (entry 6-8, 18 and 26), iodine indeed catalyses the phosphorylation in case of phosphorochloridates 1a, 1b and 1d, but it had no catalytic effect when pyrophosphate 1c or 1,2,4-triazole derivative 1e were used as phosphorylating reagents.

The explanation for this is not straightforward. It can be, however, rationalized by the assumption of the intermediate formation of iodide ions, which excert a catalytic effect. Since the formation of iodide ions in the reaction of phosphorochloridates with iodine is plausible,



but rather unlikely in the case of other phosphorylating reagents, this explanation fits the experimental results well. Thus, it is most likely that in iodine-catalysed phosphorylation reaction, iodide ions plays the role of the real catalyst.

In contradistinction to 1-alkyl derivatives of imidazole and 4-dimethylaminopyridine, which can exert their catalytic activity also in neutral solvents (e.g. acetonitrile), iodide ions and iodine catalysed phosphorylations require a basic solvent (e.g. pyridine) or an external base. It was found that phosphorylation of 3'-O-3-N-dibenzoylthymidine in acetonitrile does not occur when 1a alone or together with sodium iodide or iodine is used. However, addition of pyridine to the reaction mixture in acetonitrile containing 1a and NaI or I_2 results in phosphorylation within a few minutes (Table 1, entry 10-13).

We also tried to find out whether iodide ions or iodine can be used as catalysts in the phosphorotriester approach to oligonucleotide synthesis. Thus, 5'-O-dimethoxytritylthymidine-3'-(p-chlorophenyl) phosphate (1.1 equiv.) was reacted with nucleoside 2 (1 equiv.) in the presence of N,N-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (OXP)[10] (3 equiv.) and sodium iodide (2 equiv.) in pyridine, and formation of the expected triester, as the sole reaction product, was observed within 45 min. The analogous reaction, using N-methyimidazole (2 equiv.) instead of NaI, and also the reaction without any catalyst, were completed in 40 min and overnight, respectively. Iodine, however, did not show any noticeable

catalytic effect. These results are consistent with our findings that phosphorylation by pyrophosphate, which is the most likely intermediate involved in this type of reaction, is accelerated by iodide ions but not by iodine.

Arenesulfonyl derivatives, as coupling reagents, were found to be incompatible with sodium iodide, because of the occurrence of redox reactions.

In conclusion, the experiments presented above demonstrate that phosphorylation of nucleosides by phosphorodiester derivatives can be catalysed by iodide anions, and that the accelerating effect is similar (or slightly higher) than that of N-methylimidazole. In the case of phosphorochloridates, iodine can be used as a catalyst instead of sodium iodide. It seems that iodine is superior to sodium iodide when used in combination with phosphorochloridates, since decomposition of 1a is slower[9], and thus, phosphorylation can be carried out with only a slight excess of phosphorylating reagent 1a (Table 1, entry 8). Sodium iodide may be removed from the reaction mixture by extraction with water, which simplifies the work-up procedure as compared to that required for N-methylimidazole catalysed phosphorylation. In the latter case, troublesome and inefficient extraction with pentane[11] or work-up with acidic buffer[12] is necessary to remove an excess of catalyst from the reaction mixtures.

ACKNOWLEDGEMENTS

We are indebted to Prof. Per J. Garegg for his interest, to the National Swedish Board for Technical Development and the Swedish Natural Science Research Council for financial support.

REFERENCES AND NOTES

1. C. B. Reese, Tetrahedron, 34, 3143 (1978).
2. F. Ramirez, J. F. Marecek, Synthesis, 449 (1985).
3. H. Eibel, Chem. Phys. Lipids, 26, 405 (1980).
4. E. Kuyl-Yeheskiely, P. A. M. van der Klein, G. M. Visser, G. A. van der Marrel, J. H. van Boom, Recl. Trav. Chim. (Pays-Bas), 105, 69 (1986).
5. J. H. van Boom, P. Burgers, G. R. Oven, C. B. Reese, R. Shaffill, Chem. Comm. 869, (1971).
6. G. Höfle, W. Steglich, H. Vorbruggen, Ang. Chem., 90, 602 (1978).
7. D. G. Knorre, V. F. Zarytova, in Phosphorus Chemistry Directed Towards Biology, W. J. Stec, Ed., Pergamon Press, Oxford, (1980), p. 13.

8. ^{31}P NMR spectra of reaction mixtures containing phosphorylating agent 1 and NaI (1 equiv.) did not show detectable amounts of phosphoroiodate, indicating that the last species is probably formed in minute amount.

9. ^{31}P NMR spectra of 1a with NaI (1 equiv.) or I_2 (1 equiv.) in pyridine showed complete disappearance of 1a in 6 and 25 min respectively, and formation of tri- and tetrasubstituted pyrophosphates. In an analogous reaction with 1b, decomposition of 1b (formation of tetrasubstituted pyrophosphate) occurred to ca 50 and 25% respectively after 30 min.

10. S. B. Katti and K. L. Agarwal, Tet. Lett., 26, 2547 (1985).

11. C. Broka, T. Hozumi, R. Arentzen, K. Itakura, Nucl. Acids Res., 8, 5461 (1980).

12. W. T. Markiewicz, E. Biala, R. Kierzek, Bull. Pol. Ac. Chem., 32, 433 (1984).

Received November 18, 1986.