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Phosphorylation of heptafluorobutanol in the presence of metal chloride—ether catalytic systems

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Catalytic activity of complex catalysts based on Li, Na, K, and Cs chlorides and polydentate ligands, *viz.*, dibenzo-18-crown-6, mono-, di-, and tetraglymes, and poly(ethylene glycols) PEG-600 and PEG-1000 was examined in the phosphorylation of heptafluorobutanol with phosphorus oxychloride. The introduction of an organic ligand into a catalytic system leads to improvement in solubility of the salt used as a catalyst and to an increase in the reaction rate by a factor of 1.3—2.8. The catalytic systems based on LiCl and poly(ethylene glycols) proved to be most efficient.

Key words: catalytic phosphorylation, polyfluoroalkanols, homogeneous electrophilic catalysis, complex catalysts, Lewis acids, polydentate ligands, ethers.

The simplest and most convenient procedure for the synthesis of polyfluoroalkyl esters of oxygen-containing pentavalent phosphorus acids involves catalytic phosphorylation of polyfluoroalkanols with the corresponding phosphorus acid chlorides. This method was used for the preparation of various esters and chlorides of phosphoric,[1—3] phosphonic,[3—5] and phosphinic[6] acids based on primary,[1—6] secondary,[7—12] and tertiary[9,13] polyfluoroalkanols. Recently,[14—16] we have demonstrated that the catalytic activity of metal salts in these reactions depends substantially on the acceptor properties of the electrophilic catalysts used. Thus, weak Lewis acids exhibit higher catalytic activity than strong acids. At the same time, the weakest Lewis acids, *viz.*, chlorides of Group I metals, are less readily soluble in organic reaction media[3] because they occur as ionic salts characterized by high lattice energies, the energies of their solvation in these media being low.

The aim of the present study was to examine the catalytic activity of complex catalysts in the phosphorylation of heptafluorobutanol with phosphorus oxychloride.

Results and Discussion

To increase the solubility of catalysts utilized in the phosphorylation of polyfluoroalkanols with phosphorus acid chlorides, we used catalytic systems based on complexes of metal chlorides with organic ligands. One would expect that the addition of organic ligands will lead to an increase in solubility of the salt used as the catalyst due to improvement in conditions of cation solvation. When choosing ligands, we proceeded from the requirement that they must be stable under conditions of catalytic phosphorylation (high temperature, the presence of phosphorus acid chloride, Lewis acid, and HCl) and react with metal chloride to form complexes sufficiently stable for their solubility to be increased. At the same time, molecules of phosphorus acid chloride in the coordination sphere of the metal atom should not be completely replaced by the ligand molecules; otherwise it would lead to inhibition of the catalytic reaction. We decided to use ethers. Although there is evidence[17—19] that the C—O—C bond in ethers is cleaved under the action of Lewis acids (BCl_3, $AlCl_3$, $SnCl_4$, or $ZnCl_2$) as well as under the action of hydrogen chloride or $POCl_3$ in the presence of catalytic amounts of Lewis acids ($ZnCl_2$ or $HgCl_2$), we believed that the electron-withdrawing properties of chlorides of Group I metals are too weak to cause cleavage of the ether bond. However, this question called for experimental verification. To ensure the formation of rather stable complexes and taking into account that the oxygen atom in ethers possesses rather weak donor properties, we chose ligands containing several donor atoms capable of forming chelate complexes, *viz.*, dibenzo-18-crown-6 (DB18C6), mono-, di-, and tetraglymes, and poly(ethylene glycols) PEG-600 and PEG-1000.

We examined catalytic systems of this type based on LiCl, NaCl, KCl, and CsCl in the model reaction of 2,2,3,3,4,4,4-heptafluorobutanol (**1**) with $POCl_3$.

$$3\ \underset{\mathbf{1}}{C_3F_7CH_2OH} + POCl_3 \xrightarrow[-HCl]{\text{Catalyst, 160 °C}} \underset{\mathbf{2}}{(C_3F_7CH_2O)_3PO}$$

Metal chloride and the ligand were taken in a molar ratio such that there were six donor oxygen atoms per metal atom (five oxygen atoms in the case of

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tetra(ethylene glycol) dimethyl ether). The activity of the catalysts was estimated from the time it took for the reaction to be completed, which was judged visually from cessation of evolution of hydrogen chloride. The effect of the addition of the ligand on the efficiency of the catalyst was evaluated by comparing the duration of the reaction in the presence of the initial metal chloride (control) with that in the presence of a catalytic system containing the organic ligand. The reproducibilities of the reaction time and the yield of the product were ±5% and ±0.5%, respectively.

We examined the catalytic systems involving chlorides of Group I metals and dibenzo-18-crown-6. It appeared that the addition of this ligand to the reaction system led to acceleration of the reaction by a factor of 1.3—2.4 compared to the reactions proceeding in the presence of the corresponding pure metal chloride. Apparently, this is due to the gain in solubility of the catalyst and an increase in its effective concentration in the solution (Table 1). Thus, unlike LiCl, which was only partially soluble in the reaction mixture, the LiCl + DB18C6 catalytic system formed a homogeneous solution already at the initial stage of the reaction. Although the catalyst gradually precipitated, the overall reaction time decreased by a factor of 1.3.

The reaction was even more accelerated (1.5 times) in the presence of the NaCl + DB18C6 system in spite of the fact that the catalyst was dissolved incompletely. In this series of catalysts, the maximum acceleration of the reaction (2.4 times) was observed in the case of the KCl + DB18C6 system, *i.e.*, in the case of the cation whose diameter (2.66 Å) corresponds most closely to the size of the cavity of this crown ether (2.90 Å).[20] This catalytic system, like the lithium salt, was completely soluble only at the initial stage of the reaction. A further increase in the size of the cation (the catalytic system based on CsCl; the diameter of the cation was 3.34 Å)[20] led to an insignificant decrease in the coefficient of acceleration (to 2.3), the solubility of the catalyst being also somewhat improved compared to that of pure CsCl.

It should be noted that all catalytic systems in question are sufficiently stable under the reaction conditions, which made it possible to obtain phosphate **2** in good yield.

We also examined the possibility of the use of catalytic systems involving acyclic polydentate ethers with a flexible chain, which are capable of adapting themselves to the coordination polyhedron of the metal atom, and studied the effect of the structure of these ligands on the efficiency of catalysis. Taking into account that the use of LiCl in the systems with dibenzo-18-crown-6 provided the maximum rate of phosphorylation, we carried out comparison using catalytic systems based on this salt.

All linear ligands under study also improved the solubility of LiCl in the reaction mixture and the catalytic systems involving these ligands ensure acceleration of the reactions compared to those performed in the presence of pure LiCl (the initial stage of the reaction always proceeded under homogeneous conditions). In the LiCl + $3MeOCH_2CH_2OMe$ and LiCl + $2MeO(CH_2CH_2O)_2Me$ catalytic systems, there are six donor oxygen atoms per metal atom. However, the reaction in the presence of the catalytic system based on monoglyme proceeded somewhat more slowly (was accelerated by a factor of 1.5—1.6) than in the presence of the system based on diglyme (was accelerated by a factor of 1.9). It should be noted that phosphate **2** was obtained in equal yields in both cases. The observed deceleration of the reaction is, apparently, associated with the lower boiling point of monoglyme

Table 1. Catalytic phosphorylation of heptafluorobutanol with phosphorus oxychloride

Catalyst	Reaction time/h	Yield of phosphate **2** (%)	Solubility of the catalyst*
LiCl	3.6	93.8	p
LiCl + DB18C6	2.7	86.9	c → p
NaCl	19—20	91—92	i
NaCl + DB18C6	13.0	86.4	p
KCl	32—34	91—92	i
KCl + DB18C6	13.6	83.8	c → p
CsCl	15.0	85.6	c → i
CsCl + DB18C6	6.5	81.4	c → p
LiCl + $3MeOCH_2CH_2OMe$	2.3	91.3	c → p
LiCl + $2MeO(CH_2CH_2O)_2Me$	1.9	91.3	c → p
LiCl + $MeO(CH_2CH_2O)_4Me$	2.7	92.5**	c → p
LiCl + PEG-600	1.3	82.0	c
LiCl + PEG-1000	1.3	83.8	c

* The visual solubility of the catalysts: c, completely soluble; p, partially soluble; i, insoluble to a noticeable extent. The direction of the change of the catalyst solubility in the course of the reaction is indicated by an arrow.

** The product contained a tetraglyme impurity.

compared to that of diglyme resulting in a decrease in the temperature of the boiling reaction mixture.

Apparently, a decrease in the number of the donor oxygen atoms per metal atom to five in the LiCl + $MeO(CH_2CH_2O)_4Me$ catalytic system is responsible for a slight increase in the reaction time due to a decrease in the solubility of the catalyst compared to the catalytic systems based on other oligo(ethylene glycol) ethers. Moreover, the essential drawback of tetraglyme as a component of a catalytic system is that its boiling point is close to the boiling point of the target phosphate **2** resulting in reduction in the purity of the product due to which additional purification is required.

It should be noted that all ethers of ethylene glycols used also proved to be stable under conditions of catalytic phosphorylation as evidenced, in particular, by the high yields of phosphate **2**.

Homogeneous catalytic systems providing the maximum reaction rate were prepared with the use of poly(ethylene glycols) with the molecular weights of 600 and 1000 (PEG-600 and PEG-1000) as ligands. The amounts of the ligands in these systems corresponded to the following ratio: six O atoms of ether per Li atom. The use of these catalysts led to a decrease in the reaction time by a factor of 2.8 compared to the reaction in the presence of pure LiCl. A substantial decrease in the yield of the phosphate in the case of the catalytic systems based on poly(ethylene glycol) is attrubutable to consumption of $POCl_3$ in chlorination of the terminal hydroxyl groups of the ligands.

The experimental data demonstrated that the solubility of the above-mentioned catalysts decreased as the content of polyfluoroalkanol in the reaction mixture decreased in the course of the reaction, which indicates that heptafluorobutanol **1** solvates salts of the catalyst more efficiently than the final phosphate **2** and less basic intermediate phosphorochloridates and $POCl_3$. Unlike phosphoryl ligands, which solvate only cations, polyfluoroalkanol can solvate both cations (coordination at the oxygen atom of the hydroxyl group) and the chloride ion (hydrogen bonding). Acceleration of the reaction due to an increase in the solubility of salts used as the catalyst in the presence of small additives of polydentate ethers indicates that these ethers rather efficiently solvate chlorides of Group I metals and are superior to $POCl_3$ and phosphorylation products in this respect.

The probable reaction mechanism of catalytic phosphorylation can be represented as follows. At the first stage, dissolution of the catalyst in the reaction mixture gives rise to mixed complexes with an ether ligand and phosphoryl halide involved in the inner coordination sphere of the metal atom

$$\mathrm{MCl} + n\mathrm{L} + \mathrm{>POCl} \rightleftharpoons (\mathrm{>POCl})\cdot\mathrm{MCl}\cdot\mathrm{L}_n\,,$$

where M is the Group I cation and L is alcohol, ether, or a phosphoryl ligand, which does not undergo chemical conversions in this catalytic cycle.

The inner coordination spheres of these complexes involve the starting phosphorus acid chloride, polydentate ether, and, probably, polyfluoroalkanol. Coordination of acid chloride to the metal cation through the oxygen atom of the phosphoryl group (see Ref. 16 and references cited therein) ensures activation of this ligand due to an increase in the effective positive charge on the phosphorus atom and promotion of the nucleophilic substitution of the chlorine atom at the phosphorus atom.

Due to the low dielectric constant of the medium and rather weak donor properties of phosphoryl compounds and ethers present in solutions, the counterion (chloride) is, apparently, also involved in the inner coordination sphere of the metal atom. The formation of an active complex containing the chlorine atom in the inner coordination sphere of the metal atom (a contact ion pair) is also indicated by the high catalytic activity of the LiCl + polydentate ether systems comparable with that of the best homogeneous catalysts based on lithium salts.[14,15] This is associated with the fact that the displacement of the anion from the inner coordination sphere of the catalytic complex giving rise to solvent-separated ion pairs (for example, in the case of $LiClO_4$) leads to a sharp decrease in the catalytic activity.[14]

The next stage involves the nucleophilic substitution of the chlorine atom at the phosphorus atom in coordinated phosphoryl halide:

$$(\mathrm{>POCl})\cdot\mathrm{MCl}\cdot\mathrm{L}_n \xrightarrow[-\mathrm{HCl}]{+\mathrm{ROH}} (\mathrm{>PO_2R})\cdot\mathrm{MCl}\cdot\mathrm{L}_n\,,$$

where R is polyfluoroalkyl.

Then the active complex is regenerated through the displacement of the phosphoryl ligand in the coordination sphere of metal by the molecule of the unreacted initial acid chloride

$$(\mathrm{>PO_2R})\cdot\mathrm{MCl}\cdot\mathrm{L}_n \xrightarrow[-\mathrm{>PO_2R}]{+\mathrm{>POCl}} (\mathrm{>POCl})\cdot\mathrm{MCl}\cdot\mathrm{L}_n\,,$$

and the catalytic cycle is closed.

The resulting phosphate **2** can be readily isolated from the reaction mixture by vacuum distillation. The yields of **2** in the reactions with the use of some catalytic systems, though somewhat lower than those obtained in the reactions involving pure metal chloride, exceed 90% and approach the maximum yield obtained in the reaction with the use of pure LiCl as the catalyst.

On the whole, the results of the present study provide evidence that the approach proposed by us has promise in the design of efficient homogeneous catalytic systems for the phosphorylation of polyfluoroalkanols with phosphorus acid chlorides based on complexes of weak Lewis acids with organic ligands of the polyether type. The approach allows one to substantially accelerate the reaction with retention of a good yield of polyfluoroalkyl phosphate.

Experimental

We used the following compounds of reagent grade: $POCl_3$ purified by double distillation (b.p. 107 °C), 2,2,3,3,4,4,4-heptafluorobutanol (**1**) distilled successively over concentrated H_2SO_4 and P_2O_5 (b.p. 96 °C), and dimethyl ethers of mono-, di-, and tetra(ethylene glycols) purified by distillation over metallic sodium. Their physicochemical properties are identical with the published data. Dibenzo-18-crown-6 of chemically pure grade was used without additional purification. Poly(ethylene glycols) PEG-600 and PEG-1000 (Loba Chemie) were dried before use in a desiccator over concentrated H_2SO_4 at ~20 °C.

Catalytic phosphorylation of heptafluorobutanol (1) with $POCl_3$ (general procedure). A mixture of heptafluorobutanol (**1**) (17.0 g, 0.085 mol), $POCl_3$ (3.8 g, 0.025 mol), metal chloride (2 mmol), and the corresponding amount of an organic ligand was refluxed on a bath at 160 °C using a reflux condenser equipped with a bubble counter (filled with concentrated H_2SO_4) until evolution of HCl ceased. Excess polyfluoroalkanol was removed *in vacuo* using a water-aspirator pump at the bath temperature <100 °C. The residue was distilled *in vacuo* and phosphate **2** was obtained, b.p. 78—80 °C (0.5 Torr), n_D^{20} 1.3105 (*cf.* lit. data[1]). The catalysts, the metal chloride : polyether ratios, the reaction duration, and the yields of phosphate **2** are given in Table 1.

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