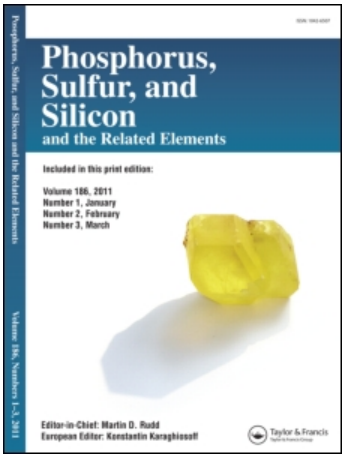

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P(III)-AMINES AS PHOSPHORYLATING AGENTS FOR ALCOHOLS AND AMINES. MODERN ASPECT OF THE PROBLEM.

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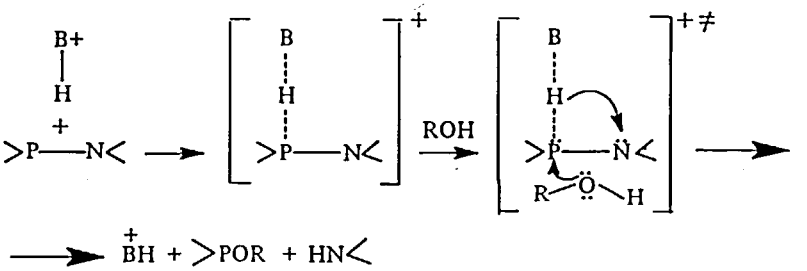
Abstract The factors governing the reactivity of P(III)-amines towards protonodonor nucleophiles are discussed. The last data on mechanism of acid catalysis, intramolecular catalysis and possibility of stereoselective phosphorylation by phosphoroamidites are represented.

Previously we have found that alcoholysis of phosphoroamidates in the presence of amines hydrochlorides occures according to **general acid catalysis**.

$$>\text{P-NEtPh} + \text{MeOH(t-BuOH)} \xrightarrow{\overset{+\,-}{\text{HBCl}}} >\text{P-OMe(-OBu-t)} + \text{HNEtPh}$$

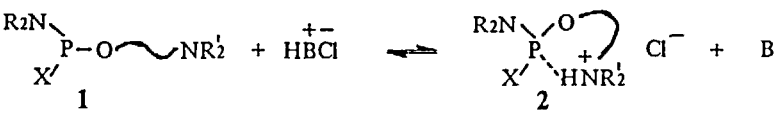
With using of Brønsted equation it was shown that catalytic process proceeds via the formation of the catalytic hydrogen-bonded complex incorporating the substrate and the catalyst as a whole:[1]



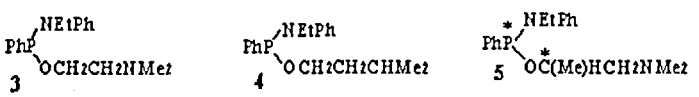
Further investigation of completely protonated phosphoroamidites allowed to discover that the presence of the bases in the reaction mixture and their tendency to the

prototropic processes have decisive meaning to the reactivity of phosphoroamidites.The obtained data testify that in the catalytic H-complex proton fulfills two functions: firstly, it activates the phosphorus atom in the electrophilic reaction, for example with an alcohol, and secondly, during the reaction proton migrates from the phosphorus to the nitrogen atom, thereby assisting the breakage of the P-N bond.[2]

This observation was the basis for our investigation of possible asymmetric induction resulting from the interaction of racemic P(III)-amine with optically active alcohols in the presence of optically active amine hydrochlorides. The stereoselectivity of the reaction we studied revealed only small enrichment and did not exceed 10% d.e., apparently as a result of a weak association of phosphoproamidite and a catalyst in the catalytic H-complex.[3] Taking this fact into consideration, we undertook the task of creating phosphorylation by means of a new type of aminoalkylphosphoroamidite of form **1**. This novel molecular design was based upon the idea that compounds of this structure should be protonated by amine(B) salts and form chelates with strong intramolecular bonds **2** thus creating the high effective catalyst concentration at the reaction center.



It was supposed that such hydrogen bonds will conformationally stabilize the reaction center and activate it for phosphorylation. If, in our system, chiral fragments were incorporated into **2**, favorable conditions for stereoselectivity during phosphorylation might ensue. Phosphonite **3**, which under protonation may form a stable 6-membered cycle, and its analog **4** in which the dimethylamino group is substituted for the isosteric isopropyl group, were chosen for nitial studies.[4]



The comparing methanolysis rates of racemic phosphonites **3** and **4** in the presence of amines hydrochlorides, which are essentially different in basicity, revealed that alcoholysis of phosphonite **3** *occures 300 times faster* than that of phosphonite **4**, although kinetic studies showed no dependence on acidity of catalysts in the rate of **3**. Comparison

of these rates allowed to conclude that effective **intramolecular catalysis** does occur during methanolysis of phosphonite **3** in the presence of an acid catalyst.

This novel intramolecular catalysis was used for increasing the stereoselectivity of phosphorylation. Phosphonite **5**, containing a second chiral center exactly in the "catalytic" part of the molecule, was investigated for stereoselective phosphorylation of optically active alcohols: sugar derivatives and quinine. During phosphorylation the maximum stereoselectivity equaled to 75% d.e. has been reached.[4] This result is considerably higher when only optically active phosphorylation catayst was used (as mentioned above[3]).

Acid catalysed stereospecific phosphorylation may have some practical applications in organic synthesis. The enrichment of racemic mixtures of alcohols turned out to be possible provided that the P(III)-amine contains an optically active fragment in the "catalytic" part of the molecule. The principal distinction of the proposed separation scheme from the standard ones based upon the usage of optically active reagents, consists in using of an intramolecular catalysis for ensuring of effective contact of reagents at the reaction center, containing an optically active residue. And this effect may be reinforced due to bulky chiral matrix, including effects of "guest - host" type.

For the realisation of this approach the effective methods of phosphorylation of complex natural compounds with specifically orientated in space hydroxyl groups, namely dianhydro-D-mannitol, -D-sorbitol, cyclodextrines, cellulose and chitozane have been elaborated by us. We studied factors having an influence upon the effectivity and direction of phosphorylation of indicated systems. The main difficulty, because of effective hydrogen bonds, consisted in competitive bis- and cyclophosphorylation closed in space hydroxyl groups. The phosphoro(III)azoles turned out to be the best phosphorylation means, which reduced to minimum the undesirable cyclophosphorylation.With using of phosphoro(III)azoles we obtained phosphorylated derivatives of cellulose and chitozane with high content of bonded phosphorus in their macromolecules. On the base of these phosphorylated macromolecules we have got complexes with rhodium and platinum. These complexes turned out to be very effective catalysts for hydrogenation of some unsaturated organic compounds with high stereoselectivity.[5] It is especially expected that chiral cavity of cyclodextrines will be an effective asymmetric inductor during phosphorylation. Additionally, they are of interest as chiral framework ligands for

coordination chemistry, metallocomplex catalysis and as valuable reagents for supramolecular and biomimetic chemistry.

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