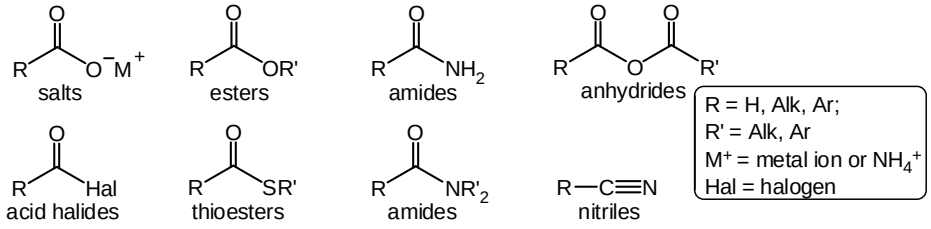
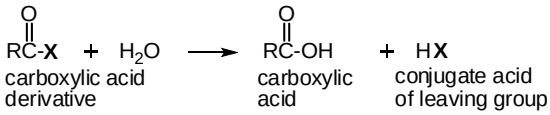
№ 29. FUNCTIONAL DERIVATIVES OF CARBOXYLIC ACIDS – CHARACTERISTICS AND TYPES. SELECTED CHEMICAL PROPERTIES

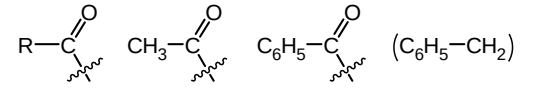
I. General characteristics.



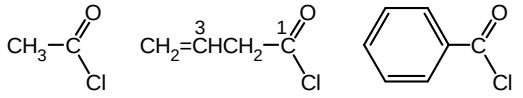
The class of carboxylic acids is a parent for several families that are collectively called acid derivatives. These functional derivatives include: salts, esters, amides, acid anhydrides, acid halides (such as chlorides and bromides), thioesters, and nitriles. The name functional derivative comes from the fact that all of them can be made from acids, and they can be hydrolyzed back to the parent acids.



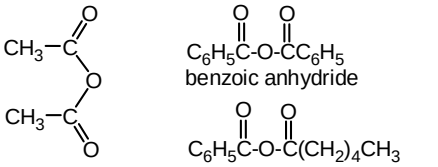
With the exception of nitriles, all carboxylic acid derivatives consist of an **acyl group** (R-CO-) attached to an oxygen, nitrogen, or halogen atom. Acyl groups are named by replacing *–ic acid* ending of the corresponding carboxylic acid by *–yl*. Examples are:



Acyl halides are named by placing the name of the appropriate halide after that of the acyl group, e.g.:

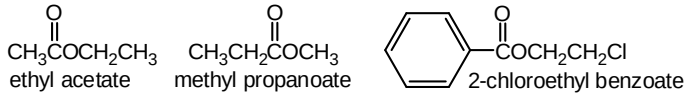


In naming *carboxylic acid anhydrides* in which both acyl groups are the same, one simply specifies the acid and adds the word anhydride. When the acyl groups are different, they are cited in alphabetical order, e.g.:

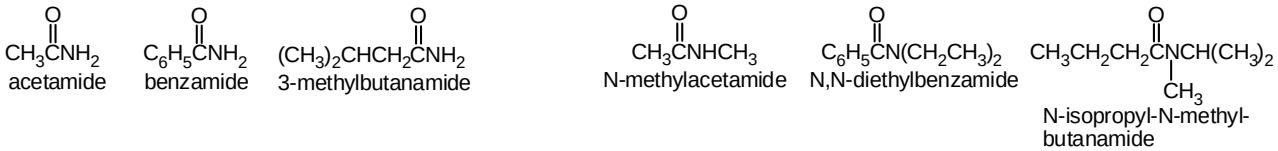


Cyclic anhydrides have their –CO-O-CO- unit as part of a ring. They are related to dicarboxylic acids and are named accordingly, e.g. succinic anhydride, maleic anhydride, phthalic anhydride.

The alkyl group and the acyl group of an *ester* are specified independently. Esters are named as *alkyl alkanoates*. The alkyl group R' of R-COOR' is cited first, followed by the acyl portion R-CO-. The acyl portion is named by substituting the suffix *–ate* for the *–ic* ending of the corresponding acid. Analogously are named also aryl esters of type R-COOAr.

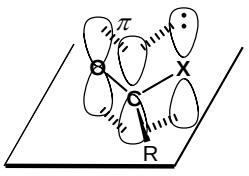


The names of *amides* of the type R-CONH$_2$ are derived from carboxylic acids by replacing the suffix *–oic acid* or *–ic acid* by *–amide*. Substituted on the nitrogen (secondary and tertiary) amides of the type R-CONHR' and R-CONR'$_2$ are named as *N*-alkyl- and *N,N*-dialkyl-substituted derivatives of a parent amide.

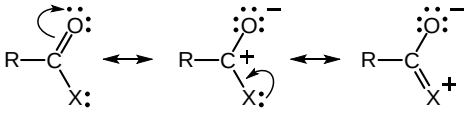


Substitutive names for *nitriles* add the suffix *–nitrile* to the name of the parent hydrocarbon chain that includes the carbon of the cyano group. Alternatively, they are sometimes named as alkyl cyanides.

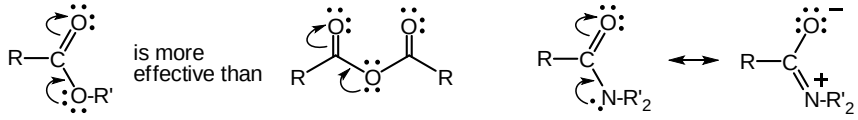
II. Structure of carboxylic acid derivatives. All derivatives of carboxylic acids have a planar arrangement of bonds to their carbonyl group. An important structural feature of acyl chlorides, anhydrides, esters, and amides is that the atom (X) attached to the acyl group (R-CO-) bears an unshared pair of electrons that is capable of



interacting with the carbonyl π system. The electron delocalization in carboxylic acid derivatives is represented with contributions from the following structures:

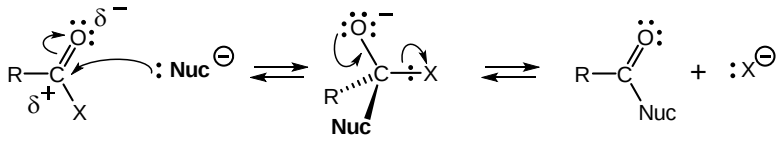


Electron release from the substituent X stabilizes the carbonyl group and decreases the partial positive charge on the carbonyl carbon (its electrophilic character). The extend of this electron delocalization depends on the electron donating properties of the substituent X. Generally, the less electronegative X is, the more it will donate electrons to the carbonyl group. Stabilization in acid chlorides is not great and pronounced as in other derivatives of carboxylic acids. This effect determines the high reactivity of acid chlorides (compare with the reactivity order below).



Acid anhydrides are better stabilized than acyl chlorides. The carbonyl group of an ester is even more stabilized than that of an anhydride, because in the latter both acyl groups compete for the oxygen lone pair and each carbonyl is stabilized less than the single carbonyl group of an ester. Esters are stabilized to about the same extend as carboxylic acids but not as much as amides. Nitrogen is less electronegative than oxygen and so is better able to donate an electron pair to a carbonyl group. This gives rise to a number of structural effects in amides. Unlike pyramidal structure in ammonia and amines, the bonds to nitrogen in amides lie in the same plane. The energy barrier for rotation around carbon-nitrogen bond in amides is unusually high for a single bond. This indicates that the C-N bond possesses a significant degree of double bond character, as the polar structure above suggests. The efficient electron release from nitrogen decreases the rate at which nucleophiles attack the carbonyl group in amides. An extreme example of carbonyl group stabilization is seen in carboxylate anions (salts). The negatively charged oxygen substituent is powerful electron donor to the carbonyl group. Electron delocalization causes the negative charge in a carboxylate ion to be shared equally by both oxygens (see Handout № 33). Thus, the conjugation effect is more effective than in all other derivatives.

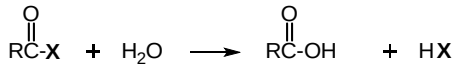
III. Reactivity. The reactions by which the carboxylic acid derivatives are prepared as well as the reactions they undergo, either *in vitro* or *in vivo*, generally occur as acyl group transfer reactions called nucleophilic acyl substitution. The general mechanism is:



The ability to transfer an acyl group (R-CO-) from X onto Nuc varies widely among the acid derivatives. Usually one acid derivative can be converted to another if the reaction leads to a more stabilized carbonyl group. Therefore, the reactivity in a nucleophilic acyl substitution reaction decreases in the order: **acyl chlorides (most reactive) > acid anhydrides > thioesters > esters > carboxylic acids > amides (least reactive).**

Carboxylic acids that have a poor leaving group (X = OH) require acid catalysis in order to undergo nucleophilic acyl substitution whereas acyl chlorides which have a good leaving group (X = Cl) do not require catalysis. The reactions of acid anhydrides and esters are usually slow unless catalysis (acid or base) is employed.

IV. Typical reactions. **1. Hydrolysis**

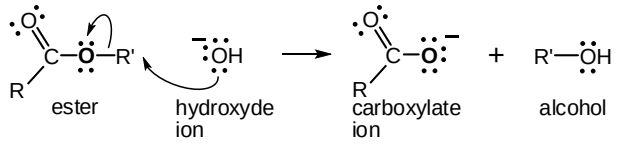


The hydrolysis may occur in acid or base medium and also under the catalytic action of enzymes called hydrolases. The enzyme hydrolysis is one of the fundamental steps in the metabolism of proteins, lipids, and polysaccharides. Actually, the proteins are polyamides and lipids are esters, i.e. carboxylic acid derivatives.

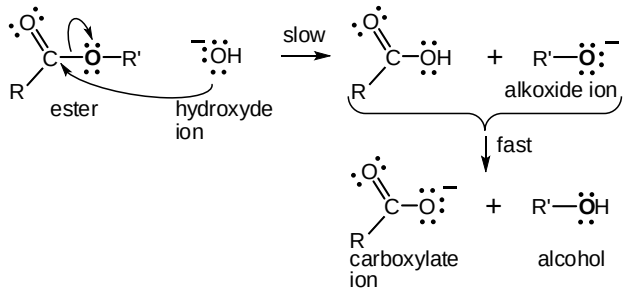
Examples of hydrolysis reactions:

The irreversible, base promoted ester hydrolysis is called saponification and it gives alkali carboxylates. In one of the earliest kinetic studies of an organic reaction (over a century ago) the rate of hydrolysis of ethyl acetate in aqueous sodium hydroxide was shown to be first-order in ester and first-order in base – rate = $k.[CH_3COOC_2H_5][NaOH]$. Overall, the reaction exhibits second-order kinetics. Both the ester and the base are involved in the rate-determining step or in a rapid step that precedes it. Two, shown on the right processes, are consistent with second-order kinetics and both involve hydroxide ion as a nucleophile. They differ in the side of nucleophilic attack. One of these processes is simply S_N2 reaction in which hydroxide displaces carboxylate from the alkyl group of the ester. This pathway involves *alkyl-oxygen cleavage*, because it is the bond between oxygen and the alkyl group of the ester that breaks. The second process involves *acyl-oxygen cleavage*, where the hydroxide attacks the carbonyl group. The second pathway obtained convincing evidence from using isotopic labeling. When an ester labeled with ^{18}O in the ethoxy group (R' = C_2H_5) was hydrolyzed with base, all the ^{18}O was found in the ethyl alcohol; there was no ^{18}O enrichment in the sodium carboxylate, as shown in the scheme.

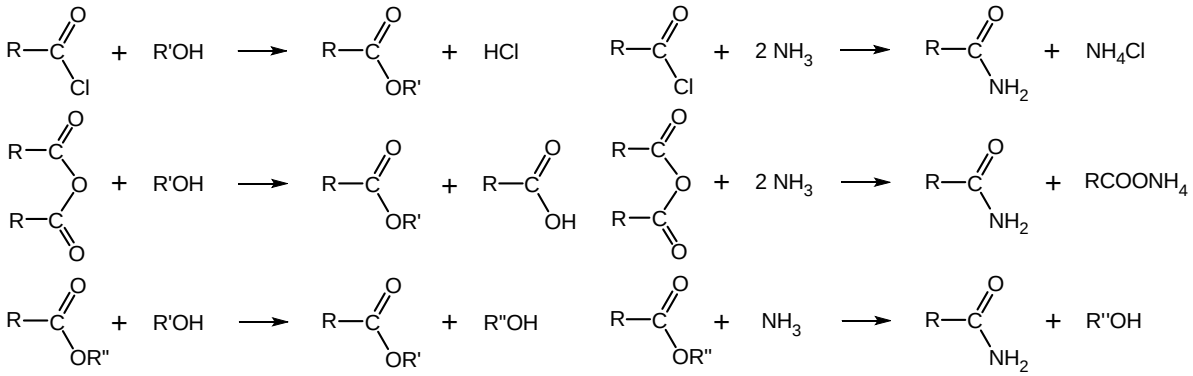
Alkyl-oxygen cleavage



Acyl-oxygen cleavage



2. Reactions with alcohols (alcoholysis) For the mechanism – see esterification in Handout № 33. These reactions allow for synthesis of variety of esters beginning from the most convenient and cheap reagent.



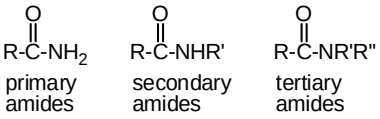
3. Reactions with ammonia (ammonolysis). These reactions lead to primary amides from different sources. Secondary and tertiary amides are best obtained from highly active carboxylic acid derivatives such as acid chlorides or anhydrides and primary or secondary amines.

IV. Specific characteristics and biological significance. **1. Salts**. The salts (carboxylates) are derivatives of carboxylic acids in whose molecules the hydrogen atom of the carboxyl group is replaced by a metal cation or ammonium cation (NH_4^+). In solid state salts have ionic crystalline structure. Many of them are soluble in water. The salts of the long chain fatty acids are called soaps. As defined earlier, the base-promoted hydrolysis of esters is saponification which means "soap making". More than 2000 years ago, soap was made by heating animal fat with wood ashes. Animal fat is rich in glycerol triesters, and wood ashes are a source of potassium carbonate. Base-promoted cleavage of the fats produced a mixture of long-chain carboxylic acids as their potassium salts. Potassium and sodium salts of long-chain carboxylic acids form micelles that remove grease and have cleansing properties. Salts are grouped depending on the type of the cation and the carboxylate anion, for example:

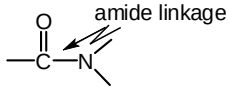
$CH_3COO^-K^+$	$CH_3(CH_2)_{16}COO^-Na^+$	$C_6H_5COO^-Na^+$	$(HCOO^-)_2Ca^{2+}$
potassium acetate	sodium stearate	sodium benzoate	calcium formate

2. Amides.

The general formula for amides takes into account the possibility for nitrogen substitution, as in:

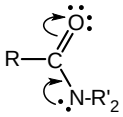


The bond between an acyl group and nitrogen atom in an amide molecule is known as amide linkage. The same linkage is found in protein molecules, then it is called a peptide bond.

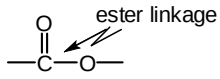


Unlike amines, amides are not proton acceptors, i.e. amides are not basic. They are not acidic either because the donation of a proton is to a very limited extend. In particular, in aqueous solutions, amides are neutral in an acid-base sense. A dissolved compound containing amide group does not affect the pH of an aqueous solution.

The conjugation effect between the electron-withdrawing carbonyl group and the nitrogen atom's lone pair causes the acid-base neutrality of amides. Although both an amide and an amine have unshared pair of electrons on nitrogen, in the amide this pair is involved so tightly in conjugation with the carbonyl π system, that the shown electron pair on the nitrogen atom of the amide cannot actually accept and hold the proton.



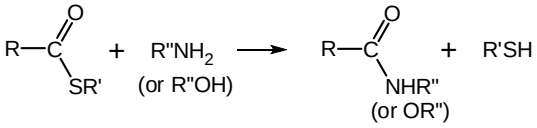
3. Esters. The functional group of an ester is the central structural feature of all the edible fats and oils, as well as of a number of constituents of living cells. The ester group is recognized by the connection between an acyl group and an oxygen atom that is connected to alkyl or aryl residue. The single bond between the carbonyl C and the O that holds ester's alkyl group is called an ester linkage. It is the bond that breaks when ester is hydrolyzed by water.



Esters are moderately polar. Dipole-dipole interactions contribute to the attractive forces that cause esters to have higher boiling points than hydrocarbons of similar molecular weight. Because they lack OH groups, esters cannot form hydrogen bonds to each other; consequently, esters have lower boiling points than alcohols.

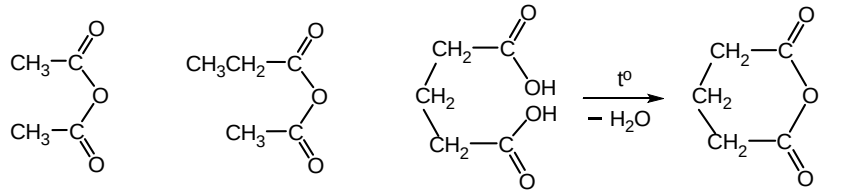
Many esters are naturally occurring substances. Those of low molecular weight are volatile; and many have pleasant odors, in contrast to the corresponding acids with vile odors. Esters often comprise a significant fraction of the fragrant oil of fruits and flowers.

4. Thioesters. Thioesters are the acyl derivatives of thiols and contain the linkage –CO—S-C-. The reactions of thioesters are similar to those of acid anhydrides and esters but their reactivity is closer to the anhydrides. Nucleophilic acyl substitution of a thioester gives a thiol along with the product of acyl transfer, for example:



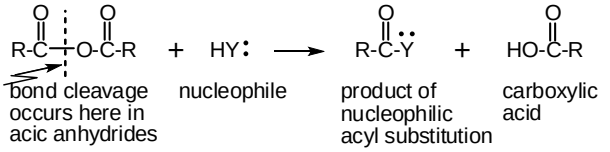
Nucleophilic acyl substitution reactions in thioesters occur faster and are characterized by a more negative ΔG^{o} than those of simple esters. This has important consequences for biochemistry. The selection of thioesters for biochemical reactions is partly due to their enhanced reactivity. They easily transfer acyl group, e.g. to amines as shown above. Carboxylic acids are frequently incorporated into metabolic processes in cells via the formation of their esters with coenzyme A (CoA—SH), a complex thiol which, nevertheless, shows typical reactions of a simple thiol. Because sulfur does not donate electrons to an attached carbonyl group as well as oxygen does, compounds of the type RCO-SR' (thioester) are better acyl transfer agents than is RCO-OR' (ester).

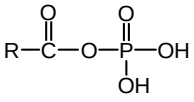
5. Anhydrides. Anhydrides can be derived from one monocarboxylic acid as is acetic anhydride which is the most readily available anhydride, produced in millions of tons annually. Acetic anhydride has several commercial applications, including the synthesis of aspirin and the preparation of cellulose acetate for use in plastics and fibers. Anhydrides can be derived also from two different acids, as in acetic propionic



acetic anhydride | acetic propionic anhydride | glutaric acid | glutaric anhydride

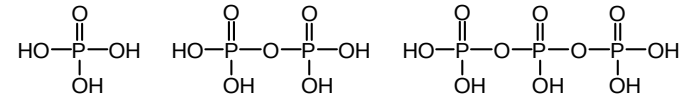
anhydride. Internal (cyclic) anhydrides are obtained from one dicarboxylic acid, e.g. glutaric anhydride. Two cyclic anhydrides, maleic anhydride and phthalic anhydride, are industrial chemicals. After acyl halides, the next most reactive class of carboxylic acid derivatives is acid anhydrides. The most important reactions of acid anhydrides involve cleavage of a bond between oxygen and one of the carbonyl groups. One acyl group is transferred to an attacking nucleophile; the other retains its single bond to oxygen and becomes the acyl group of a carboxylic acid.





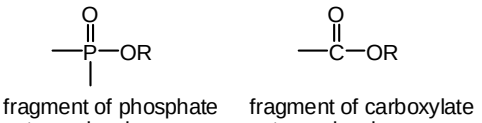
Anhydrides can be derived also from one carboxylic acid and one inorganic acid, for instance mixed anhydrides with phosphoric acid.

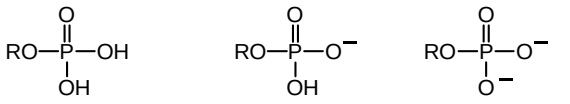
6. Organophosphate esters and anhydrides. Anions of esters of phosphoric acid, diphosphoric acid, and triphosphoric acid are some of the most widely found substances in living organisms. Phosphoric acid appears in several forms in the body but phosphoric acid, diphosphoric acid and triphosphoric acid are the three fundamental parents to all forms. They are all polyprotic acids, releasing various number of protons that depends on medium pH. At the slightly alkaline pH of body fluids they exist as mixtures of differently charged anions. The net charge on each anion and their relative amount are function of pH.



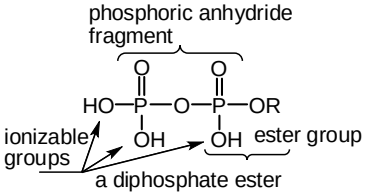
6.1. Esters of alcohols and phosphoric acid are monophosphate esters. Portion of the structure of phosphoric acid resembles a carboxyl group:

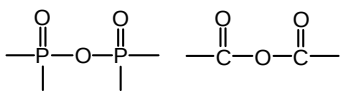
Therefore, it is not surprising that esters of phosphoric acid exist and they are structurally similar to esters of carboxylic acids. One significant difference between the two classes of esters is that an ester of carboxylic acid is neutral in aqueous solution whereas a phosphate ester is still a diprotic acid. Its molecules still carry two proton-donating –OH groups. Therefore, depending on pH, a phosphate ester exists in aqueous solution in any of the three forms (on the left), and usually there is an equilibrium mixture of all three. The uncharged phosphate ester, which is diprotic acid, is favored at low pH, the monoanion (singly ionized, monoprotic acid) – at pH values just below 7, and the dianion (doubly ionized form) is dominant form at pH values above 7 (in alkaline medium). At physiological pH (slightly more than 7) phosphate esters exist mostly as the doubly ionized species, as the dianion. Enzymatic *phosphorylation* is the general term describing biochemical formation of a phosphate ester by reaction of a –OH group, e.g. of serine in a protein, and phosphate group. Besides protein phosphorylation, the reaction is known to occur with sugars and ADP to give ATP (see below).





6.2. Diphosphoric acid gives diphosphate esters with alcohols. A diphosphate ester contains three types of functional groups: an ester group, three ionizable, proton-releasing –OH groups, and a phosphoric anhydride system:

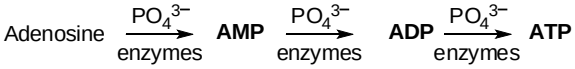




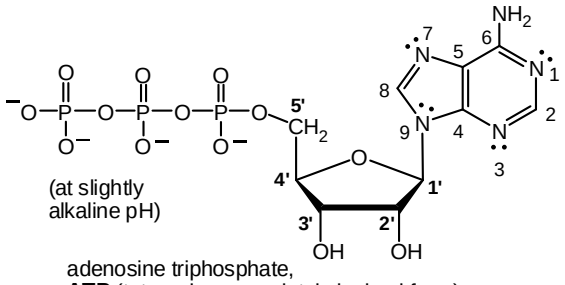
There is profound similarity between fragment of this ester and a fragment of an anhydride of carboxylic acid. The diphosphate ester behaves in aqueous solution similarly to a phosphate ester, with the only difference that the former can release three protons, depending on the pH of the medium.

6.3. Triphosphoric acid forms triphosphate esters with alcohols. Adenosine triphosphate or ATP is the most

common and widely occurring member of a small family of energy-rich triphosphate esters.



The biosynthesis of adenosine triphosphate, shown schematically via monophosphate (AMP) and diphosphate (ADP), is a sequence of enzymatic phosphorylation reactions: the first one is phosphorylation of a sugar –OH group, the next two – formation of phosphoric anhydride bonds. The energy to drive each step comes from carbohydrates by the process of glycolysis. It is convenient to view ATP as the storage vessel for the energy released during conversion of carbohydrates to CO_2 and H_2O. That energy becomes available to the cells when ATP undergoes hydrolysis. The hydrolysis of ATP to ADP and phosphate has a ΔG^{o} value of –35 kJ/mol (–8.4 kcal/mol). Since the triphosphates have two phosphoric anhydride systems in each molecule, they are among the most energy-rich compounds in the body (on mole base). They are called "power-houses of cells".



adenosine triphosphate,
ATP (tetraanion, completely ionized form)

The negatively charged oxygen atoms in the phosphoric anhydride system of ADP and ATP screen the phosphorus atoms. These charges deflect incoming nucleophiles (electron-rich particles), like molecules of an alcohol or water, whose oxygen atom could reach the anhydride's phosphorus atoms. This is the reason why phosphoric anhydride systems hydrolyze slowly in cells with water, or react sluggishly with ROH, unless specific enzyme is present. When the enzyme is involved, the large chemical energy of the phosphoric anhydride becomes available to the cell.