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PROGRESS IN THE CHEMISTRY OF THE CARBODIIMIDES

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1. INTRODUCTION

The carbodiimides form a class of organic compounds the membership of which is determined by the presence of the carbodiimide grouping $-N=C=N-$. The general formula of the carbodiimides may be represented as follows:

$$R-N=C=N-R',$$

where R and R′ are alkyl or aryl groups.

Carbodiimides may be regarded as alkyl (aryl) derivatives of the simplest representative of the class HN=C=NH, which exists mainly as the tautomeric form of cyanamide, $H_2N-C\equiv N$.[1] Carbodiimides form one of several classes of organic compounds with cumulative double bonds (isocyanates, ketens, allenes, ketenimines). Although some aromatic carbodiimides were first synthesised 80 years ago, it is only in recent years that interest in them has been aroused[1]. Recently polymeric carbodiimides $(-R-N=C=N-)_x$ with fibre- and film-forming and other valuable practical properties have been obtained.

In Russian literature there are only references of the most general kind to the carbodiimides[2].

2. PREPARATION OF CARBODIIMIDES

Up to recently the method of synthesising carbodiimides by eliminating hydrogen sulphide from disubstituted thioureas had the most importance preparatively[3].

$$RNHCSNHR' \xrightarrow{-H_2S} RN=C=NR'.$$

The starting thioureas are obtained from amines or disulphides. Aliphatic amines first form the salt of a substituted dithiocarbamic acid:

$$RNHCS\overline{S}R'\overset{+}{N}H_3 \xrightarrow{t^\circ} RNHCSNHR'+H_2S.$$

The thioureas are treated with mercury(II) oxide, lead(II) oxide, or sodium hypochlorite, and carbodiimides are formed. A large number of aliphatic, aromatic, and mixed carbodiimides have been synthesised in this way. When thioureas are treated with mercury(II) oxide or sodium hypochlorite the yield of carbodiimides is fairly high: with dicyclohexylcarbodiimide the yield reaches 90%.[4-10]

In an original method of preparing dicyclohexylcarbodiimide developed by Amiard, water is eliminated from *NN'*-dicyclohexylurea with the aid of *p*-toluenesulphonyl chloride and pyridine[11]. The starting symmetrical dicyclohexylurea is obtained in good yield by heating urea with cyclohexylamine:

$$2C_6H_{11}NH_2 + NH_2CONH_2 \rightarrow C_6H_{11}NHCONHC_6H_{11} + 2NH_3,$$

$$C_6H_{11}NHCONHC_6H_{11} + 2p\text{-}CH_3C_6H_4SO_2Cl \longrightarrow$$

$$\longrightarrow C_6H_{11}N=C=NC_6H_{11} + (p\text{-}CH_3C_6H_4SO_2)_2O + 2HCl.$$

Diethylcarbodiimide was first synthesised by the interaction of ethyl isocyanate and tetraethylphosphine imide; the latter can be obtained from triethylphosphine and ethyl azide[12]:

$$(C_2H_5)_3P+C_2H_5N_3 \rightarrow (C_2H_5)_3P=NC_2H_5+N_2,$$

$$(C_2H_5)_3PNC_2H_5+C_2H_5NCO \rightarrow C_2H_5N=C=NC_2H_5+(C_2H_5)_3PO.$$

Some aromatic carbodiimides were first prepared by the prolonged heating of isocyanates. For example, diphenylcarbodiimide is prepared by heating phenylisocyanate for 24 h at 180° in the absence of air[13]:

$$2C_6H_5NCO \longrightarrow C_6H_5N=C=NC_6H_5+CO_2.$$

Prolonged heating converts diisocyanates into polycarbodiimides. Thus, when methylenebis-(4-phenylisocyanate) was heated at 220° in the absence of air, the content of isocyanate groups fell from 33.5 to 25.8% in 11 h and to 22.8% in 24 h and methylenediphenyl-4,4'-poly(carbodiimide) was formed. An empirical formula relating the degree of conversion of isocyanates into carbodiimides with the temperature and duration of the reaction has been derived from a study of the kinetics of the thermal conversion of a number of isocyanates into carbodiimides[14]:

$$g = 100 - at^2,$$

where g is the amount of unreacted isocyanate groups expressed as a percentage of the initial quantity, t the time of heating in hours, and a an empirical temperature coefficient (at 220° this varies from 0.1 to 0.6, and at 180° it varies from 0.01 to 0.06).

It has been demonstrated that the thermal conversion of isocyanates into carbodiimides is autocatalytic.

The conversion of isocyanates into carbodiimides on heating presumably proceeds through intermediate unsymmetrical cyclic dimers. The decarboxylation of such dimers is greatly facilitated by the non-uniform distribution and displacement of electron density in the ring[15]:

$$2RNCO \xrightarrow{t^\circ} \left[\begin{array}{l} R-N=C-O \\ \quad\quad\ \ \vdots \\ R-N-C=O \end{array}\right] \longrightarrow R-N=C=N-R + CO_2.$$

The method of preparing carbodiimides by heating isocyanates has not been widely used because a large amount of by-products is formed in the reaction.

The method of preparing carbodiimides by the catalytic decarboxylation of isocyanates, which has been developed in recent years, is in practice the most important method[16-23]. Carbodiimides are prepared by this method by adding a decarboxylation catalyst to isocyanates, in the pure state or in an inert solvent; heating for several hours produces a vigorous evolution of carbon dioxide and carbodiimides are formed in high yield

$$2RNCO \xrightarrow[\text{catalyst}]{t^\circ} RN=C=NR+CO_2.$$

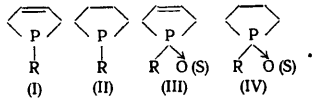
The following examples illustrate the method. *p*-Nitrophenylisocyanate is heated with catalyst (1-ethyl-3-methyl--3-phospholine-1-oxide) and there is a vigorous evolution of carbon dioxide; after 1–2 min the reaction mass solidifies and, after removal of the residual carbon dioxide, 4,4'-dinitrophenylcarbodiimide is obtained in 100% yield[19].

Aliphatic carbodiimides are formed in low yield by this method, but the yield of product can be increased, however, by selecting suitable conditions. Thus, when 50 g of butylisocyanate was boiled with 0.7 g of 3-methyl-1--phenylphospholen 1-oxide for 15 h only 6.2 g (15.5% yield) of dibutylcarbodiimide was obtained; when, however, the same amount of butyl isocyanate was heated in decahydronaphthalene with double the amount of catalyst, 24 g (60% yield) of dibutylcarbodiimide was obtained 15 min after the beginning of the reaction[20]. Diethylcarbodiimide has been obtained in 50% yield by heating a solution of ethyl isocyanate in toluene (1 : 1 by volume) in the presence of 3-methyl--1-phenylphospholen 1-oxide (3% of the weight of isocyanate) for 6 h at 100–105°.[17]

Polycarbodiimides are obtained from diisocyanates by the same method. The reaction is, as a rule, carried out in a solvent (light petroleum, benzene, toluene, xylene) in the presence of 2–3% of decarboxylation catalyst.

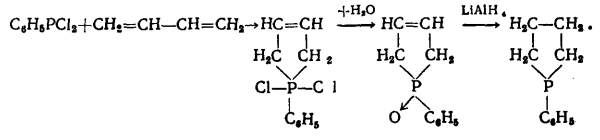
A great many compounds have been used as catalysts for the decarboxylation of isocyanates. However, the greatest catalytic activity is shown by substituted phosphocyclopentenes, phospholens (I), and their saturated analogues, the

phospholans (II), and also by the oxides and sulphides of the phospholens (III) and phospholans (IV):[24]

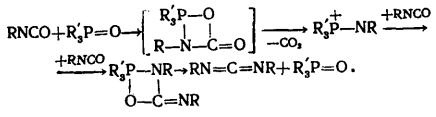


(I) (II) (III) (IV)

These organophosphorus catalysts are obtained by fairly simple methods, for example, by the reaction of alkyl- or aryl-dichlorophosphines with isoprene or butadiene, or in other ways[18,20,25]:



In addition to the phospholens, trialkylphosphine oxides have been proposed as catalysts for the decarboxylation of isocyanates. The mechanism of formation of carbodiimides when these catalysts are used is represented as follows[21-23]:



A number of other organophosphorus, and also organoarsenic, compounds, with a strongly polarised P=O or As=O bond have fairly high catalytic activity; examples are, the phosphates $(RO)_3PO$, the phosphonates $(RO)_2P(O)R'$, triarylarsine oxides Ar_3AsO, etc.[21,26] The activities of different catalysts have been compared by studying the kinetics of the decarboxylation of isocyanates[15,22].

3. PHYSICAL PROPERTIES OF CARBODIIMIDES

Aliphatic carbodiimides are colourless or slightly coloured distillable liquids with a characteristic odour. The aromatic carbodiimides are generally crystalline compounds that decompose or become partly polymerised on long storage or on being heated. For example, dicyclohexylcarbodiimide, which is widely used in laboratory practice, is a crystalline compound with m.p. 35–36° under normal conditions. It is fairly stable and can be kept for several months; it is readily soluble in inert organic solvents and in alcohol, with which it virtually does not react even on being heated; in this it differs from other carbodiimides. The stability of carbodiimides increases with increasing chain length and branch of side-chains.[27,28] For example, diethylcarbodiimide polymerises after a few days, but diisopropyl- or dicyclohexyl-carbodiimides are stable when stored for several months[12,28]. Unsaturated dialkenecarbodiimides with an unbranched chain (diallyl- and allylbromo-carbodiimides) are stable as monomers only when a polymerisation inhibitor has been added[29].

The aromatic carbodiimides differ considerably in their stability[10]. For example, di-*p*-iodophenylcarbodiimide polymerises very readily. The freshly prepared unsubstituted diphenylcarbodiimide is a mobile liquid, but after a few days it is converted to a solid pasty mass. Di-*p*-tolylcarbodiimide is a solid crystalline compound that remains stable for several months. Bis-(*p*-dimethylaminophenyl)-carbodiimide is stable for three years. Alcoholic solutions of aromatic carbodiimides are more sensitive to heat than solutions of aliphatic carbodiimides.

TABLE. Carbodiimides prepared by decarboxylation of isocyanates.

Carbodiimide	B.p., °C/mmHg	Literature reference
Dipropyl	56—58/11	18
Diisopropyl	36—37/10	33
Diallyl	58—60/10	18
Diisopropenyl	73/43	
Diphenyl	171/12	18
Dicyclohexyl	154/12	22
4,4'-Dinitrophenyl	m.p. 164—166	19

The decomposition and polymerisation products of carbodiimides are basic, but their composition and structure have not been sufficiently studied. The dimers and trimers of diphenyl- and di-*p*-tolyl-carbodiimides have been most studied[10].

The physical properties and stability of the poly(carbodiimides) depend on the methods by which they are prepared and the degree of polymerisation. Poly(carbodiimides) may be obtained as elastic vulcanisates, glasslike blocks, moulding powders, film, and fibres. They are soluble in organic solvents. The poly(carbodiimide) obtained from toluene-2,4-diisocyanate melts at 113–115°; the poly-(carbodiimide) of methylenebis-(4-phenylisocyanate), which melts at 250°, is similar to Nylon-6.[16]

An intense absorption band characteristic of the –N=C=N– group occurs in the 2100–2130 cm^{-1} region of the infrared spectrum of carbodiimides[15,16,19]. It is interesting that allenes have a characteristic absorption band in the 1875–2000 cm^{-1} region[25,30]; isocyanates have a band in the 2180–2270 cm^{-1} region[31], and ketimines a band at about 2000 cm^{-1}.[32] Table 1 shows some carbodiimides obtained by the decarboxylation of isocyanates.

4. CHEMICAL PROPERTIES OF CARBODIIMIDES

The chemical properties of the carbodiimides are determined primarily by their unsaturation, and therefore by their tendency to enter into addition reactions. This refers in particular to reactions with compounds having an active hydrogen atom.

a. Reactions with weak acids. Carbodiimides combine with hydrogen sulphide to form *sym*-dialkyl(aryl)-thioureas[5,34]:

$$RN=C=NR+H_2S\rightarrow RNHCSNHR.$$

With hydrogen selenide the carbodiimides form the corresponding selenoureas[35]:

$$RN=C=NR+H_2Se\rightarrow RNHCSeNHR.$$

Carbodiimides react with hydrogen cyanide to form α-cyano-*NN'*-dialkyl(aryl)formamidines[36,37]:

$$RN=C=NR+HCN\rightarrow RNHC(=NR)CN.$$

b. Reactions with phenols. When carbodiimides are heated with phenols, crystalline ethers of pseudoureas are formed[3]:

$$RN=C=NR+ArOH\rightarrow RNHC(=NR)OAr.$$

c. Reactions with carboxylic acids. Carbodiimides react with carboxylic acids to form acyl ureas or

acid anhydrides and ureas, according to the reaction conditions [27,34]:

$$RN{=}C{=}NR + R'COOH \begin{cases} \nearrow RNHCONHR + (R'CO)_2O \\ \searrow R'CONRCONHR \end{cases}.$$

Carbodiimides react analogously with dicarboxylic acids [38,39]. Oxalic acid forms disubstituted ureas with carbodiimides [10]. This reaction is used for the identification of carbodiimides. Carbodiimides are quantitatively determined in the following manner [40]. A known amount of oxalic acid dissolved in dioxan is added to the carbodiimide sample, the mixture is heated under reflux, and the solution is titrated against sodium methoxide dissolved in a mixture of benzene and methanol in the presence of Thymol Blue indicator.

The use of the reactions of carbodiimides with carboxylic acids is considered in greater detail below, in the Section dealing with applications of carbodiimides. This also applies to the reactions of carbodiimides with phosphoric acids.

d. Reactions with phosphoric acid. Carbodiimides react vigorously with esters of phosphoric acid to give esters of pyrophosphoric acid in quantitative yield [41]:

$$2(RO)_2POOH + RN{=}C{=}NR \longrightarrow R\overset{+}{N}H{=}\overset{\cdot}{C}{-}\overset{\cdot}{N}HR + \bar{O}P(OR)_2 \longrightarrow$$

$$\longrightarrow (RO)_2P(O)-O-P(O)(OR)_2 + RNHCONHR$$

The reaction with alkylsulphonic acids occurs in a similar manner with the formation of acid anhydrides and ureas [10]:

$$2R'SO_3OH + RN{=}C{=}NR \rightarrow R'SO_2{-}O{-}SO_2R' + RNHCONHR.$$

e. Reactions with alcohols. On being heated, alcohols combine with carbodiimides to form substituted ureas. The reaction goes best in the presence of acid catalysts [42,43]:

$$RN{=}C{=}NR \xrightarrow{H^+} R\overset{+}{N}H{=}C{=}NR \xrightarrow{+R'OH} RNHC(=NR)OR' + H^+.$$

f. Other addition reactions. In the presence of catalytic quantities of their sodium derivatives, malonic ester, acetoacetic ester, and acetylacetone form substituted amidines with carbodiimides [44], for example:

$$RN{=}C{=}NR + CH_2(COOC_2H_5)_2 \rightarrow RNHC(=NR)CH(COOC_2H_5)_2.$$

Substituted amidines are also formed by the reaction of carbodiimides with Grignard reagents [45]:

$$RN{=}C{=}NR + R'MgBr \rightarrow RNCR'{=}NRMgBr \xrightarrow{H_2O} RNHCR'{=}NR + MgOHBr.$$

Ammonia combines with carbodiimides to give disubstituted guanidines [5]:

$$RN{=}C{=}NR + NH_3 \rightarrow RNHC(=NR)NH_2.$$

Carbodiimides react with amines to form trisubstituted guanidines [5,6]:

$$RN{=}C{=}NR + R'NH_2 \rightarrow RNHC(=NR)NHR'.$$

With cyanamide they form disubstituted cyanoguanidines [46]:

$$RN{=}C{=}NR + H_2NC{\equiv}N \rightarrow RNHC(=NR)NHCN.$$

Aliphatic carbodiimides react with cyanamide in the presence of sodium ethoxide.

Diazomethane combines with aromatic carbodiimides to form triazole derivatives [47,48]:

$$ArN{=}C{=}NAr + CH_2N_2 \rightarrow ArNHC(=CH{-}N{=}N){-}NAr.$$

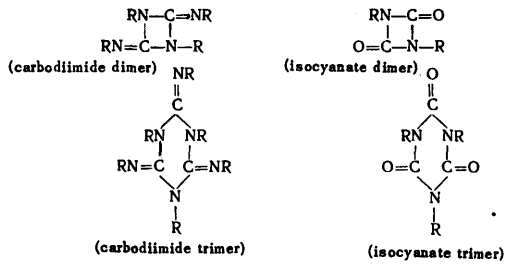
Derivatives of tetrazole are formed by the addition of hydrazoic acid to carbodiimides [49,50]:

$$ArN{=}C{=}NAr + HN_3 \rightarrow ArN{=}C(N_3){-}NHAr \rightarrow ArN{-}C(=N{-}N{=}N){-}NHAr.$$

Dry hydrogen chloride reacts vigorously with diphenylcarbodiimide [10]. The reaction proceeds with appreciable evolution of heat and leads to the addition of one or two molecules of hydrogen chloride, depending on the proportions of the reagents. In the presence of water this reaction leads to the formation of *sym*-diphenylurea

$$C_6H_5N{=}C{=}NC_6H_5 \begin{cases} \xrightarrow{HCl} C_6H_5NH{-}CCl{=}NC_6H_5 \\ \xrightarrow{2HCl} C_6H_5NH{-}CCl_2NHC_6H_5 \\ \xrightarrow[HCl]{H_2O} C_6H_5NHCONHC_6H_5 \end{cases}.$$

g. Formation of dimers and trimers. The carbodiimides form dimers and trimers similar in structure to isocyanate dimers and trimers [3,51]:

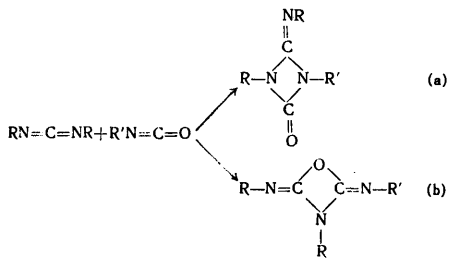


The chemical properties of the carbodiimides given above show that these are similar to those of other classes of compounds with cumulative double bonds, in particular to those of the isocyanates. However, under ordinary conditions the carbodiimides react less vigorously than the isocyanates with acids, alcohols, and amines [51]. The aliphatic carbodiimides are less reactive than the aromatic [15].

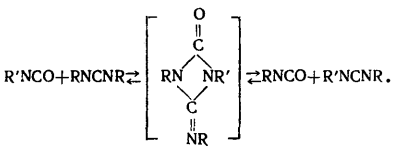
The chemical properties of the polycarbodiimides have been little studied up to now. Some of them, for example the polycarbodiimide obtained by decarboxylation of methylene-bis-(4-phenylisocyanate) react slowly with acids, alkalis, and amines, even on heating [15]. In contrast, the polycarbodiimide obtained from toluylenediisocyanate readily reacts with alcohols and ammonia [17,18].

5. REACTIONS OF CARBODIIMIDES WITH ISOCYANATES

Several years ago it was shown that carbodiimides react with isocyanates to form thermally unstable adducts [15]:



Compound with structure (a) was identified by infrared spectroscopy as the main product of the reaction. Compounds of this type are called uretonimines by analogy with uretdiones, the dimerisation products of isocyanates [15]. When heated, uretonimines decompose into the starting materials and products in which the radicals are completely or partially exchanged:



It is possible to exchange completely or partly the radicals of carbodiimides and isocyanates by suitable choice of reagents and reaction conditions.

Uretonimines are obtained from carbodiimides and isocyanates by heating them in the absence of air and moisture to 100–160°. Copper and copper salts are used as catalysts. Uretonimines are high-boiling liquids or solid compounds. For example, the uretonimine obtained from diisopropylcarbodiimide and phenyl isocyanate is a yellowish crystalline compound under ordinary conditions [52].

Diisocyanates react with carbodiimides to form two types of end-products [15]:

$$RNCNR+OCNR'NCO\rightarrow RNCNR'NCO+RNCO,$$
$$\text{(a)}\ RNCNR'NCO+RNCNR\rightarrow RNCNR'NCNR+RNCO,$$
$$\text{(b)}\ RNCNR'NCO+OCNR'NCO\rightarrow OCNR'NCNR'NCO+RNCO,$$

where $R = C_6H_{11}$; $R' = (CH_2)_6$.

In the last stage of the reaction, polymers of different chain length and with different end-groups can be obtained; the product depends on the proportions of the reagents used. Thus, if dicyclohexylcarbodiimide is added to an excess of hexamethylenediisocyanate, a poly(carbodiimide) of the following structure is obtained:

$$C_6H_{11}—[—(CH_2)_6—N=C=N—]_x—C_6H_{11}$$
$(x=1, 2, 3).$

If the diisocyanate is used in excess, the poly(carbodiimide) will have the isocyanate end-groupings:

$$O=C=N—(CH_2)_6—[—N=C=N—(CH_2)_6—]_x—N=C=O$$
$(x=1, 2, 3).$

In both cases, products of more branched structure are obtained along with these compounds. These products are formed by the direct reaction of carbodiimides with isocyanate groups according to the scheme given above for the formation of uretonimines [15].

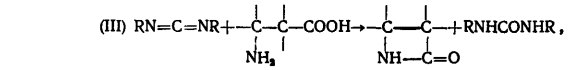
6. APPLICATIONS OF CARBODIIMIDES

As already mentioned, until a method of preparing carbodiimides by the catalytic decarboxylation of isocyanates was developed, they had no industrial applications and were used in laboratory synthesis and analysis for characterising carboxylic acids, identifying amino-acids in peptides, etc. [2]

Carbodiimides are also used as dehydrating agents for the production of ester (I), amide (II), lactam (III), and peptide (IV) bonds:

(I) $RN=C=NR+R'OH+R''COOH\rightarrow R''COOR'+RNHCONHR,$

(II) $RN=C=NR+R'NH_2+R''COOH\rightarrow R''CONHR'+RNHCONHR,$

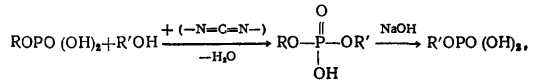
(III) 

(IV) $RN=C=NR+R'CHNH_2COOH+R''COOH\rightarrow R''CONHCHR'COOH+RNHCONHR.$

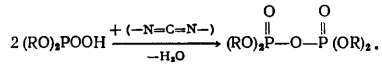
These reactions are quantitative with dicyclohexylcarbodiimide [2].

The β-lactam ring in penicillinoic acid was first closed to form penicillin by means of carbodiimides [2].

Other examples of the use of carbodiimides in dehydrating reactions are known in addition to the cases given above. Thus, carbodiimides have been used for phosphorylation reactions [2]:



and also for the preparation of pyrophosphoric acids:



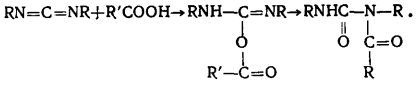
Peptides can be selectively degraded by means of carbodiimides:

$$CH_3CONHCH_2CONHCH_2COOH+RN=C=NR\rightarrow$$
$$\rightarrow CH_3CONHCH_2CONRCONHR\xrightarrow{NaOH} CH_3CONHCH_2COOH+NH_2CH_2CONRCONHR.$$

Carbodiimides have been successfully used in the synthesis of nucleotides, polynucleotides, coenzymes, etc. [43]

Polycarbodiimides have not yet found wide practical applications. But studies of the properties of polycarbodiimides give grounds for regarding them as promising polymer materials with film-forming and fibre-forming capabilities. Poly(carbodiimides) are outstandingly stable to heat and to the action of corrosive liquids [15,18,19,23].

The tendency of carbodiimides to form acylated substituted ureas by reaction with carboxylic acids has been utilised in employing them as anti-aging additives to polyurethanes. In these cases, the reaction of carbodiimides with acids goes according to the following scheme:



It is well known that when plastics containing ester groupings age, carboxylic compounds are formed that accelerate the reaction autocatalytically. It has been shown that poly-(carbodiimides) are effective inhibitors of this process. They are very compatible with plastics, stable on storage, non-volatile, etc.[15,53]

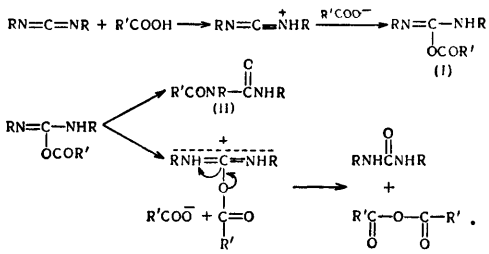
Carbodiimides can be used as anti-shrink additives in the treatment of textiles[54].

Some carbodiimides are physiologically active[54]. The toxicity of dicyclohexylcarbodiimide for the rat (LD_{50}) is 2.6 g kg^{-1}. Carbodiimides have herbicidal and fungicidal activity[55].

The use of carbodiimides in acylation reactions. The ability of carbodiimides to combine with carboxylic acids with the formation of *NN'*-diaryl- or *NN'*-dialkyl-ureides has been used for the identification of these acids[56]. The same reaction has been used for the detection of traces of acids in animal and vegetable oils[57]. In this reaction the best results are obtained with dicyclohexylcarbodiimide.

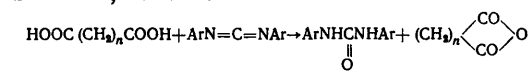
The nature of the end-products in this reaction depends on the structure of the carbodiimide and on the type of solvent. Ureides are the main products formed from diarylcarbodiimides; in those cases where dicyclohexylcarbodiimide was used, acid anhydrides and dicyclohexylurea were obtained as the main products. Zetzsche, using dicyclohexylcarbodiimide, obtained the anhydrides of butyric and stearic acids in 90% yield[56]. Ether, benzene, acetone, cyclohexane, and light petroleum were used as solvents in these reactions. Ureides of *NN'*-dicyclohexylurea were obtained in pyridine or alcohol solution.

According to Khorana[43], the mechanism of formation of acid anhydrides together with ureides may be represented as follows:



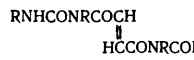
In accordance with the proposed scheme, a molecule of acid combines with one of the double bonds of carbodiimide to form an intermediate compound (I), which either rearranges to a more stable form with the formation of a ureide (II) or reacts with a second molecule of acid, if this is present in excess, to give an acid anhydride and a substituted urea. In alcoholic solution, compound (I) reacts with the alcohol to form an acid ester.

Khorana, who analysed the different directions the reactions of carbodiimides with carboxylic acids may take, has made the following observations[10]. With aromatic acids the reaction goes mainly in the direction of forming alkylureas. Ether, benzene, dioxan, and pyridine may be used as solvents; the use of alcohols is undesirable as they form polymeric by-products. Under very mild conditions an acyl urea is formed quantitatively. Since acylureas crystallise very well, this reaction may be used to characterise carboxylic acids. The most suitable carbodiimide for this purpose is *sym*-bis-(*p*-dimethylaminophenyl)carbodiimide. Malonic, succinic, and glutaric acids mainly form disubstituted ureas and cyclic anhydrides. Evidently, cyclisation occurs after 1,2-addition:



where n = 1, 2, 3.

Similarly, phthalic acid and maleic acid form cyclic anhydrides, but fumaric acid gives the normal adduct:



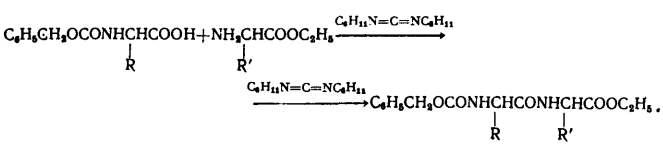
Adipic acid forms the monoacyl- and diacyl-ureas. The higher acids give normal derivatives, and each carboxylic group reacts independently.

Aliphatic carbodiimides, as a rule, form disubstituted ureas and anhydrides with carboxylic acids. However, by controlling the reaction an acylurea can be obtained. For example, when the reaction is carried out in hot pyridine and the carboxylic acid is added in portions to dicyclohexylcarbodiimide, the acylurea is obtained in satisfactory yield. Dicyclohexylurea is formed when dicyclohexylcarbodiimide reacts with an aqueous solution of acetic acid. To obtain diisopropylurea, the reaction between diisopropylcarbodiimide and acetic acid is carried out in acetone[58].

Methyl benzoate has been obtained from methanol and benzoic acid in the presence of dicyclohexylcarbodiimide[59]. A patent has also been obtained for the preparation of esters by the reaction of chloroacetic, phenoxyacetic, and salicyclic acids with methanol and 2-chloroethanol in the presence of dicyclohexylcarbodiimide. The desired products were obtained in 72–100% yield[60]. Butyranilide has been obtained by the reaction of butyric acid with aniline in the presence of dicyclohexylcarbodiimide[59]. This interesting observation was further applied in carrying out syntheses, with the use of amino-acids and carbodiimides. Like ordinary organic acids, in this reaction amino-acids form ureides, many of which have been prepared by Khorana[41].

Khorana noted that when the reaction was carried out with dicyclohexylcarbodiimide in pyridine solution cleavage of the ureide occurred[41]. When alcohol was used as a solvent, a certain amount of urea was formed in addition to the ureides. This suggests that in the course of the reaction dehydration of two molecules of amino-acid occurred with the possible formation of a peptide.

A new method of synthesising peptides has been developed[61], consisting in a reaction between a benzyloxycarbonylamino-acid, or a phthaloylamino-acid, and the ethyl ester of another amino-acid in the presence of dicyclohexylcarbodiimide:



In this way the ethyl ester of benzyloxycarbonylglycyl--*L*-phenylalanylglycine, benzyloxycarbonyl-*L*-serylglycine, phthaloyl-*L*-phenylalanylglycine, and phthaloyl-*L*--phenylalanyl-*L*-leucine have been obtained; the yield of peptide in these reactions was 70–90%.

Peptides were also obtained by Khorana, but in lower yield (20–50%)[62]. In addition to peptides, he isolated ureides

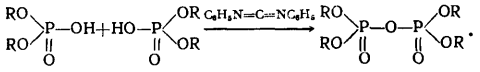
of *NN'*-dicyclohexylurea of the type $C_6H_{11}NHCONRC_6H_{11}$, where R = *N*-(*p*-toluenesulphonyl)-*DL*-phenylalanyl or *NN'*-phthaloyl-*DL*-phenylalanyl.

Using these methods, Amiard obtained a number of dipeptides of methionine, protecting the amino-groups with trityl groups $C(C_6H_5)_3$ and then condensing the protected methionine with esters of glycine and leucine[63]. The reaction was carried out in methyl chloride; the yield was 80–90%. Using the same method, Amiard[64] synthesised α- and γ-glutamylpeptides, and Sheehan[65] synthesised di- and tri-peptides containing hydroxyamino-acids (serine and threonine).

The use of carbodiimides for the synthesis of peptides is of great preparative value. Previous methods were based on the activation of the carboxyl group taking part in the reaction, after which derivatives were obtained, for example acyl chlorides, azides, etc.[66] The use of cyclohexylcarbodiimide eliminated the necessity of using these derivatives, since in the presence of carbodiimides, peptides are formed directly as a result of the reaction of the free carboxyl group of one amino-acid molecule with the free amino-group of another molecule. The use of carbodiimides in the synthesis of peptides is dealt with in a number of original papers[67-70].

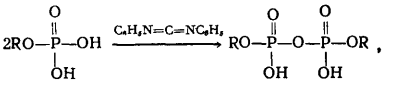
The use of carbodiimides in the synthesis of phosphorus-containing compounds. We have already noted that carbodiimides react with esters of phosphoric acid to form derivatives of pyrophosphoric acid[41]. In this way various esters and anhydrides of phosphoric acid can be obtained together with other compounds such as nucleotides, oligonucleotides, some coenzymes, etc.[66] Depending on the properties of the reagents, the phosphorylation reaction in the cold in aqueous pyridine solution, in anhydrous pyridine, or in dimethylformamide may take from several minutes to several hours[66].

sym-Tetrabenzyl-, tetraphenyl-, and tetra-*p*-nitrophenyl-pyrophosphate esters are obtained by condensing diesters of phosphoric acid[71]:



Adenosine diphosphate and adenosine triphosphate[72] and also a series of other important biochemical products[73-76] are obtained by the interaction of orthophosphoric acid with adenosine-5′ phosphoric acid in the presence of dicyclohexylcarbodiimide.

A symmetrical diester of pyrophosphoric acid is obtained by condensing two molecules of adenosine-5′ phosphoric acid in the presence of dicyclohexylcarbodiimide[77]:



where R is adenosine.

Todd and coworkers have synthesised nicotinamide–adenine dinucleotide in this way[78]. Another important coenzyme, flavin–adenine dinucleotide, was obtained in a similar way, but di-*p*-tolylcarbodiimide was used as a dehydrating and condensing agent[79]. Cytidine diphosphate choline and cytidine diphosphate ethanolamine were obtained with the aid of the same carbodiimide[80].

The use of carbodiimides in the synthesis of mixed acid anhydrides. Mixed acid anhydrides formed by the reaction of an amino-acid with adenosine-5′ phosphoric acid participate in the synthesis of protein, and interest in the synthesis of this type of compound is understandable[81]. The methods previously used for the synthesis of mixed acid anhydrides[82,83], for example the reaction of an acid chloride with the silver salt of adenosine-5′ phosphoric acid, or the action of amino-acid esters on the sodium salt of adenosine-5′ phosphoric acid, gave low yields.

The use of carbodiimides has enabled great progress to be made in this important field of synthesis. Berg[84] obtained derivatives of the anhydrides of *L*-serine, *L*-phenylalanine, *L*-tryptophan, and *D*-methionine by reaction of amino-acids with adenosine-5′ phosphoric acid in the presence of dicyclohexylcarbodiimide. Other important mixed anhydrides have been obtained with the aid of carbodiimides[84-86]. A mixed anhydride of adenylic and sulphuric acid (adenosine-5′ phosphosulphate), which is of biochemical interest, has been obtained in 40–50% yield by the action of concentrated sulphuric acid on adenosine-5′ phosphoric acid in the presence of dicyclohexylcarbodiimide in aqueous pyridine solution[87].

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In conclusion, it should be noted that the cases of the use of carbodiimides which we have considered are of great preparative value and primarily lead to a reduction in the number of intermediate stages and to an increased yield of the desired products compared with other methods. When carbodiimides are used, complicated multi-stage syntheses are reduced to one or two steps in the majority of cases. Another important advantage of syntheses with the use of carbodiimides is the simplicity of these compounds as condensing and water-removing agents. Reactions in which carbodiimides are used are usually carried out under mild conditions at room temperature, or at a slightly higher temperature, with the use of such accessible solvents as ether, pyridine, or dimethylformamide. Dicyclohexylurea, which is formed as a result of these reactions, is poorly soluble in these solvents, and this facilitates the purification and separation of the reaction products. Moreover, the course of the reaction can be followed by observing the amount of substituted urea precipitated. These reactions, as a rule, do not take more than a few hours.

Because of the development of new methods of synthesising carbodiimides by the catalytic decarboxylation of isocyanates, they have become more accessible and the range available has been extended. On the whole, the outlook for the wide use of carbodiimides and poly(carbodiimides) is very promising.

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ELECTROMIGRATION IN LIQUID METALS

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