# Chemistry and Technology of Carbodiimides

HENRI ULRICH



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### Preface

Carbodiimides are the diimides derived from carbon dioxide, and they are extensively used in the formation of peptide amide bonds from carboxylic acids and amines. This reaction was utilized by the Nobel laureate Sheehan in the total synthesis of penicillin. He also was the first to use water soluble carbodiimides to crosslink gelatin. Khorana, another Nobel laureate, demonstrated that carbodiimides can also be used in the synthesis of nucleotides. Today, carbodiimides are used extensively in the synthesis and modification of proteins. Proteomics is the new frontier of chemical research.

I became involved in carbodiimide chemistry in my research work on isocyanates at the former Donald S. Gilmore Research Laboratories of the Upjohn Company in North Haven, CT. Carbodiimides are readily synthesized from isocyanates using a phospholene oxide catalyst. This reaction can be conducted without a solvent, and the byproduct is carbon dioxide. We used this reaction in the manufacture of a liquid version of MDI (4,4'-diisocyanatodiphenylmethane), which today is sold in huge quantities worldwide. By reacting MDI with dicarboxylic acids in a vented extruder we manufactured a family of thermoplastic polyamide elastomers, which are sold today by the Dow Chemical Company. Also, N-sulfonylcarbodiimides were synthesized for the first time in our laboratories. They are the precursors of the antidiabetic sulfonamides, such as Upjohn's Tolbutamide (Orinase). Because of the close relationship of isocyanates with carbodiimides we studied many linear and cyclic carbodiimide reactions, especially their cycloaddition reactions.

This book reviews the technical literature on carbodiimides with emphasis on the last decades of the old century and the new century. The carbodiimides are subdivided into alkyl and aryl isocyanates, which cover a major portion of the book.

The remaining chapters are carbodiimides with unsaturated substituents, halogenated carbodiimides, acyl-, thioacyl- and imidoylcarbodiimides, silicon substituted carbodiimides, nitrogen substituted carbodiimides, phosphorous substituted carbodiimides, sulfur substituted carbodiimides, metal substituted carbodiimides, cyclic carbodiimides, polymeric carbodiimides and application of carbodiimides.

The last chapter includes the numerous biochemical applications of carbodiimides, and the chapters on silicon substituted carbodiimides and metal substituted carbodiimides include their role as precursors for ceramic materials.

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Environmental considerations, spectroscopic properties, and the toxicology of carbodiimides are discussed in the general introduction.

The text should prove valuable to researchers and technologists in organic and biochemistry, especially in the new emerging fields of proteomics and nanotechnology. The future of these vibrant fields with endless possibilities is bright indeed.

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In the initial carbodiimide research the valuable contributions of Prof. Dr W. von Eggers-Doering of Harvard University are acknowledged, and special thanks go to Prof. Dr D.M. Crothers, the former Chairman of the Chemistry Department of Yale University in New Haven, Connecticut, who allowed my access to Yale's fine technical libraries, which helped immensely in the compilation of the literature to this book.

Last but not least I would like to thank my wife Franziska for her patience, constant encouragement and support of this undertaking.

## 1 General Introduction

Carbodiimides are a unique class of reactive organic compounds having the heterocumulene structure R—N=C=N—R. They can be formally considered to be the diimides of carbon dioxide or the anhydrides of 1,3-substituted ureas, and they are closely related to the monoimides of carbon dioxide, the isocyanates. The substituent R can be alkyl, aryl, acyl, aroyl, imidoyl or sulfonyl, but nitrogen, silicon, phosphorous and metal substituted carbodiimides are also known. The unsubstituted carbodiimide HN=C=NH is isomeric with cyanamide, H<sub>2</sub>NCN. Mono substituted carbodiimides, generated in the thermolysis of 1-substituted tetrazoles, can be isolated at liquid nitrogen temperature but isomerize to the cyanamides at higher temperatures.<sup>1</sup>

Cyanamide is a relevant molecule in prebiotic chemistry, and it was recently shown that water-ice catalyzes the rearrangement of cyanamide to carbodiimide. Carbodiimide could act as a condensation agent in the assembly of amino acids into peptides.<sup>2</sup> In the peptide synthesis, using substitued carbodiimides as condensation agents, formation of L—L bonds is favored over D—D bonds by a ratio of 6:1.<sup>3</sup>

Carbodiimides are widely used to mediate the attachment of biomarkers to polypeptides. Examples include carbodiimides with ferrocenyl substituents. Also, peptides are covalently modified with ferrocenecarboxylic acid using EDCCl and N-hydroxy-succinimide to promote the coupling to surface lysines. They also mediate the attachment of substituents to single walled nanotubes (SWNTs) and multiwalled nanotubes (MWNTs). Also, microdots are attached to virus molecules using a water soluble carbodiimide. The attachment of viral DNA to gold particles is used in the manufacture of a new type of vaccine.

The first synthesis of carbodiimides was reported by Weith in 1873.<sup>4</sup> However, carbodiimides were already synthesized by Hinterberger<sup>5</sup> and Zinin<sup>6</sup> in 1852, and Biziro<sup>7</sup> in 1861. The earlier authors obtained carbodiimides by desulfurization of 1,3-disubstituted thioureas' but did not recognize their structure.

Carbodiimides are exceedingly useful compounds in organic synthesis. Of particular significance is their use as dehydrating agents in the synthesis of  $\beta$ -lactam antibiotics,

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nucleotides and peptides. In 1953, Khorana and Todd<sup>8</sup> reported the use of carbodiimides, especially dicyclohexylcarbodiimide, in the synthesis of ortho- and pyrophosphate esters. The use of carbodiimides in the synthesis of peptides was reported by Sheehan and Hess in 1955.<sup>9</sup> Sheehan and Henery-Logan used dicyclohexylcarbodiimide in the total synthesis of penicillic acid in 1957.<sup>10</sup> Sheehan published a book on the synthesis of penicillin in 1982.<sup>11</sup> He also used a water soluble carbodiimide to crosslink gelatin.<sup>12</sup>

Merrifield received the nobel price in 1985 for the synthesis of polypeptides using polymeric substrates.<sup>13</sup> Dicyclohexylcarbodiimide (DCC) is used in this automated stepwize synthesis of polypeptides to activate the carboxyl group. The Merrifield method allows the synthesis of polypeptides, such as ribonuclease A, consisting of 124 amino acids. Oligonucleotides are also synthesized using a carbodiimide in the automated condensation step.<sup>14</sup> Carbodiimides are also 'zero length' protein crosslinking agents, which promote formation of covalent crosslinks between reactive side groups of amino acids, but do not remain as a part of the crosslink. Also, blocked carbodiimides are used as crosslinking agents.<sup>15</sup>

The most widely used carbodiimides are dicyclohexylcarbodiimide (DCC) and diisopropylcarbodiimide (DICDI). Carbodiimides with primary alkyl substituents are usually less stable. The most stable aliphatic carbodiimide is di-t-butylcarbodiimide. For racemization free esterifications, peptide couplings and for dehydration reactions bis[[4-(2.2dimethyl-1,3-dioxolyl)]methyl]carbodiimide (BDDC) was introduced in 1994.<sup>16</sup> Another group of important aliphatic carbodiimides are the water soluble aliphatic carbodiimides. They usually contain a tertiary amino group in the side chain. Numerous carbodiimides with one alkyl substituent having a terminal t-amino group attached to the side chain have been synthesized. They are usually converted to the more water soluble quaternary ammonium salts by alkylation with MeI or other alkylating agents. Examples include N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDC), and its hydrochloride (EDCCl, sometimes referred to as EDAC). For the solid phase synthesis of peptides a polymeric version of EDC was obtained by treating Merrifield resins with EDC in DMF at 100 °C or in refluxing acetonitrile.<sup>17</sup> Polyamine carbodiimides combining the phosphate activating property of EDC with the DNA binding property of spermine have also been synthesized from the corresponsing thiourea and HgO.<sup>18</sup> Another useful carbodiimide is ferrocenylcarbodiimide (FCDI) which reacts with guanine and thymine bases of single stranded DNA.<sup>19</sup> Also, a bipyridyl-tagged carbodiimide, used as a chelating tag, was synthesized.20

In the aromatic series, carbodiimides having a substituent in the *o*-position are preferred. Examples include N,N'-di-*o*-tolylcarbodiimide and N,N'-di-2,6-diethylcarbodiimide, the latter being a useful stabilizer for polyester based polyurethanes.<sup>21</sup>

The use of carbodiimides in organic synthesis includes the Moffat oxidation of primary alcohols to aldehydes using a dicyclohexylcarbodiimide/DMSO adduct as reagent. Also, conversion of alcohols or phenols into hydrocarbons via hydrogenation of acylisoureas derived from the corresponding carbodiimide adducts is a useful reaction. Furthermore, aldoximes, on treatment with carbodiimides, are converted into nitriles, and numerous uses of carbodiimides as condensation agents or catalysts are known (see Chapter 13).

Another useful synthetic method for the synthesis of complex heterocyclic compounds is the aza-Wittig reaction, involving carbodiimides as intermediates.<sup>22</sup> This reaction was discovered by Staudinger and Hauser in 1921.<sup>23</sup> Carbodiimides have also found use as agricultural chemicals and pharmaceutical intermediates. For example, N-arenesulfonyl-N'-alkylcarbodiimides are precursors of the antidiabetic sulfonyl ureas.<sup>24</sup> Sulfonylureas are also potent herbicides.

Carbodiimides are used in numerous industrial applications. Their reactivity with carboxylic acids is being utilized in the stabilization of many polyester based polymers. For this purpose sterically hindered aromatic carbodiimides are used.<sup>25</sup> Isocyanato substituted oligomeric and polymeric carbodiimides are also being used in some polymer applications.<sup>26</sup> The elimination of chlorofluorocarbons (CFCs) as blowing agents for rigid polyurethane insulation foams prompted the development of partially or totally carbon dioxide blown foams based on polymeric isocyanates, having polycarbodiimide segments in their backbone structure. The use of efficient carbodiimide catalysts in combination with the more costly HFCs (hydrogen containing fluorocarbons) affords partially carbon dioxide blown rigid foams. Of course, low density open cell carbodiimide foams are also obtained from polymeric isocyanates using a phospholene oxide catalyst.<sup>27</sup> The reaction of 4,4'-diphenylmethane diisocyanate (MDI) with a carbodiimide catalyst is used to formulate a liquid MDI product for RIM (reaction injection molding) and thermoplastic polyurethane elastomer applications.<sup>28</sup>

The use of dicarbodiimides as monomers in polyaddition reactions have not as yet found wide utility. However, polymers containing carbodiimide groups are known, and further nucleophilic reactions of these polymers with numerous substrates are reported. Carbodiimides, generated *in situ* from isocyanates are used as catalyst in the formation of polyamides from diisocyanates and dicarboxylic acids.<sup>29</sup> Also, homoleptic lanthanide amidinates, made from carbodiimides, exhibit high catalytic activity for the ring opening polymerization of  $\varepsilon$ -caprolactone at room temperature.<sup>30</sup>

Polymeric nanoaggregates are the result of self-assembly of block copolymers. For example, PEO-b-PAA on reaction with EDC methiodide undergoes self-association to form short rods, vesicles, encapsulated spheres and long fibers.<sup>31</sup> The attachment of nanotubes and microdots to engineered viruses is also mediated using EDC.<sup>32</sup>

Review articles on carbodiimides were published by Khorana in 1953,<sup>8</sup> by Kurzer and Douraghi-Zadeh in 1967,<sup>33</sup> by Mikolajczyk and Kielbasinski in 1981<sup>34</sup> and by Williams and Ibrahim in 1981.<sup>35</sup> Carbodiimides containing silicon, germanium, tin and lead substituents were reviewed by Gordetsov and coworkers in 1982,<sup>36</sup> N-functionalized carbodiimides by Vovk and Samarai in 1992<sup>37</sup> and polycarbodiimides by Pankratov in 1993.<sup>38</sup> A review on the synthesis of heterocycles by the aza-Wittig reaction appeared in 1991.<sup>39</sup>

Aliphatic and aromatic carbodiimides are liquids or solids at room temperature. The stability of substituted dialkylcarbodiimides increases as follows:  $RCH_2 < R_2CH < R_3C$ .<sup>40</sup> Dimethylcarbodiimide should be used freshly prepared, but it can be stored for several days below room temperature. Unsaturation in the aliphatic substituents decreases the stability of carbodiimides. For example, diallylcarbodiimide is unstable.

In the aromatic carbodiimides, the solid products are more stable than the liquid products. N-alkyl-N'-arylcarbodiimides are less stable than diarylcarbodiimides. The introduction of electron attracting groups into the aromatic substituents seems to increase the polymerization tendency of the resulting carbodiimide. In contrast, electron donating substituents on the aromatic ring of arylalkylcarbodiimides enhance their reactivity with carboxylates.<sup>41</sup>

The cumulative bonds in carbodiimides are not linear. X-ray studies show bond angles variing from 166° to 170° for N,N'-diaryl- as well as N-aryl-N'-alkylcarbodiimides.<sup>42</sup> The bonding of the -N=C=N- bond may be due to steric interaction between the two

nitrogen substituents. A geometry search, using the INDO method, revealed that the lowest energy state of dimethylcarbodiimide has a dihedral angle of 90°.<sup>43</sup> The configurational flexibility of diisopropylcarbodiimide has been studied by <sup>1</sup>H-NMR measurement.<sup>44</sup> Carbodiimides are best characterized by their infrared spectra, which show a very strong absorption between 2150 and 2100 cm<sup>-1</sup> attributable to the -N=C=N- stretching.<sup>45</sup> Aliphatic carbodiimides give rise to a single peak in the 2140–2125 cm<sup>-1</sup> range, while aromatic carbodiimides exhibit two bands in this region. Vibrational dynamics of the -N=C=N- stretching in DCC was investigated by the transient grating method.<sup>46</sup> The Raman spectrum of carbodiimides shows a strong absorption at 1460  $\text{cm}^{-1}$  which can be attributed to the symmetric vibrations.<sup>47</sup> In <sup>13</sup>C-NMR spectra the chemical shift of the sp-hybridized center carbon is approximately 135 to 140 ppm.<sup>48</sup> This signal can be used to differentiate between carbodiimide and cyanamide structures, because in cyanamides the signal appears at 112 to 117 ppm. Dicyclohexylcarbodiimide shows a single signal in the <sup>14</sup>N-NMR spectrum indicating a symmetric structure.<sup>49</sup> The <sup>15</sup>N-NMR spectra of carbodiimides were also investigated and the chemical shift is about 270 ppm. It was found that the spectrum of N-ethyl-N'-(3-dimethylamino)propylcarbodiimide hydrochloride indicated the presence of three isomers.<sup>50</sup> At neutral pH, the cyclic forms account for approximately 7 %.

Similar results were obtained in another NMR study.<sup>51</sup> A study of the conformation of DCC by <sup>1</sup>H-NMR at low temperature showed that the carbodiimide group exerts a significant preference for the equatorial position.<sup>52</sup> The He(I) photoelectronic spectrum of dimethylcarbodiimide shows bands at 9.5, 11.55 and 12.26 eV; the first maximum consists of two ionizations representing two orbitals on the -N=C=N- part with both  $\pi$  and n character.<sup>53</sup> Also, electron energy loss spectra of DCC, polysilyl- and polytitanyl-carbodiimides are recorded.<sup>54</sup> The UV absorption spectrum of dimethylcarbodiimide in heptane solution shows a strong band at 206.6 nm and three bands at 247.5, 254 and 260 nm due to the allowed n– $\pi$  transitions polarized perpendicularly to the plane of the CNC angle.<sup>55</sup> The extinction coefficient of 1-ethyl-3-(3-dimethylamino)propylcarbodiimide (EDC) in water is  $\varepsilon$  (214 nm) = 6 × 10<sup>3</sup> L/mol/cm. The UV assay is used for testing of side reactions.<sup>56</sup> Also, <sup>13</sup>C and <sup>15</sup>N-labeled EDC were synthesized.<sup>57</sup>

Substituent effects on the stability of carbodiimides show that electron negative substituents, such as F, Cl, OH and NH<sub>2</sub> destabilize carbodiimides, while electropositive substituents increase the stability of carbodiimides. However, the electronegative substituent NO<sub>2</sub> stabilizes carbodiimides by a  $\pi$ -acceptor complex.<sup>58</sup>

Carbodiimides have chiral structures similar to allenes, i.e., they can exist in optically active forms. Schloegl and Mechtler<sup>60</sup> were the first to report a partial optical separation of N,N'-diferrocenylcarbodiimide into enantiomers by chromatography on acetylated cellulose, but other authors doubt the validity of these results. According to theoretical calculations a separation of carbodiimide enantiomers is not possible.<sup>59</sup> N,N'diferrocenylcarbodiimide was also obtained in optically active form by kinetic resolution in the reaction with (-)-S-6,6'-dinitrodiphenic acid.<sup>60</sup> Cervinka and coworkers isolated both enantiomers of (R,S)-N,N'-bis( $\alpha$ -phenylethyl)carbodiimide, and they found that they undergo racemization at room temperature.<sup>61</sup> A recent study on the racemization mechanism of macrocyclic carbodiimides indicates that the open chain as well as the large ring carbodiimides racemize by nitrogen inversion or *trans*-rotation, while medium size cyclic carbodiimides racemize by *cis*-rotation.<sup>62</sup> The cycloaddition of chiral (-)menthylcarbodiimide with prochiral ketenes affords chirally selective cycloadducts.<sup>63</sup> In the reaction of an optically active alcohol with dicyclohexylcarbodiimide complete inversion of the configuration occurs after hydrolysis.<sup>64</sup> Treatment of arenesulfenic acids with alcohols, thiols or secondary amines in the presence of optically active carbodiimides affords the corresponding optically active arenesulfenic acid derivatives.<sup>65</sup> DCC is used to convert an optically active selenoxide into the corresponding optically active selenimide with TsNH<sub>2</sub>.<sup>66</sup>

Carbodiimides are used in the laboratory as stabilizing agents, coupling agents and as condensation agents and a potential for exposure exists during these operations. The aliphatic carbodiimides are reported to be irritating to the skin, eyes and the respiratory tract. Contact dermatitis caused by DCC was reported.<sup>67</sup>

DCC has a higher contact hypersensitivity in the mouse ear swelling test than DICDI.<sup>68</sup> Exposure to diisopropylcarbodiimide can cause temporary blindness.<sup>69</sup>

The mammalian toxicity of carbodiimides is low. For example, DCC has a  $LD_{50}$  in rats of 2.6 g kg<sup>-1</sup>.<sup>70</sup> DCC also shows antitumor activity in mice.<sup>71</sup> The oral  $LD_{50}$  of diisopropylcarbodiimide in mice is 36 mg/Kg. Carbodiimide (EDC) modified glycosaminoglycans are a new class of anticancer agents.<sup>72</sup> EDC hydrochloride, when administered to animals, exerts a carcinostatic effect on experimental tumors.<sup>73</sup> Di(triphenylmethyl)carbodiimide is more toxic to a malignant than a normal cell line. EDC is used in the preparation of a meningococcal group C polysaccharide-tetanus toxoid conjugate used as human vaccine.<sup>74</sup> No epidemiological studies have associated carbodiimides with cancer risk in humans.

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2

### **Alkyl- and Arylcarbodiimides**

### 2.1 Introduction

The alkyl-, alkylaryl- and diarylcarbodiimides are the diimides derived from carbon dioxide, however, no direct formation of carbodiimides from amines and carbon dioxide is known. Interestingly, carbodiimides can be obtained from amines and carbon dioxide via a switterionic titanium complex (see Section 2.2.8).<sup>1</sup> The major starting materials for the synthesis of carbodiimides are isocyanates, 1,3-disubstituted ureas or 1,3-disubstituted thioureas. The synthesis of isocyanates requires the use of the toxic carbonyl chloride or its oligomers. A book on the synthesis and reactions of isocyanates appeared in 1996.<sup>2</sup>

Symmetrical carbodiimides, i.e., molecules with the same substituent on both nitrogen atoms, are best prepared from alkyl or aryl isocyanates in the presence of a phospholene oxide catalyst, the byproduct being carbon dioxide gas. No solvent is required for this reaction. Unsymmetrical carbodiimides or alkylarylcarbodiimides are also obtained from isocyanates, either by reaction with amines and subsequent dehydration of the intermediate 1,3-disubstituted ureas, or by reaction of isocyanates with iminophosphoranes (aza-Wittig reaction).

Iminophosphoranes can also be used to synthesize symmetrical carbodiimides. In this case they are reacted with carbon dioxide, thereby mimicking the synthesis of carbodiimides from amines and carbon dioxide. Another useful synthesis of unsymmetrical carbodiimides, not requiring the use of carbonyl chloride, is the reaction of carbonimidoyl dihalides with amines. The synthesis and chemistry of carbonimidoyl halides was reviewed in 1968.<sup>3</sup>

Isothiocyanates are also major starting materials for carbodiimides either by converting them into 1,3-disubstituted thiourea intermediates, which are subsequently desulfurized, or by treating them with iminophosphoranes.

In many of the carbodiimide reactions N,N'-dicyclohexylcarbodiimide (DCC) is used. However, N,N'-diisopropylcarbodiimide (DIPCD) is also often used. Aliphatic carbodiimides, having secondary alkyl groups as substituents, are more stable than carbodiimides

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with primary alkyl groups as substituents. N,N'-di-t-butylcarbodiimide is the most stable aliphatic carbodiimide, but it is also the least reactive. For example, in N-methyl-N'-t-butylcarbodiimide cycloaddition reactions occur across the less sterically hindred C=N bond (see Section 2.4.2.1)

Steric as well as electronic factors determine the reactivity of carbodiimides. For example, N-alkyl-N'-arylcarbodiimides with substituents  $R = NMe_2$  or Me in the *p*-position of the aryl group react faster than N-alkyl-N'-arylcarbodiimides with  $R = NO_2$  in the *p*-position.<sup>4</sup>

Often reactions of carbodiimides are performed in an aqueous system requiring the use of water soluble carbodiimides. The workhorse in this application is N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDC) and its hydrochloride salt (EDCl).<sup>5</sup> However, many other water soluble carbodiimides are also used. Nobel laureat Sheehan used water soluble carbodiimides in the synthesis of penicillins.

Also, oligomeric and polymeric carbodiimides are used extensively in solid state chemistry as shown in Chapter 12.

A major use of DCC is in the formation of peptide bonds, as demonstrated by the Nobel laureat Khorana in 1955.<sup>6</sup> His discovery of the reaction of dibenzyl phosphate with DCC to give tetrabenzyl pyrophosphate laid the foundation for most of his work with nucleotides.

### 2.2 Synthesis of Alkyl- and Arylcarbodiimides

### 2.2.1 From Thioureas, Isothioureas and Selenoureas

The synthesis of carbodiimides by desulfurization of 1,3-disubstituted thioureas is the most general method of synthesis because dialkyl-, alkylaryl- and diarylcarbodiimides with the same or different substituents are obtained. The desulfurization of N,N'-disubstituted thioureas **1** with yellow mercuric oxide is the classical method of synthesis of carbodiimides **2** used by Weith in 1873.<sup>7</sup>

$$\frac{\text{RNHCSNHR} + \text{HgO} \longrightarrow \text{RN=C=NR} + \text{HgS} + \text{H_2O}}{1 \qquad 2}$$
(2.1)

The reaction proceeds best in benzene or acetone, but xylene and carbon disulfide have also been used as solvents. Since water generated in the reaction may add to the carbodiimide to form a urea, dehydrating agents, such as CaCl<sub>2</sub>, Na<sub>2</sub>SO<sub>4</sub>, MgSO<sub>4</sub> or MgCO<sub>3</sub> are added to the reaction mixture. For example, N-cyclohexyl-N'-isopropyl-carbodiimide is obtained in 80 % yield by conducting the desulfurization in the presence of MgSO<sub>4</sub>.<sup>8</sup> The water can also be removed by azeotrope distillation. However, the water is not detrimental in the synthesis of aliphatic carbodiimides.<sup>9</sup>

Also, several N-(tosylmethyl)carbodiimides 4 are prepared similarly from the corresponding thiourea  $3.^{10}$ 

$$4-\text{MePhSO}_2\text{CH}_2\text{NHCSNHR} + \text{HgO} \longrightarrow 4-\text{MePhSO}_2\text{CH}_2\text{N=C=NR}$$

$$3 \qquad 4 \qquad (2.2)$$

R	[%]	mp °C (bp)
$\begin{array}{c} Me \\ CMe_3 \\ CPh_3 \\ C_6H_{11} \\ Ph \end{array}$	95 75 90 90 94	Oil (115/0.01 Torr) 138–139 Oil Oil

In addition to dialkyl-, alkylaryl- and diarylcarbodiimides, heterocyclic carbodiimides, such as 1.4-dioxan-2-ylcarbodiimides **6** are obtained by desulfurization of the corresponding thiourea 5.11



This method is also used in the synthesis of <sup>13</sup>C and <sup>15</sup>N labeled EDC, which is obtained in 57 % yield.<sup>12</sup> Symmetrical and unsymmetrical glycosyl carbodiimides are also obtained in good yields in the desulfurization of the corresponding thioureas with HgO.<sup>13</sup> Bis-Boc-carbodiimide is obtained similarly as an intermediate in the reaction of N,N'-di (t-butoxycarbonyl)thiourea with primary amines in the presence of Et<sub>3</sub>N in DMF.<sup>14</sup>

A spin labeled carbodiimide derivative  $\mathbf{8}$  is synthesized from the thiourea  $\mathbf{7}$  and HgO.<sup>15</sup>



This carbodiimide is useful for probing protonation reactions in proton-pumping enzymes.

Also, highly fluorescent N-alkyl- or N-aryl-N'-[4-(5-phenyloxazol-2-yl)benzyl]carbodiimides **10** are prepared from the corresponding thioureas **9** and HgO.<sup>16</sup>



(2.5)

R	mp°C	[%]
Et	41	58
i-Pr	59	70
Ph	78	53

Lead and silver oxide can also be used to affect desulfurization of thioureas. Generally, a 1.5 to 2.5 molar excess of the finely divided oxide gives optimal yields. The oxides and salts of other elements have also been used to affect the desulfurization of thioureas. Examples include zinc oxide and salts<sup>17</sup> (ZnO, ZnCl<sub>2</sub>, ZnSO<sub>4</sub>), aluminumoxide,<sup>18</sup> arsenic oxide<sup>19</sup> and lead salts.<sup>20</sup>

The desulfurization of thioureas is also accomplished by either sulfur dioxide or carbon disulfide. The reaction of thioureas<sup>21</sup> or dilithium salts of thioureas<sup>22</sup> with sulfur dioxide at 0 °C affords carbodiimides in 38–81 % yield. Thermolysis of dilithio- or bis(bromomagnesio)thioureas, or reaction of the salts with carbon disulfide below room temperature also produces carbodiimides.<sup>23</sup>

Another useful method to convert thioureas into carbodiimides involves their reaction with reactive chlorine compounds, such as  $SOCl_2$ ,  $SO_2Cl_2$ ,  $SCl_2$  or  $S_2Cl_2$ . The use of the sulfur chlorides involves chloroformamidines as intermediates (see Section 2.2.6).<sup>24</sup> The reaction of thioureas **11** with methanesulfonyl chloride in methylene chloride in the presence of triethylamine/DMAP (4-dimethylaminopyridine) at room temperature produces carbodiimides **12** in 85–100 % yield<sup>25</sup>

R	$R^1$	[%]
Ph	Me	91
Ph	i-Pr	97
Ph	$-CH_2CH_2Ph$	97
Ph	2-furfuryl	85
Ph	Ph	95
2-Cl-5-MePh	n-Pr	100

$RNHCSNHR + MeSO_2$	$Cl \longrightarrow RN = C = NR$	(2.6)
11	12	(2.0)

Sheehan and Hlavka<sup>9</sup> used benzenesulfonyl chloride and aqueous potassium carbonate to synthesize several N-alkyl-N'-(aminoalkyl)carbodiimides **14** from the corresponding thioureas **13**.

$$\frac{\text{RNHCSNH}(\text{CH}_2)_n \text{NR}_2^1 + \text{PhSO}_2\text{Cl} \longrightarrow \text{RN}=\text{C}=\text{N}(\text{CH}_2)_n \text{NR}_2^1}{13}$$
(2.7)

Di-2-pyridylsulfite has also been used to desulfurize thioureas. The yields of carbo-diimides  $RN=C=NR^1$  ( $R=R^1=n$ -Bu,  $C_6H_{11}$ , Ph and R=Ph,  $R^1=Me$ ) are 76–90 %.<sup>26</sup>

The reaction of N,N'-disubstituted thioureas **15** with phosgene (carbonyl chloride) affords aliphatic and aromatic carbodiimides **16** in good yields.<sup>27</sup> For example, addition of phosgene