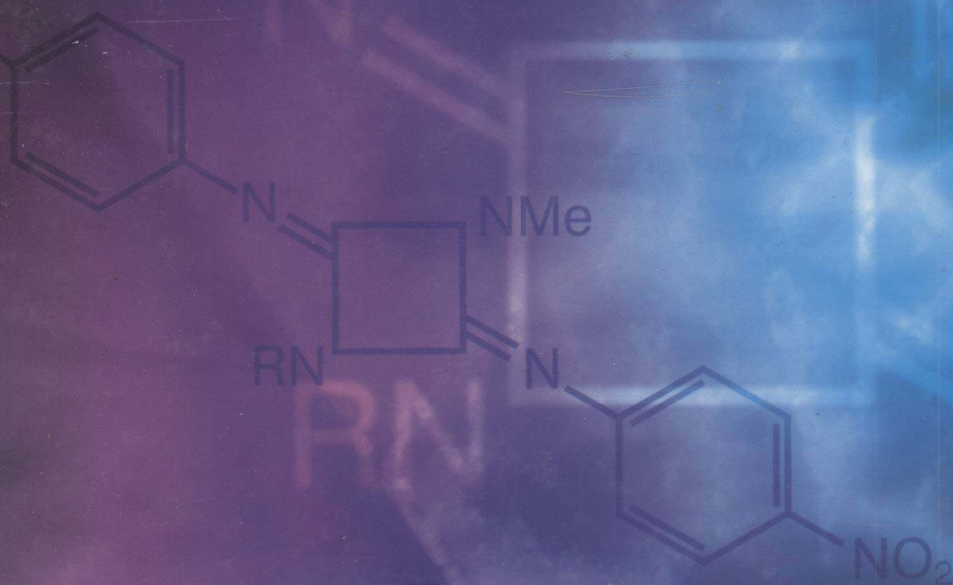


HENRI ULRICH

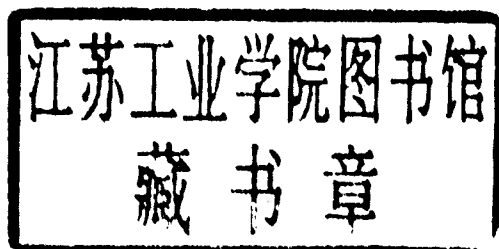
CHEMISTRY AND TECHNOLOGY OF
CARBODIIMIDES



 **WILEY**

Chemistry and Technology of Carbodiimides

HENRI ULRICH



John Wiley & Sons, Ltd

Copyright © 2007 John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester,
West Sussex PO19 8SQ, England
Telephone (+44) 1243 779777

Email (for orders and customer service enquiries): cs-books@wiley.co.uk
Visit our Home Page on www.wileyeurope.com or www.wiley.com

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except under the terms of the Copyright, Designs and Patents Act 1988 or under the terms of a licence issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1T 4LP, UK, without the permission in writing of the Publisher. Requests to the Publisher should be addressed to the Permissions Department, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, or emailed to permreq@wiley.co.uk, or faxed to (+44) 1243 770620.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The Publisher is not associated with any product or vendor mentioned in this book.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the Publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The Publisher and the Author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. The advice and strategies contained herein may not be suitable for every situation. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the Publisher nor the Author shall be liable for any damages arising herefrom.

Other Wiley Editorial Offices

John Wiley & Sons Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 42 McDougall Street, Milton, Queensland 4064, Australia

John Wiley & Sons (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons Ltd, 6045 Freemont Blvd, Mississauga, Ontario L5R 4J3, Canada

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Anniversary Logo Design: Richard J. Pacifico

Library of Congress Cataloging-in-Publication Data

Ulrich, Henri, 1925–

Chemistry and technology of carbodiimides / Henri Ulrich.
p. cm.

Includes bibliographical references.

ISBN 978-0-470-06510-5 (cloth)

1. Carbodiimides. I. Title.

TP248.C24.U57 2007

661'.894–dc22

2007013946

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 978-0-470-06510-5

Typeset in 10/12pt Times by Aptara Inc., New Delhi, India

Printed and bound in Great Britain by Antony Rowe Ltd, Chippenham, Wiltshire

This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

Chemistry and Technology of Carbodiimides

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 imidoacylcarbodiimides, 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.

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.

Acknowledgements

I would like to acknowledge the contributions of my former co-workers at the Donald S. Gilmore Research Laboratories of the Upjohn Company, especially Dr R.H. Richter and B. Tucker who were involved in the synthesis and cycloaddition reactions of carbodiimides; Dr L.M. Alberino who participated in the synthesis of polycarbodiimides; Dr K. Onder and Dr W.J. Farrissey, Jr, who played a major role in the development of thermoplastic polyamides based on carbodiimide chemistry; Dr H.W. Temme and Dr C.P. Smith, who developed novel polymeric catalysts for the conversion of isocyanates into carbodiimides; and A. Odinak, who developed the liquid MDI process. I would especially like to acknowledge the encouragement of the late Dr A.A.R. Sayigh.

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.

Contents

Preface	xiii
Acknowledgements	xv
1 General Introduction	1
1.1 References	5
2 Alkyl- and Arylcarbodiimides	9
2.1 Introduction	9
2.2 Synthesis of Alkyl- and Arylcarbodiimides	10
2.2.1 From Thioureas, Isothioureas and Selenoureas	10
2.2.2 By Dehydration of Ureas	16
2.2.3 From Isocyanates or Isothiocyanates	17
2.2.4 From Cyanamides	25
2.2.5 By Nitrene Rearrangements	25
2.2.6 From Haloformamidines or Carbonimidoyl Dihalides	28
2.2.7 By Thermolysis Reactions	29
2.2.8 By Miscellaneous Other Methods	33
2.3 References I	36
2.4 Reactions of Alkyl- and Arylcarbodiimides	41

2.4.1	Oligomerization and Polymerization	41
2.4.2	Cycloaddition Reactions	46
2.4.3	Reaction of Ylides with Carbodiimides	76
2.4.4	Insertion Reactions	78
2.4.5	Nucleophilic Reactions	83
2.4.6	Heterocycles from Carbodiimides	104
2.4.7	Use of Carbodiimides In Condensation Reactions	113
2.4.8	Miscellaneous Reactions	125
2.5	References II	130
3	Unsaturated Carbodiimides	147
3.1	Introduction	147
3.2	Synthesis of Unsaturated Carbodiimides	148
3.2.1	From Thioureas	148
3.2.2	From Unsaturated Isocyanates	148
3.2.3	From Unsaturated Iminophosphoranes and Isocyanates or Isothiocyanates	148
3.2.4	By Other Methods	154
3.3	Reactions of Unsaturated Carbodiimides	154
3.3.1	Polymerization Reactions	154
3.3.2	Cycloaddition Reactions	154
3.3.3	Other Reactions	162
3.4	References	162
4	Halogenated Carbodiimides	165
4.1	Introduction	165

4.2	Synthesis of Halogenated Carbodiimides	165
4.2.1	From α -Haloisocyanates	165
4.2.2	By Halogenation of Carbodiimides	166
4.2.3	From Carbonimidoyl Dichlorides or Imidoyl Chlorides	166
4.2.4	By Other Methods	167
4.3	Reactions of Halogenated Carbodiimides	168
4.3.1	Cycloaddition Reactions	168
4.3.2	Nucleophilic Reactions	169
4.3.3	Other Reactions	170
4.4	References	171
5	Acyl-, Thioacyl- and Imidoylecarbodiimides	173
5.1	Introduction	173
5.2	Synthesis of Acyl-, Thioacyl- and Imidoylecarbodiimides	174
5.2.1	From Thioureas	174
5.2.2	From Ureas	176
5.2.3	From Isocyanates	177
5.2.4	From Carbonimidoyl Dichlorides or Chloroformamidines	178
5.2.5	From Cyanamides	179
5.2.6	From Other Carbodiimides	179
5.2.7	By Other Methods	179
5.3	Reactions of Acyl-, Thioacyl- and Imidoylecarbodiimides	180
5.3.1	Cycloaddition Reactions	180
5.3.2	Other Reaction	180

5.4	References	180
6	Silicon Substituted Carbodiimides	183
6.1	Introduction	183
6.2	Synthesis of Silicon Substituted Carbodiimides	183
6.2.1	From Cyanamides	183
6.2.2	From Ureas	184
6.2.3	From Isocyanates and Isothiocyanates	184
6.2.4	From Silylamines	185
6.2.5	From Other Carbodiimides	186
6.2.6	By Other Methods	186
6.3	Reactions of Silicon Substituted Carbodiimides	187
6.3.1	Oligomerization Reactions	187
6.3.2	Cycloaddition Reactions	188
6.3.3	Other Reactions	190
6.4	References	191
7	Nitrogen Substituted Carbodiimides	195
7.1	Introduction	195
7.2	Synthesis of Nitrogen Substituted Carbodiimides	195
7.3	Reactions of Nitrogen Substituted Carbodiimides	198
7.4	References	198
8	Phosphorous Substituted Carbodiimides	199
8.1	Introduction	199
8.2	Synthesis of Phosphorous Substituted Carbodiimides	199

8.2.1	From Thioureas	199
8.2.2	From Iminophosphoranes	200
8.2.3	From Carbonimidoyl Dichlorides	200
8.2.4	From Cyanamides	201
8.2.5	From Other Carbodiimides	202
8.2.6	By Other Method	203
8.3	Reactions of Phosphorous Substituted Carbodiimides	203
8.4	References	204
9	Sulfur Substituted Carbodiimides	205
9.1	Introduction	205
9.2	Synthesis of Sulfur Substituted Carbodiimides	205
9.2.1	From Thioureas or Ureas	205
9.2.2	From Carbonimidoyl Dichlorides or Imidoyl Chlorides	206
9.2.3	By Fragmentation Reactions	207
9.2.4	From Other Carbodiimides	208
9.2.5	By Other Methods	208
9.3	Reactions of Sulfur Substituted Carbodiimides	209
9.4	References	210
10	Metal Substituted Carbodiimides	213
10.1	Introduction	213
10.2	Synthesis of Metal Substituted Carbodiimides	214
10.2.1	From Cyanamides	214
10.2.2	From Isocyanates	215

10.2.3	From Other Carbodiimides	216
10.2.4	By Other Methods	217
10.2.5	Synthesis of Metal Carbodiimide Adducts	218
10.3	Reactions of Metal Substituted Carbodiimides	222
10.4	References	223
11	Cyclic Carbodiimides	227
11.1	Introduction	227
11.2	Synthesis of Cyclic Carbodiimides	229
11.2.1	From Cyclic Thioureas	229
11.2.2	By Nitrene Rearrangement	230
11.2.3	From Bisaryliminophosphoranes and Isocyanates or Isothiocyanates	231
11.3	Reactions of Cyclic Carbodiimides	236
11.3.1	Nucleophilic Reactions	236
11.3.2	Oligomerization Reactions	237
11.3.3	Cycloaddition Reactions	238
11.3.4	Other Reactions	240
11.4	References	241
12	Polymeric Carbodiimides	243
12.1	Introduction	243
12.2	Isocyanate Terminated Polycarbodiimides	243
12.3	Oligomeric Carbodiimides	247
12.4	Linear Homopolymers via Addition Across the C=N Bonds	248

12.5	Polymers Derived from Unsaturated Carbodiimides	250
12.6	Linear Polymers	251
12.7	Crosslinked Homo- and Copolymers	252
12.8	Modification of Linear Polymers with Carbodiimides	253
12.8.1	Crosslinking of Polymers	253
12.8.2	Modification of Linear Polymers	254
12.8.3	Modification of Crosslinked Polymers	254
12.9	References	255
13	Applications of Carbodiimides	259
13.1	Introduction	259
13.2	Applications in Organic Synthesis	260
13.3	Biological Applications	261
13.3.1	Antibiotic Synthesis	261
13.3.2	Protein and DNA Synthesis	261
13.3.3	Modification of Proteins	264
13.3.4	Crosslinking of Proteins	266
13.3.5	Carbodiimides in Pharmaceuticals, Herbicides and Pesticides	267
13.4	Polymer and Industrial Applications	268
13.4.1	Use in Polymer Synthesis	268
13.4.2	Use in Polymer Applications	269
13.4.3	Polymer Modifications	271
13.4.4	Carbodiimides as Stabilizers	271

13.4.5 Carbodiimides in Dye Applications	272
13.4.6 Other Applications	273
13.5 References	274
Index	283

1

General Introduction

Carbodiimides are a unique class of reactive organic compounds having the heterocumulative 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, imido or sulfonyl, but nitrogen, silicon, phosphorous and metal substituted carbodiimides are also known. The unsubstituted carbodiimide $HN=C=NH$ is isomeric with cyanamide, H_2NCN . 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.¹

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.² In the peptide synthesis, using substituted carbodiimides as condensation agents, formation of $L-L$ bonds is favored over $D-D$ bonds by a ratio of 6:1.³

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 EDCI 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 1873.⁴ However, carbodiimides were already synthesized by Hinterberger⁵ and Zinin⁶ in 1852, and Biziro⁷ 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 β -lactam antibiotics,

nucleotides and peptides. In 1953, Khorana and Todd⁸ 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 1955.⁹ Sheehan and Henery-Logan used dicyclohexylcarbodiimide in the total synthesis of penicillic acid in 1957.¹⁰ Sheehan published a book on the synthesis of penicillin in 1982.¹¹ He also used a water soluble carbodiimide to crosslink gelatin.¹²

Merrifield received the nobel price in 1985 for the synthesis of polypeptides using polymeric substrates.¹³ Dicyclohexylcarbodiimide (DCC) is used in this automated stepwise 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.¹⁴ 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.¹⁵

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-(2,2-dimethyl-1,3-dioxolyl)methyl]carbodiimide (BDDC) was introduced in 1994.¹⁶ 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.¹⁷ Polyamine carbodiimides combining the phosphate activating property of EDC with the DNA binding property of spermine have also been synthesized from the corresponding thiourea and HgO.¹⁸ Another useful carbodiimide is ferrocenylcarbodiimide (FCDI) which reacts with guanine and thymine bases of single stranded DNA.¹⁹ 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.²¹

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.²² This reaction was discovered by Staudinger and Hauser in 1921.²³ Carbodiimides have also found use as agricultural chemicals and pharmaceutical intermediates. For example,