

Khorana H G. Observations on the use of dicyclohexylcarbodiimide in the synthesis of peptides. *Chem. Ind.—London* 1955:1087-8.
[British Columbia Res. Council, Univ. British Columbia, Vancouver, Canada]

The application of dicyclohexylcarbodiimide for the formation of peptide bonds by the condensation of protected peptides carrying free carboxyl groups with the amino groups of amino acid esters has been investigated. A mechanistic analysis of the reaction intermediates and products, including the desired and side products, has been provided. [The SCI® indicates that this paper has been cited in over 175 publications since 1955.]

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My encounter with carbodiimides turned out to be one of the happiest accidents in my research. Carbodiimides marked my entry into peptides and later into nucleotides and were influential in determining the experimental approaches to chemical work in the nucleic acid field for more than 12 years. In other organic chemistry laboratories, carbodiimides aroused enormous interest as efficient reagents for a wide variety of transformations and as synthetic reagents. In biochemical work, carbodiimides found additional specific and useful applications. (See, for example, reference 1.)

After my PhD degree at the University of Liverpool, I had wanted very much to spend a period of time on the European continent, preferably in a laboratory in a German-speaking region of Europe. I was fortunate in joining Vladimir Prelog's laboratory at the Federal Institute of Technology, Zurich. To improve my ability to read scientific literature and to understand the lectures given in German, I devoted time to reading German literature and translating papers into English. It was during one of my visits to the departmental library, in between experiments, that I came across a paper, completely unrelated to what I was then doing, but a paper that began to mean a great deal to me two years hence. This was a paper by Fritz Zetzsche and coworkers. Zetzsche had been publishing a series of papers in the German literature

on the use of carbodiimides for the identification of carboxylic acids.² Indeed, after a systematic study of a very large number of carbodiimides, Zetzsche had proposed *bis-p*-dimethylaminophenyl carbodiimide, which bears his name, as a general and useful reagent for the purpose.

Two years later, when working in Cambridge, England, I was interested in developing methods for the synthesis and stepwise degradation of peptides. Controlled degradation of peptide chains from the carboxyl end by chemical methods was (and remains) an unsolved and challenging problem. It was in connection with this problem that I thought of carbodiimides as a handle for cleaving off amino acids from the carboxyl terminus one at a time. Following adduct formation with a carbodiimide, the *c*-terminal amino acid was to be released as a five-membered hydantoin derivative. Although the idea worked and I tried different types of carbodiimides, side reactions also occurred, and I did not succeed in developing a completely satisfactory degradative method. The work appeared in the *Journal of the Chemical Society (London)* in 1952.³

During the above investigation, I learned a great deal about carbodiimides as well as peptides. Thoughts about new applications of carbodiimides and the mechanisms of their reactions came with increasing frequency. In December 1951, while still in Cambridge, I discovered the instantaneous and exothermic formation of tetrabenzyl pyrophosphate on mixing dicyclohexylcarbodiimide with dibenzyl phosphate. This observation laid the foundation for most of my work with nucleotides in the 1950s.⁴

Other important applications that I investigated were in the syntheses of esters, amides, and peptides. Detailed studies led to the work and mechanistic analysis that forms the subject of the article now under review.

During my contacts and conversations with various chemists in England and on the European continent in 1951-1952, I found that practically no one had heard of the carbodiimides. Essentially, all of the literature I could find on the subject was in the German language. I therefore decided to write a review to draw attention to these easily accessible reagents that promised useful applications. This review² evidently stimulated wide interest in them. Subsequently, publications on and applications of the reagents increased rapidly. Periodic reviews, more and more voluminous, began to appear.^{5,6}

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2. Khorana H G. The chemistry of carbodiimides. *Chem. Rev.* 53:145-66, 1953. (Cited 315 times since 1955.)
3. Keener G W & Khorana H G. Peptides. Part II. Selective degradation by removal of the terminal amino acid bearing a free amino group. The use of alkyl alkoxydithioformates (dialkyl xanthates). *J. Chem. Soc.* 386:2076-81, 1952. (Cited 30 times since 1955.)
4. Khorana H G. *Some recent developments in the chemistry of phosphate esters of biological interest.* New York: Wiley, 1961. 141 p. (Cited 250 times.)
5. Kurzer F & Doaragh-Zadeh K. Advances in the chemistry of carbodiimides. *Chem. Rev.* 67:107-52, 1967. (Cited 235 times.)
6. Mikolajczyk M & Kiełbasinski P. Recent developments in the carbodiimide chemistry. *Tetrahedron* 37:233-84, 1981.