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THE PEPTIDE SYNTHESIS USING UNSYMMETRICAL CARBODIIMIDES

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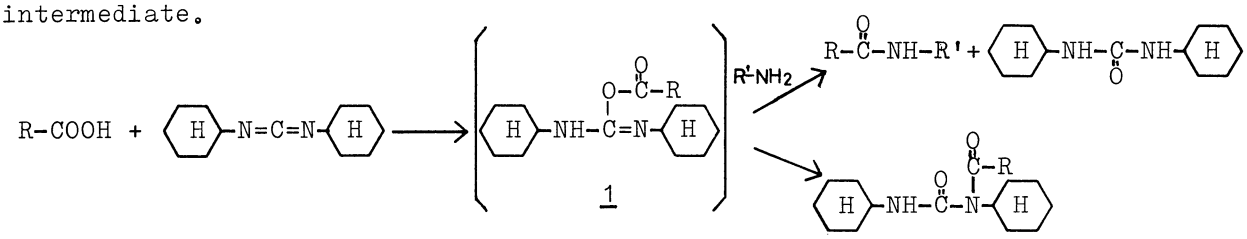
When a peptide was synthesized by use of an unsymmetrical carbodiimide in which the electron density on one nitrogen atom is lower than that on the other, it has been found that the formation of N-acylurea is markedly suppressed and the racemization of the product is limited to a less extent in comparison with the case using DCC(dicyclohexylcarbodiimide).

When peptides are synthesized by the DCC method,[1] some N-acyl derivatives of urea[2] are liable to be brought about as by-products. These not only lower the yield of the desired peptide derivatives but also make sometimes the purification of them exceedingly difficult. The N-acylurea (2) has been thought to form via the intramolecular rearrangement of acylisourea (1), a reaction intermediate.



1 2

Our present aim is to lower such an undesirable rearrangement reaction to occur by using an unsymmetrical carbodiimide in which the electron density on one nitrogen atom is lower than that on the other. Thus 1-benzyl-3-ethylcarbodiimide (6) was synthesized as an unsymmetrical carbodiimide essentially by the meyhod of Amiard and Heymes[3] and used for the preparation of peptides.

Ethylisocyanate (4) was allowed to react at 0 °C with benzylamine (3) in ether to give N-benzyl-N'-ethylurea (5) (mp 103 - 104 °C). 1-Benzyl-3-ethyl-

carbodiimide (6) (bp 44 °C/ 0.05 mmHg, IR; 2130 cm^{-1}) was obtained when 5 was heated at 70 °C for 1 hr together with pyridine and p-toluenesulfonyl chloride.

$$\underset{3}{C_6H_5CH_2NH_2} + \underset{4}{Et\text{-}NCO} \longrightarrow \underset{5}{Et\text{-}NH\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}CH_2C_6H_5} \longrightarrow \underset{6}{Et\text{-}N{=}C{=}N\text{-}CH_2C_6H_5}$$

In the presence of 6 and DCC in THF respectively, Dnps[4](2,4-dinitrophenylthio)-Gly and L-Val-OMe were coupled and the quantities of resulting Dnps-Gly-L-Val-OMe and a by-product, N-acylurea were determined at definite time intervals. The results are shown in Fig. 1.

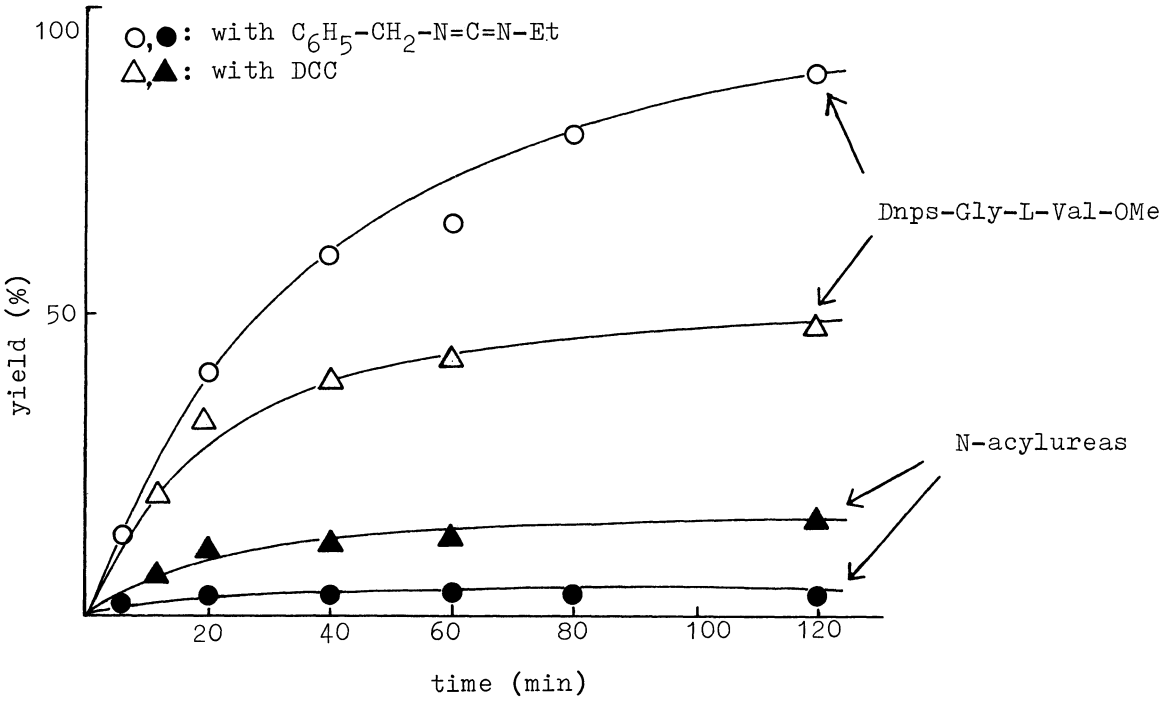


Fig. 1. Formation of Dnps-Gly-L-Val-OMe and N-acylurea during coupling reaction of Dnps-Gly with L-Val-OMe in THF in the presence of DCC or 1-benzyl-3-ethylcarbodiimide as determined by thin-layer chromatography on silica gel.

These results indicate that the formation of N-acylurea is significantly depressed by use of the unsymmetrical carbodiimide.

In order to investigate the influence of a substituent in an unsymmetrically substituted carbodiimide on racemization, some carbodiimides were synthesized by the method similar to that described above and the Young test[5] was performed.

Table 1. The characteristics of unsymmetrical carbodiimides.

carbodiimides	Yield(%)	Bp (°C/mmHg)	Young test* (L-isomer %)
$C_6H_5CH_2$-N=C=N-Et	65	44/0.05	30
$CH_3C_6H_4$-N=C=N-Et	77	73/0.94	74
C_6H_5-N=C=N-Et	80	51/0.05	82
DCC			17

* The $[\alpha]_D$ of benzoyl leucylglycine ethyl ester synthesized by coupling was measured after separation from the reaction mixture by thin-layer chromatography on silica gel.

From the results of the Young test, the degree of racemization was found to decrease in the following order :

DCC > $C_6H_5CH_2$-N=C=N-Et > $CH_3C_6H_4$-N=C=N-Et > C_6H_5-N=C=N-Et

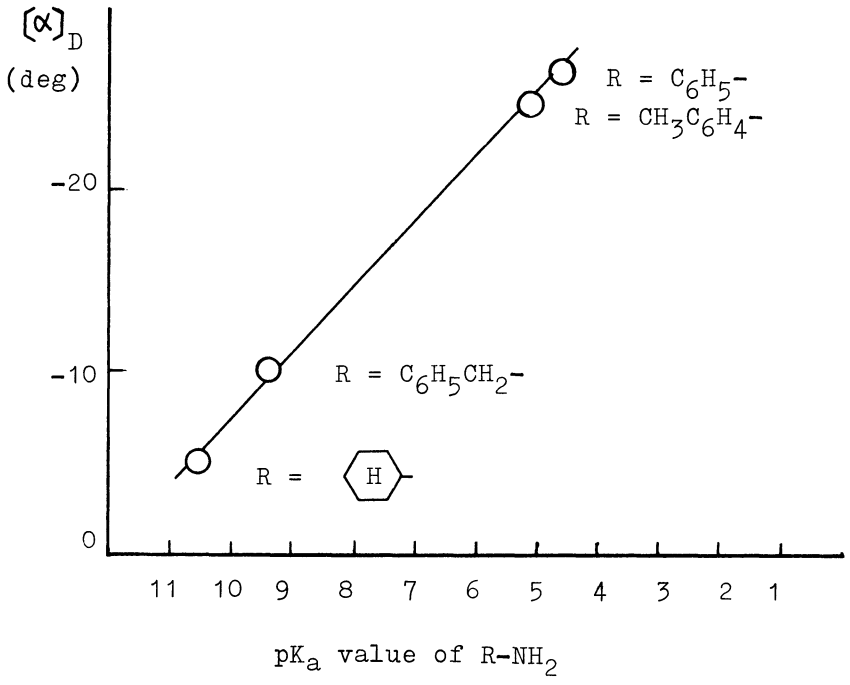


Fig. 2. Relationship between pK_a values of R-NH_2 and $[\alpha]_D$ of benzoyl leucylglycine ethyl ester prepared by use of R-N=C=N-Et.

Then pK_a value of $R-NH_2$, which is considered to be a measure of electron density on one nitrogen atom of unsymmetrical carbodiimide, was plotted against the specific rotation of benzoyl leucylglycine ethyl ester synthesized in the presence of each carbodiimide as shown in Fig. 2. These results suggest that racemization occurs to a less extent by using carbodiimide with decreasing electron density on one nitrogen atom.

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