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Synthesis of Peptides Containing α,α'-Iminodicarboxylic Acids#

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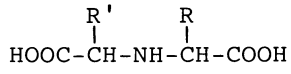
The peptides containing α,α'-iminodicarboxylic acids which are hardly prepared by the conventional methods of peptide synthesis, were well synthesized by the four-component condensation. The diastereomers were isolated, and their configurations were determined.

α,α'-Iminodicarboxylic acids (IDCA) (**1**) are receiving increased attention because of their biological importance. They seem to be specific markers for crown gall tumors,[1] and a series of synthetic dipeptides containing IDCA (**1**) have demonstrated to be potently active as inhibitors of angiotensin-converting enzyme[2] and some other enzymes.[3]



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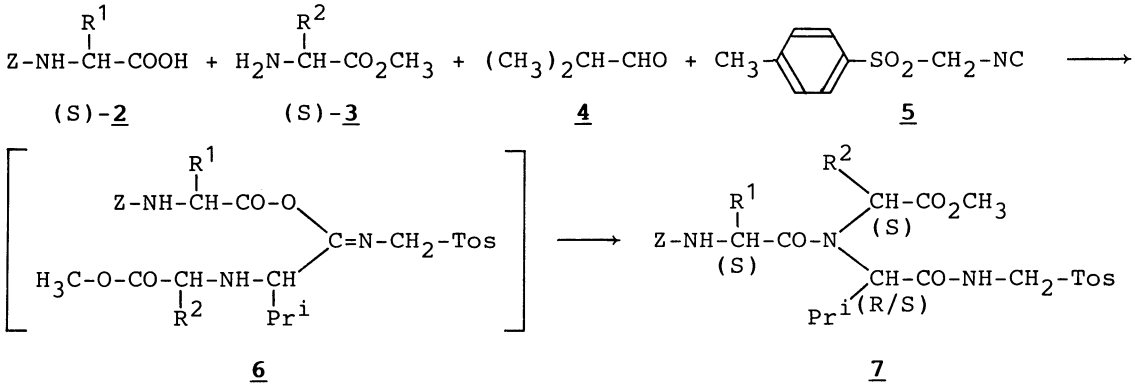
During our studies on N-carboxymethylamino acids (CmAA), a simple type of IDCA (**1**, R'=H), it has been shown that the imino group of a CmAA has remarkably poor reactivity.[4] Recently we could considerably overcome this difficulty by the application of high pressure (10 kbar) to the coupling reactions of Z-AA-ONSu with CmAA diesters.[5] The coupling yields, however, remained very low in some reactions between relatively bulky amino acids.

Now we wish to report the successful synthesis of the peptides containing IDCA (**1**) by the use of the four-component condensation (4CC) or Ugi reaction.[6] The reaction, as shown in Scheme 1, of a Z-amino acid[7] (**2**), an amino acid methyl ester



Scheme 1.

#This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

(3), isobutylaldehyde (4) and p-tolylsulfonylmethyl isocyanide (TosMIC)[8] (5) in methanol expectedly provided the desired peptide (7) containing IDCA (1) in moderate to good yield (Table 1). Remarkably, even 7j which contains three bulky isopropyl groups could be obtained in a 76% yield.

In a typical procedure, to a cold solution of Z-amino acid (10 mmol), amino acid methyl ester hydrochloride (10 mmol), triethylamine (10 mmol) and isobutylaldehyde (11 mmol) in methanol (15 ml) was added TosMIC (11 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and then at 20 °C for 7 days.[9] The reaction mixture was worked up in the usual manner to give a crude product (7), which was purified chromatographically. These products were characterized by elemental analyses and ^{1}H and ^{13}C-NMR. In the case of 7c, α-adduct intermediate (6) was also isolated in a 20% yield.

All of the peptides (7), except 7a, were obtained as the mixture of two diastereomers, which were well separated by HPLC except in the case of 7c (Table 1). The ratios (A/B) of diastereomers (A and B) of 7 are markedly affected by the side-chain structure (R^2) of the amine component (3), while the change of the acid component (2) has no effect. The more bulkiness of the side-chain (R^2) of 3 provides the larger diastereomer ratio, but unexpectedly, the ratio in R^2=Bu^t is

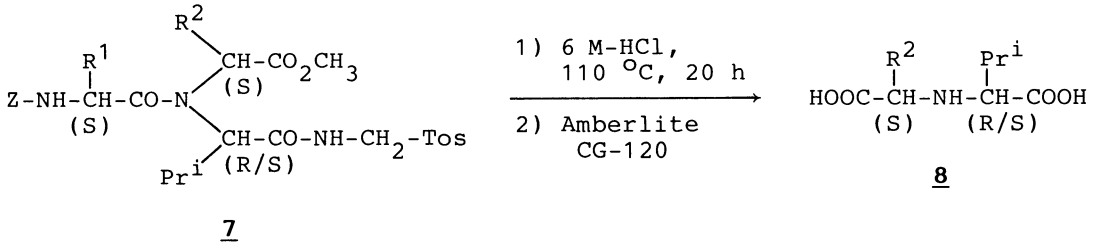
Table 1. Synthesis of Peptides (7) Containing α,α'-Iminodicarboxylic Acid by 4CC

Compound	R^1		R^2		Yield	HPLC Analysis of Diastereomers[a] t_R(A)	t_R(B)	Ratio
					%	min	min	A/B
7a	H	(Gly)[b]	H	(Gly)[c]	84	4.52		
7b	Me	(Ala)	H	(Gly)	73	5.32	6.31	50/50
7c	Pr^i	(Val)	H	(Gly)	39	10.44	10.44	---
7d	H	(Gly)	Me	(Ala)	72	5.21	5.69	58/42
7e	Me	(Ala)	Me	(Ala)	80	5.88	7.46	60/40
7f	Pr^i	(Val)	Me	(Ala)	73	9.22	14.28	59/41
7g	Bu^t	(Tle)	Me	(Ala)	75	12.51	20.84	59/41
7h	H	(Gly)	Pr^i	(Val)	84	7.57	10.11	81/19
7i	Me	(Ala)	Pr^i	(Val)	80	9.46	13.47	81/19
7j	Pr^i	(Val)	Pr^i	(Val)	76	15.48	28.46	81/19
7k	H	(Gly)	Bu^i	(Leu)	68	12.42	14.22	78/22
7l	Me	(Ala)	Bu^i	(Leu)	66	15.13	18.17	79/21
7m	Pr^i	(Val)	Bu^i	(Leu)	77	24.69	38.23	78/22
7n	H	(Gly)	Bu^t	(Tle)	59	10.27	15.01	70/30
7o	Me	(Ala)	Bu^t	(Tle)	37	13.37	19.93	69/31
7p	H	(Gly)	Bzl	(Phe)	78	12.81	14.93	77/23
7q	Me	(Ala)	Bzl	(Phe)	69	16.66	20.57	79/21
7r	Pr^i	(Val)	Bzl	(Phe)	78	29.16	41.60	78/22
7s	H	(Gly)	Ph	(Phg)	77	7.07	8.62	54/46
7t	Me	(Ala)	Ph	(Phg)	60	8.27	11.42	55/45
7u	Pr^i	(Val)	Ph	(Phg)	72	13.00	23.40	55/45
7v	H	(Gly)	Pe^n	(Mle)	65	15.73	18.87	81/19
7w	Me	(Ala)	Pe^n	(Mle)	87	21.12	23.87	81/19
7x	Pr^i	(Val)	Pe^n	(Mle)	59	36.03	51.64	82/18

a) Conditions: Column, Cosmosil $5C_{18}$ (4.6 mm I.D. × 150 mm); Mobile phase, 70% MeOH aq.; Flow rate, 1.0 ml/min; Column temperature, 30 °C; Detection, 254 nm. b) Amino acid of the acid component (2). c) Amino acid of the amine component (3). Abbreviations: Tle, t-leucine; Phg, phenylglycine; Mle, γ-methylleucine; Pe^n, neopentyl.

smaller than those in R^2=Pr^i, Bu^i, Bzl, or Pe^n. In all cases, the diastereomer (A) which elutes faster than B in HPLC arises in excess.

Isolation of each diastereomer of **7** was easily accomplished by silica gel chromatography or by reversed-phase, medium-pressure liquid chromatography using ODS column (Table 2). The configuration on the newly formed chiral center could be determined by isolating IDCAs (**8**) (Scheme 2) and measuring their optical rotations (Table 3). IDCAs (**8u**) were hydrogenolyzed into valine by using 5% Pd-C. Hydrolysates (**8d**) were converted to TMS derivatives with BSTFA[10] and analyzed by GLC.[11]



7 **8**

Scheme 2.

These results indicate that the configuration on the new chiral center in every diastereomer (**7**-A) is opposite to those of amino acids used as the acid and amine components, unless the configurations of both components are different each other. On the other hand, all chiral centers in every diastereomer (**7**-B) have the same configuration. Every diastereomer of IDCA (**8**) produced in excess has S-R configuration. Interestingly, all of the nitrogenous opines, naturally occurring IDCA (**1**), are known to have S-R configuration.[13] The steric requirement of the 4CC shown in Scheme 1 seems to be related to stereochemistry in the formation of S-R opines, which may occur by enzymatic reduction of the Schiff base of an L-amino acid and such common metabolites as pyruvic acid and α-ketoglutaric acid.[13]

Further studies using isocyanides derived from amino acids are in progress.

Table 2. Isolation of Diastereomers of Peptides (**7**)

Compound		R^1	R^2	t_R/min	$[\alpha]_D^{25}$/° (DMF)	Config. of New Chiral Center
7b	A	Me (Ala)	H (Gly)	5.32	+30.0 (c 1.00)	R
	B			6.31	-53.3 (c 1.00)	S
7d	A	H (Gly)	Me (Ala)	5.21	- 5.1 (c 0.96)	R
	B			5.69	-25.1 (c 0.89)	S
7e	A	Me (Ala)	Me (Ala)	5.88	+18.3 (c 0.42)	
	B			7.46	-97.0 (c 0.90)	
7f	A	Pr^i (Val)	Me (Ala)	9.22	+22.8 (c 1.00)	R
	B			14.28	-98.3 (c 1.00)	S
7h	A	H (Gly)	Pr^i (Val)	7.57	-27.9 (c 1.14)	
	B			10.11	-14.2 (c 1.03)	
7i	A	Me (Ala)	Pr^i (Val)	9.46	- 3.6 (c 1.00)	R
	B			13.47	-72.9 (c 1.00)	S
7j	A	Pr^i (Val)	Pr^i (Val)	15.48	-14.8 (c 1.00)	R
	B			28.46	-84.3 (c 1.00)	S
7u	A	Pr^i (Val)[a]	Ph (Phg)[a]	13.00	+10.4 (c 1.00)	S
	B			23.40	+143.7 (c 1.00)	R

a) (R)-Isomers were used.

Table 3. Determination of Configurations of IDCA (**8**) Obtained from Peptides (**7**)

IDCA		R^2	$[\alpha]_D^{25}$/° (solvent)	Config.
8b	A	H (CmVal)	- 5.2 (c 1.0, H_2O)	R
	B		+ 4.5 (c 1.0, H_2O)	S
8d	A	Me (CeVal)	(GLC of TMS deriv.)[11]	S-R
	B			S-S
8f	A	Me (CeVal)	-10.4 (c 1.0, H_2O)	S-R
	B		+ 5.5 (c 0.8, H_2O)	S-S
8i	A	Pr^i (CiVal)	0 (c 0.5, 1 M-HCl)	S-R
	B		+30.1 (c 1.0, 1 M-HCl)	S-S
8j	A	Pr^i (CiVal)	0 (c 0.5, 1 M-HCl)	S-R
	B		+30.1 (c 1.0, 1 M-HCl)	S-S
8u	A	Ph (CbVal)	- 7.1 (c 1.0, MeOH)	R-S
	B		-49.1 (c 1.0, MeOH)	R-R
		Val : A	+30.7 (c 0.8, 6 M-HCl)	S
		B	-20.4 (c 0.7, 6 M-HCl)	R

Lit. CmVal (**8**, R^2=H): (S), $[\alpha]_D^{25}$ +6.8° (c 1.0, H_2O).[4a] CeVal (**8**, R^2=Me): (S-R), $[\alpha]_D^{25}$ -14.8° (c 1.0, H_2O); (S-S), +10.0° (c 0.8, H_2O).[12] Val: (S), $[\alpha]_D^{20}$ +28.8° (c 3.4, 6M-HCl).

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References

1) J. Tempe, "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," ed by B. Weinstein, Marcel Dekker, New York (1983), Vol. 7, p.113.
2) A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, M. T. Wu, D. Taub, E. R. Peterson, T. J. Ikeler, J. ten Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N. S. Lohr, R. D. Hoffsommer, H. Joshua, W. V. Ruyle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson, R. Hirschmann, C. S. Sweet, E. H. Ulm, D. M. Gross, T. C. Vassil, and C. A. Stone, Nature, 288, 280 (1980); M. Vincent, G. Remond, B. Portevin, B. Serkiz, and M. Laubie, Tetrahedron Lett., 23, 1677 (1982).
3) A. L. Maycock, D. M. DeSousa, L. G. Payne, J. ten Broeke, M. T. Wu, and A. A. Patchett, Biochem. Biophys. Res. Commun., 102, 963 (1981); M. C. Fournie-Zaluski, P. Chaillet, E. Soroca-Lucas, H. Marcais-Collado, J. Costentin, and B. P. Roques, J. Med. Chem., 26, 60 (1983); E. T. Maggio and E. F. Ullman, Biochim. Biophys. Acta, 522, 284 (1978).
4) a) T. Miyazawa, Bull. Chem. Soc. Jpn., 53, 2555 (1980); b) T. Miyazawa, ibid., 53, 3661 (1980); c) T. Miyazawa, S. Hiramatsu, Y. Tsuboi, T. Yamada, and S. Kuwata, ibid., 58, 1976 (1985).
5) T. Yamada, Y. Manabe, T. Miyazawa, S. Kuwata, and A. Sera, J. Chem. Soc., Chem. Commun., 1984, 1500.
6) "Isonitrile Chemistry," ed by I. Ugi, Academic Press, New York (1971), Chap. 8; I. Ugi, D. Marquarding, and R. Urban, "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," ed by B. Weinstein, Marcel Dekker, New York (1982), Vol. 6, p.245.
7) L-Amino acids are always used here, unless otherwise specified.
8) B. E. Hoogenboom, O. H. Oldenziel, and A. M. van Leusen, Org. Synth., Vol. 57, 102 (1977).
9) The reaction for 7 days seems to be not always necessary.
10) TMS, trimethylsilyl; BSTFA, bis(trimethylsilyl)trifluoroacetamide. See, C. W. Gehrke and K. Leimer, J. Chromatogr., 57, 219 (1971).
11) t_R : S-R isomer, 12.02 min; S-S isomer, 13.02 min [FID; 2 m × 3 mm stainless column (OV-11); Carrier gas, N_2 ; Column temp, 150 °C; Inject temp, 260 °C.]
12) T. Miyazawa, et al., unpublished results.
13) W.S.Chilton, K.L.Rinehard,Jr., and M.D.Chilton, Biochemistry, 23, 3290 (1984).

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