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Cis-trans Relationship between the Two Amino-acids Obtained by Hydrogenation of *p*-Aminomethyl Benzoic Acid

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In order to establish which of the two isomers of 1,4-aminomethyl-cyclohexane-carboxylic acid is the *cis* and which the *trans* form, the crystal structure of the hydrobromide of the amino-acid which is "inactive" as an antifibrinolytic agent has been determined. It was found that the inactive amino-acid is the *cis* isomer and consequently the "active" amino-acid the *trans* form. Details of the crystal structure of the hydrobromide of the "inactive" amino-acid are presented.

One of the two stereo-isomers obtained from *p*-aminomethyl benzoic acid by hydrogenation exhibits a strong antifibrinolytic activity, the other almost none.[1] It appeared to be of interest to decide which of the two isomers is the *trans* and which the *cis* isomer. This may, of course, be done by X-ray crystallographic examination of the two amino-acids themselves. These crystal structure determinations involve a considerable amount of work, however, because all the atoms which contribute significantly to the scattering of X-rays have nearly the same scattering power. We have, therefore, preferred to tackle the problem by determining the crystal structure of one of the hydrobromides, and chose that of the "inactive" isomer. Results of the two-dimensional structure determination shows conclusively that the "inactive" amino-acid is the *cis*, and that consequently the "active" amino-acid must be the *trans* isomer.

Crystals of the hydrobromide of the "inactive" isomer are *monoclinic* with the lattice parameters:

$$a = 5.48 \text{ Å}, \; b = 33.29 \text{ Å}, \; c = 7.96 \text{ Å}, \; \beta = 131°$$

The space group is $P2_1/c$ and the number (Z) of formula units in the cell is *four*.

The intensity material consisted of photometric measurements of integrated zero-layer Weissenberg diagrams with rotation about [10$\bar{1}$] (Cu$K\alpha$-radiation) and of precession diagrams along [100] (Mo$K\alpha$-radiation). Prelim-

inary bromine parameters were derived from Patterson syntheses and atomic coordinates from Fourier maps and refined using least squares methods. *Anisotropic B* values were computed for the bromine atoms only. The final *R* value thus obtained including all observed reflections is 6.5 %.

The following conclusions were reached: The skeleton of the "inactive" positively charged amino-acid ion corresponds to the *cis* configuration with the carboxylic group in the axial, the $CH_2NH_3^+$ group in the equatorial position. The distances from the nitrogen atom to the three nearest bromine ions are identical within the probable limits of error, the individual values being 3.30, 3.32, and 3.33 Å, respectively. The mean value of the three Br—N—Br angles is 111.5° and the environment of the nitrogen atom therefore nearly "tetrahedral". Each bromine ion has three NH_3^+ neighbours with N—Br—N angles all approximately equal to 90°. The COOH groups of two neighbouring amino-acid cations are held together by two (identical) hydrogen

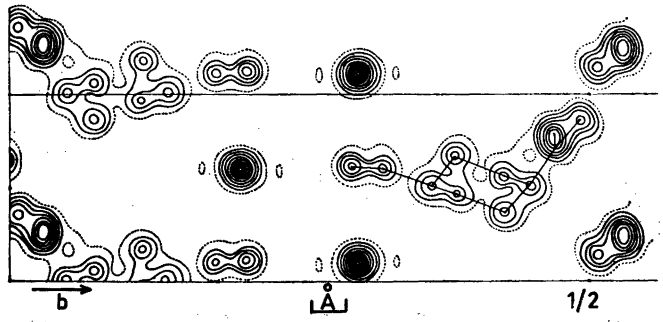

Fig. 1. Fourier projection along [10$\bar{1}$].

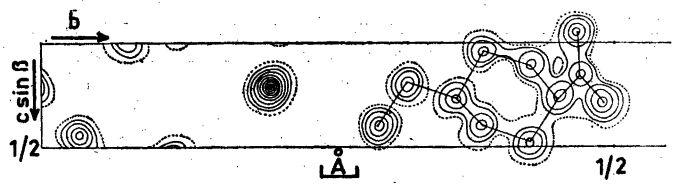

Fig. 2. Fourier projection along the *a* axis.

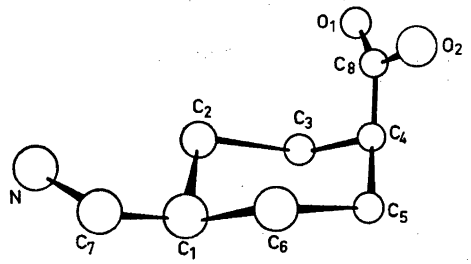

Fig. 3. Schematical drawing of the amino acid ion.

Table 3. Observed and calculated structure factors.

h k l	F_o	F_c	h k l	F_o	F_c
0 4 0	43.2	31.6	0 8 2	53.4	56.6
6	58.8	55.5	9	48.9	47.6
8	115.9	−101.5	10	58.1	− 64.2
10	119.6	127.0	11	9.7	− 9.4
12	115.5	−117.0	12	39.7	40.0
14	29.1	24.7	13	10.7	7.0
16	45.0	44.3	14	26.6	− 25.0
18	67.4	− 70.6	16	34.0	− 33.7
20	44.8	47.6	17	21.1	− 21.4
22	57.9	− 60.3	18	38.9	41.1
24	19.6	17.0	19	20.7	19.6
26	26.4	25.1	20	58.6	− 62.6
28	16.6	− 14.3	23	11.4	11.7
30	34.1	34.1	28	25.1	27.9
32	31.1	− 29.2	29	13.4	15.1
34	15.2	12.7	30	22.4	− 23.5
36	11.5	11.5	32	17.2	17.6
38	11.2	− 11.4	0 1 3	22.8	− 21.7
40	14.9	15.6	2	41.8	40.9
42	6.6	− 6.9	3	31.9	32.1
0 2 1	26.0	24.1	4	54.1	− 57.6
3	49.2	− 52.4	5	46.4	− 49.9
4	103.6	123.6	6	39.9	39.6
5	28.1	21.8	7	18.3	17.5
6	69.1	− 78.1	8	66.6	− 71.4
7	43.0	− 40.7	9	36.7	− 35.8
8	71.4	79.6	10	11.7	− 11.6
9	28.9	27.9	12	32.6	30.9
10	19.8	18.4	13	38.1	36.2
11	11.1	13.7	14	45.3	− 47.9
12	44.2	− 44.6	15	33.7	− 36.7
13	8.8	9.7	16	36.9	38.3
14	64.8	69.0	17	24.8	23.3
15	52.1	52.9	18	17.2	− 16.1
16	57.7	− 58.1	19	23.6	− 25.7
17	14.6	− 11.5	20	14.6	14.2
18	49.7	51.1	21	16.4	− 13.0
19	26.1	25.9	22	12.3	11.1
20	12.0	9.1	23	18.7	16.6
22	31.0	− 31.1	24	41.0	− 45.7
24	44.8	53.2	25	23.1	− 23.8
25	15.7	15.5	26	21.4	19.0
26	36.3	− 39.5	27	18.5	18.6
27	15.7	− 15.7	36	12.5	10.9
28	20.9	22.7	0 0 4	38.8	36.1
30	14.4	14.4	1	45.7	47.4
32	18.7	− 20.3	2	14.6	− 14.1
34	18.8	21.1	3	24.9	− 26.0
36	16.5	− 17.9	6	18.7	17.6
0 0 2	85.1	− 89.8	7	37.1	35.9
1	32.0	− 32.8	8	20.3	− 18.1
2	69.3	68.4	9	37.0	− 36.9
3	19.3	18.6	10	18.9	16.9
4	47.4	− 45.8	11	37.8	41.5
6	69.1	− 72.9	12	15.2	− 14.6
7	30.5	− 30.1	13	15.2	− 14.9

h	k	l	F_o	F_c
0	16	4	17.3	16.2
	17		16.2	14.8
	18		16.5	− 15.7
	19		25.0	− 28.5
	20		23.2	22.9
	21		14.0	14.7
	23		21.3	− 22.9
	28		12.4	− 12.0
	29		15.7	− 16.7
0	1	5	15.8	14.8
	3		13.2	− 11.2
	4		13.9	10.0
	5		23.9	25.0
	6		21.1	− 20.6
	7		20.0	− 19.8
	12		13.9	− 15.3
	15		25.1	28.0
	17		17.2	− 16.0
	23		12.5	− 12.4
	24		11.7	11.8
	25		16.0	14.7
0	0	6	11.9	− 12.3
	1		18.6	− 19.6
	9		22.0	22.2
	11		17.9	− 19.0
	19		12.6	11.1
	21		13.3	− 13.3
1	1	$\bar{1}$	56.9	− 51.9
	2		10.7	6.9
	3		14.4	− 17.1
	4		69.9	69.5
	5		136.6	134.8
	6		16.5	− 19.5
	7		29.9	− 31.7
	8		70.9	69.7
	9		40.0	40.6
	10		54.0	53.5
	11		48.9	49.4
	12		20.4	17.9
	13		38.2	− 39.3
	14		50.7	53.9
	15		44.7	46.2
	16		41.8	− 40.9
	17		49.6	− 50.4
	18		22.9	21.3
	19		20.9	18.7
	20		3.7	4.1
	21		25.1	25.8
	22		29.0	− 29.2
	23		33.8	− 33.8
	24		21.1	21.5
	25		37.6	37.2
	26		30.8	− 27.8
	27		32.7	− 30.4
	28		9.2	8.0
	29		3.3	2.6
	30		4.6	3.3
	31		25.1	21.8
	32		18.8	− 16.3
	33		15.2	− 14.0
	34		18.8	15.7
	35		16.9	17.0
	36		6.4	− 5.9
	37		13.8	− 12.7
	38		9.8	8.9
	40		6.7	6.4
	41		4.1	4.2
2	0	$\bar{2}$	36.3	34.6
	1		125.4	−118.0
	2		52.4	− 49.3
	3		82.9	71.7
	4		28.3	− 26.7
	5		19.7	18.5
	6		7.1	− 7.9
	7		52.5	− 50.5
	8		32.5	− 31.9
	9		103.7	102.9
	10		19.5	20.4
	11		82.4	− 81.1
	12		19.7	− 19.3
	13		51.8	51.9
	14		25.9	25.4
	15		15.7	15.4
	16		26.5	26.8
	17		29.2	− 29.4
	18		6.7	− 5.0
	19		57.4	57.3
	20		31.1	30.2
	21		43.0	− 42.3
	23		31.7	30.0
	24		5.5	5.0
	27		15.7	− 16.3
	28		12.3	− 10.2
	29		29.8	27.6
	31		21.9	− 19.9
	32		19.7	− 17.0
	33		22.1	− 18.0
	34		7.1	− 4.1
	37		7.4	− 7.8
	38		5.0	− 4.9
	39		11.9	12.6
	40		2.4	3.0
3	1	$\bar{3}$	24.6	− 24.5
	2		43.5	− 38.9
	4		44.7	42.7
	5		26.7	− 25.7
	6		65.6	− 62.0
	7		5.7	− 4.5
	8		22.6	19.5
	9		7.4	− 6.9
	10		17.2	− 16.4
	12		46.2	− 42.5
	13		14.3	12.0
	14		44.8	44.9
	15		18.2	− 16.3
	16		38.1	− 39.2

h	k	l	F_o	F_c
3	17	$\bar{3}$	9.5	9.0
	18		28.5	27.3
	19		7.6	— 6.4
	20		7.7	6.8
	21		19.8	— 17.6
	22		18.3	— 17.5
	24		45.2	42.5
	25		10.4	— 8.1
	26		19.3	— 19.9
	27		7.2	6.6
	28		17.5	16.9
	30		11.0	8.9
	31		2.9	— 1.9
	32		12.9	— 12.5
	33		11.4	9.1
	34		18.7	17.5
	35		6.6	— 6.1
	36		12.9	— 14.5
4	0	$\bar{4}$	43.9	— 42.7
	1		34.6	— 32.4
	2		44.5	43.1
	3		18.6	16.9
	4		16.1	— 16.9
	5		6.0	— 7.2
	6		12.5	— 13.2
	7		28.9	— 28.3
	8		38.5	38.7
	9		29.9	30.2
	10		53.3	— 54.4
	11		16.9	— 17.3
	12		12.7	12.8
	13		17.2	15.6
	14		20.4	— 21.6
	15		4.6	— 6.5
	16		18.4	— 19.3
	17		19.1	— 19.3
	18		17.4	17.5
	19		21.0	21.3
	20		26.0	— 25.2
	21		13.0	— 13.6
	22		21.2	20.8
	23		7.8	7.0
	24		8.8	— 8.7
	26		7.9	— 7.3
	27		6.4	— 6.4
	28		12.1	11.7
	29		10.3	9.9
4	30	$\bar{4}$	12.9	— 13.5
	31		12.5	— 12.8
	32		10.5	10.0
5	1	$\bar{5}$	14.7	— 14.9
	3		27.3	26.0
	4		8.7	9.6
	5		27.1	— 25.9
	6		4.6	5.2
	7		17.6	17.0
	8		6.5	5.9
	9		10.8	— 12.0
	10		3.2	— 4.6
	11		4.6	— 2.7
	12		5.6	— 6.4
	13		25.5	26.5
	15		25.4	— 25.6
	16		4.4	3.7
	17		16.2	15.7
	19		6.6	— 8.5
	20		8.0	— 4.6
	21		10.9	— 11.0
	22		5.4	— 4.0
	23		16.1	16.1
	24		2.5	— 2.4
	25		12.5	— 16.3
	26		5.0	— 4.9
	27		10.3	11.4
	28		2.6	— 2.8
6	0	$\bar{6}$	13.8	— 13.9
	1		12.8	13.5
	2		17.2	16.1
	3		12.4	— 12.0
	4		9.4	— 10.1
	6		7.4	— 6.8
	7		6.8	7.2
	8		15.5	18.2
	9		11.5	— 13.2
	10		15.5	— 17.2
	11		13.1	14.1
	12		9.9	9.6
	13		6.1	— 5.6
	15		2.3	— 3.2
	19		11.3	— 8.8
	20		7.4	— 8.6
	21		5.4	8.0
	22		4.5	9.6
	23		3.7	— 4.4

bonds 2.69 Å long. In Fig. 1 a Fourier projection along [10$\bar{1}$] is reproduced, the length of the projection axis being 6.02 Å. Fig. 2 shows the Fourier map corresponding to the [0kl] projection. In Fig. 3 a schematical drawing of the amino-acid ion is given.

Table 1 contains the final atomic coordinates and Table 2 the interatomic distances and angles within the amino-acid unit. It is seen that the mean

Table 1. Final atomic coordinates.

	x	y	z
Br	0.3117	0.1996	0.2125
O_1	0.6459	0.4923	0.2872
O_2	0.2377	0.4691	−0.0482
N	0.5218	0.2930	0.4042
C_1	0.2753	0.3615	0.2637
C_2	0.0275	0.3860	0.0426
C_3	−0.0324	0.4279	0.1054
C_4	0.2733	0.4508	0.2655
C_5	0.5310	0.4256	0.4644
C_6	0.5800	0.3849	0.4085
C_7	0.3105	0.3196	0.2023
C_8	0.3807	0.4709	0.1539

Table 2. Interatomic distances (Å) and angles(°).

C_1-C_2	1.48	$C_1-C_2-C_3$	112
C_2-C_3	1.51	$C_2-C_3-C_4$	114
C_3-C_4	1.51	$C_3-C_4-C_5$	111
C_4-C_5	1.49	$C_4-C_5-C_6$	112
C_5-C_6	1.56	$C_5-C_6-C_1$	111
C_6-C_1	1.54	$C_6-C_1-C_2$	108
C_1-C_7	1.53	$C_2-C_1-C_7$	114
C_4-C_8	1.51	$C_6-C_1-C_7$	110
C_7-N	1.50	$C_3-C_4-C_8$	114
C_8-O_1	1.25	$C_5-C_4-C_8$	112
C_8-O_2	1.31	C_1-C_7-N	111
		$C_4-C_8-O_1$	125
		$C_4-C_8-O_2$	115
		$O_1-C_8-O_2$	120

values of angles and C—C distances within the cyclohexane ring are in very good agreement with those found for cyclohexane itself.[2] Table 3 contains observed and calculated structure factors.

The crystal structure determination of the "active" amino-acid is being continued by one of the authors (P. Groth) and it is hoped that precise informations regarding the zwitterion of the *trans* form will soon be available.

It would appear interesting to compare the skeleton of the zwitterions of the two amino-acids with those present in their anions and cations, respectively.

We wish to thank the Research Department of A.B. Kabi, Stockholm, for confronting us with the present problem and for placing samples of the amino-acids and their hydrobromides at our disposal.

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