

Crystal Structures of Hydrophobic Amino Acids I. Redeterminations of L-Methionine and L-Valine at 120 K

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Dalhus, B. and Görbitz, C. H., 1996. Crystal Structures of Hydrophobic Amino Acids I. Redeterminations of L-Methionine and L-Valine at 120 K. – Acta Chem. Scand. 50: 544–548. © Acta Chemica Scandinavica 1996.

The crystal structures of L-methionine and L-valine have been redetermined by X-ray diffraction methods at 120 K. Both compounds crystallize in the monoclinic space group $P2_1$, $Z=4$, with lattice parameters $a=9.493(2)$, $b=5.201(2)$, $c=14.831(3)$ Å, $\beta=99.84(2)^\circ$ for L-Met and $a=9.682(2)$, $b=5.247(1)$, $c=11.930(2)$ Å, $\beta=90.57(1)^\circ$ for L-Val. The least squares refinements converged at $R=0.037$, $R_w=0.038$ for L-Met and $R=0.034$, $R_w=0.038$ for L-Val. The structure factors for L-Met were empirically corrected for absorption.

The overall geometries agree with the original structure determinations, but the standard deviations for geometric parameters have been reduced by a factor between 4 and 10. Also, positional parameters for all hydrogen atoms have been refined, allowing a detailed study of the hydrogen bond patterns.

Of the 20 naturally occurring amino acids, Gly (three polymorphs),^{1–3} Cys,⁴ Ile,⁵ Leu,⁶ Met,⁷ Phe⁸ and Val⁹ crystallize in monoclinic space groups with alternating hydrophobic and hydrophilic layers and largely identical hydrogen bond patterns. We intend to use these compounds as part of a database for multivariate analysis of correlations between hydrogen bond parameters. Unfortunately, the accurate experimental hydrogen atom positions required for such studies are available only for the glycine polymorphs. These are also the only structures which have been determined with high precision and low standard deviations for the geometric parameters. This situation has prompted us to undertake a program to redetermine known amino acid structures as well as to determine structures of new compounds. The hydrophobic amino acids listed above (except Phe) share a common crystal habit in forming very thin flakes. One of the obstacles in obtaining high precision structures is associated with the growth of high-quality crystals, and we have not been able to grow crystals large enough for neutron diffraction experiments. Instead we have used X-ray diffraction methods at low temperature, $T=120$ K. The current paper is the first in a series which will present the results from this work.

The structure of L-Met was first determined by Torii and Iitaka⁷ with an R -factor of 0.089 and average standard deviations in bond lengths between heavy atoms around 0.02 Å. The structure of L-Val was also first determined by Torii and Iitaka⁹ with an R -factor of

0.126 and average standard deviations in bond lengths between heavy atoms of 0.02 Å.

Experimental

Both amino acids were obtained from Sigma Chemical Co. and used as received. Crystals of L-Met suitable for X-ray structure determination were obtained by slow evaporation of 2-propanol into a tetramethoxysilane gel with L-Met at room temperature. The gel was prepared by mixing an aqueous solution of amino acid and tetramethoxysilane in the ratio 5:1. The well mixed solution was left for 2 h to polymerize¹⁰ before being subjected to the 2-propanol reservoir. The gel lowers the diffusion rate for both precipitating agent and amino acid, and the reduced crystal growth rate can enhance the crystal quality and size.¹¹

Crystals of L-Val were grown by the hanging drop technique, using a sodium acetate solution. The salt concentration in the drop was 0.5 mol dm⁻¹ (buffered with 5% sodium dihydrogen phosphate, pH 5.8) and that of the reservoir 2.0 mol dm⁻¹. The amino acid concentration in the drop was 48.8 mg mL⁻¹. The temperature was 5 °C.

The data collection procedures for L-Met and L-Val are summarized in Table 1. Cell parameters for the two amino acids were determined by a least squares fit for 25 strong reflections with 2θ in the range 30–45°, and are listed in Table 1. All reflections were corrected for Lorentz and polarizing effects. The intensity file for L-Met was corrected for X-ray absorption effects using the program DIFABS.¹²

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Table 1. Crystal data, intensity collection and refinement data for L-Met and L-Val.

	L-Met	L-Val
Formula	C ₅ H ₁₁ NO ₂ S	C ₅ H ₁₁ NO ₂
Formula weight/g mol ⁻¹	149.2	117.2
Crystal size/mm	0.85 × 0.40 × 0.10	1.20 × 0.75 × 0.15
Color, habit		Colorless plate
Crystal system		Monoclinic
Space group		P2 ₁ (No. 4)
Cell dimensions/Å, °	<i>a</i> = 9.493(2) <i>b</i> = 5.201(2) <i>c</i> = 14.831(3) β = 99.84(2)	<i>a</i> = 9.682(2) <i>b</i> = 5.247(1) <i>c</i> = 11.930(2) β = 90.57(1)
Volume/Å ³	721.5(3)	606.0(1)
Z	4	4
D _{calc} /g cm ⁻³	1.373	1.284
Diffractometer		Nicolet P3
Radiation		MoK _α (λ = 0.710 69 Å)
Monochromator		Graphite crystal
T/K	120	120
Scan mode	θ/2θ	θ/2θ
Scan speed/° min ⁻¹	3.0	3.0
Scan range/°	-1.2 to +1.4	-1.1 to +1.3
2θ range/°	4-65	4-70
Background/scan ratio	0.70	0.70
Standard reflections		3 measured every 96 reflections
Variation in standard intensities (%)	< 2	< 0.8
Index ranges	0 ≤ <i>h</i> ≤ 14 0 ≤ <i>k</i> ≤ 7 -22 ≤ <i>l</i> ≤ 22	0 ≤ <i>h</i> ≤ 16 0 ≤ <i>k</i> ≤ 8 -20 ≤ <i>l</i> ≤ 20
No. of reflections measured	2889	3597
No. of observed reflections [<i>I</i> > 2.5σ(<i>I</i>)], <i>n</i>	2529	3261
Absorption correction	None	Yes
Refinement	On <i>F</i>	On <i>F</i>
No. of parameters, <i>p</i>	250	232
$R = \sum \Delta F / F_0 ^a$	0.037	0.034
$R_w = \{ \sum [w(\Delta F)^2 / w(F_0)^2] \}^{1/2b}$	0.038	0.038
$S = \{ \sum [w(\Delta F)^2 / (n - p)] \}^{1/2}$	1.92	2.17
Residual electron density/e Å ⁻³	+0.30, -0.30	+0.38, -0.30

^a $\Delta F = |F_0| - |F_c|$. ^b $w = [\sigma^2(F_0) + 0.0004(F_0)^2]^{-1}$.

The structure of L-Met was refined using the atomic coordinates from the former solution⁷ as input for the least squares refinement. The structure of L-Val was solved with the direct methods program SIR92,¹³ and refined using least squares methods.

Positional parameters for all atoms in both structures were refined. All heavy atoms were refined anisotropically, whereas the hydrogen atoms were refined isotropically. The refinement of the two structures is summarized in Table 1. Atomic scattering factors are taken from *International Tables for X-ray Crystallography* (1974).

Results and discussion

Molecular structures. The asymmetric units of L-Met and L-Val, with two crystallographically independent molecules A and B, are shown in Figs. 1 and 2, respectively. Final atomic coordinates are listed in Table 2 for L-Met and Table 3 for L-Val. Molecular geometry parameters for both structures are given in Table 4.

There are no unusual bond lengths in L-Met or

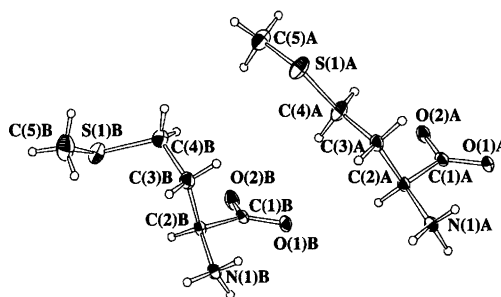


Fig. 1. ORTEP drawing of the asymmetric unit of L-Met. Heavy atoms drawn with 50% probability ellipsoids, H atoms arbitrarily scaled.

L-Val. In the original structure description significant differences between L-Met(A) and L-Met(B) were found for the bond lengths C^γ-S^δ and S^δ-C^ε, hypothesized to be due to large anisotropic thermal vibrations for the terminal side chain atoms.⁷ In the present study, at 120 K, no significant differences are observed, supporting this explanation.

Except for the C-O bonds there are no significant

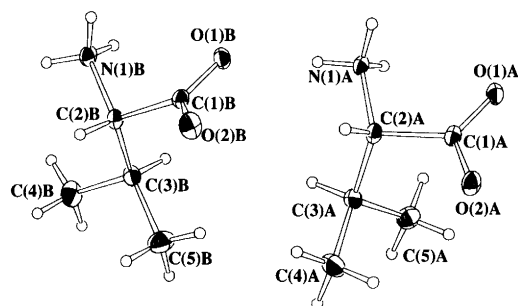


Fig. 2. ORTEP drawing of the asymmetric unit of L-Val. Heavy atoms drawn with 50% probability ellipsoids, H atoms arbitrarily scaled.

Table 2. Fractional coordinates with standard deviations and temperature factors for L-Met.

Atom	x	y	z	U_{eq}/U_{iso}^a
S(1)A	0.3776(1)	0.1112	0.10827(4)	0.027
O(1)A	0.1028(1)	-0.0468(4)	0.42267(10)	0.016
O(2)A	0.1657(2)	0.3245(4)	0.36585(11)	0.018
N(1)A	0.3555(2)	-0.2659(4)	0.42866(13)	0.015
C(1)A	0.1884(2)	0.0952(5)	0.3904(1)	0.014
C(2)A	0.3304(2)	-0.0225(5)	0.3760(1)	0.014
C(3)A	0.3348(2)	-0.0730(6)	0.2745(1)	0.017
C(4)A	0.3461(3)	0.1758(5)	0.2233(2)	0.022
C(5)A	0.3899(3)	0.4359(7)	0.0695(2)	0.028
H(1)A	0.292(3)	-0.398(7)	0.406(2)	0.02(1)
H(2)A	0.430(4)	-0.341(8)	0.424(2)	0.04(1)
H(3)A	0.355(3)	-0.239(6)	0.493(2)	0.03(1)
H(4)A	0.407(2)	0.092(6)	0.399(1)	0.01(1)
H(5)A	0.253(3)	-0.169(6)	0.249(2)	0.03(1)
H(6)A	0.413(3)	-0.170(6)	0.271(2)	0.02(1)
H(7)A	0.268(3)	0.281(6)	0.221(2)	0.02(1)
H(8)A	0.425(3)	0.273(7)	0.261(2)	0.03(1)
H(9)A	0.423(3)	0.434(9)	0.016(2)	0.05(1)
H(10)A	0.463(3)	0.541(7)	0.111(2)	0.04(1)
H(11)A	0.303(3)	0.507(8)	0.055(2)	0.05(1)
S(1)B	0.9207(1)	0.9176(2)	0.15911(4)	0.027
O(1)B	0.6197(2)	0.5521(4)	0.41225(10)	0.018
O(2)B	0.6795(2)	0.9499(4)	0.37595(12)	0.023
N(1)B	0.8776(2)	0.3650(4)	0.39205(13)	0.016
C(1)B	0.6986(2)	0.7130(5)	0.3807(1)	0.015
C(2)B	0.8246(2)	0.6010(5)	0.3412(1)	0.015
C(3)B	0.7794(3)	0.5284(5)	0.2398(2)	0.020
C(4)B	0.7579(3)	0.7558(6)	0.1750(2)	0.026
C(5)B	0.9933(3)	0.6829(7)	0.0910(2)	0.037
H(1)B	0.815(3)	0.212(7)	0.375(2)	0.03(1)
H(2)B	0.958(3)	0.331(7)	0.378(2)	0.03(1)
H(3)B	0.878(3)	0.388(7)	0.450(2)	0.03(1)
H(4)B	0.897(3)	0.728(6)	0.346(2)	0.01(1)
H(5)B	0.692(3)	0.430(8)	0.226(2)	0.04(1)
H(6)B	0.849(3)	0.406(7)	0.228(2)	0.02(1)
H(7)B	0.703(3)	0.692(8)	0.122(2)	0.04(1)
H(8)B	0.701(3)	0.876(7)	0.195(2)	0.03(1)
H(9)B	1.071(4)	0.756(8)	0.077(2)	0.04(1)
H(10)B	0.926(4)	0.645(10)	0.037(3)	0.06(1)
H(11)B	1.025(4)	0.549(9)	0.128(2)	0.06(1)

$$^a U_{eq} = \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j.$$

differences in bond lengths between the two molecules in the asymmetric unit. The carboxylate group in L-Met(A) is approximately symmetric with C–O distances of 1.252 and 1.255 Å, while in L-Met(B) the carboxylate group is

Table 3. Fractional coordinates with standard deviations and temperature factors for L-Val.

Atom	x	y	z	U_{eq}/U_{iso}^a
O(1)A	0.8728(1)	0.1115	0.3998(1)	0.016
O(2)A	0.7941(1)	-0.2619(2)	0.3353(1)	0.017
N(1)A	0.6241(1)	0.3264(2)	0.4116(1)	0.013
C(1)A	0.7785(1)	-0.0315(3)	0.3633(1)	0.013
C(2)A	0.6337(1)	0.0831(3)	0.3469(1)	0.012
C(3)A	0.5973(1)	0.1319(3)	0.2222(1)	0.015
C(4)A	0.5426(1)	-0.1114(3)	0.1666(1)	0.024
C(5)A	0.7193(1)	0.2423(3)	0.1573(1)	0.020
H(1)A	0.678(2)	0.439(3)	0.385(1)	0.015(4)
H(2)A	0.541(2)	0.379(4)	0.409(1)	0.026(4)
H(3)A	0.643(1)	0.302(4)	0.486(1)	0.018(4)
H(4)A	0.569(2)	-0.021(4)	0.379(1)	0.013(3)
H(5)A	0.523(2)	0.255(3)	0.226(1)	0.014(3)
H(6)A	0.514(2)	-0.078(4)	0.091(1)	0.028(4)
H(7)A	0.612(2)	-0.243(4)	0.167(2)	0.029(4)
H(8)A	0.467(2)	-0.181(5)	0.210(2)	0.036(5)
H(9)A	0.690(2)	0.290(4)	0.081(2)	0.030(5)
H(10)A	0.760(2)	0.380(5)	0.195(2)	0.038(4)
H(11)A	0.792(2)	0.128(4)	0.152(1)	0.020(4)
O(1)B	0.3545(1)	0.5010(2)	0.3962(1)	0.016
O(2)B	0.2756(1)	0.1045(2)	0.3678(1)	0.020
N(1)B	0.0879(1)	0.6817(3)	0.3720(1)	0.015
C(1)B	0.2651(1)	0.3415(3)	0.3626(1)	0.013
C(2)B	0.1350(1)	0.4553(3)	0.3063(1)	0.013
C(3)B	0.1663(1)	0.5376(3)	0.1848(1)	0.015
C(4)B	0.0405(1)	0.6579(3)	0.1274(1)	0.023
C(5)B	0.2172(2)	0.3116(3)	0.1156(1)	0.026
H(1)B	0.142(2)	0.820(4)	0.360(1)	0.023(4)
H(2)B	0.002(2)	0.721(4)	0.354(1)	0.022(4)
H(3)B	0.096(2)	0.651(3)	0.446(1)	0.018(4)
H(4)B	0.062(2)	0.336(3)	0.309(1)	0.012(3)
H(5)B	0.239(2)	0.655(4)	0.186(1)	0.018(4)
H(6)B	0.001(2)	0.789(5)	0.162(2)	0.039(5)
H(7)B	-0.032(2)	0.542(4)	0.122(2)	0.035(5)
H(8)B	0.059(2)	0.714(4)	0.054(2)	0.036(5)
H(9)B	0.144(2)	0.195(5)	0.113(2)	0.044(6)
H(10)B	0.294(2)	0.237(5)	0.147(2)	0.040(5)
H(11)B	0.233(2)	0.359(4)	0.040(2)	0.035(5)

$$^a U_{eq} = \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j.$$

asymmetric with C–O distances 1.246 and 1.264 Å. Similar differences are observed for L-Val; the symmetric group of L-Val(A) has C–O distances 1.257 and 1.264 Å, while the asymmetric group of L-Val(B) has C–O distances 1.250 and 1.266 Å. The asymmetry of each molecule B's carboxylate groups is most likely a result of different strengths for the hydrogen bonds to the two different oxygen atoms.

The molecular conformations are essentially the same as reported in the original papers. As in all amino acid structures with two molecules in the asymmetric unit, the side chain conformations are different for molecules A and B.

Crystal structures and hydrogen bonding. The molecules in both L-Met and L-Val form structures with alternating hydrophobic and hydrophilic layers parallel to the *xy*-plane (Fig. 3, PLUTO¹⁵ drawing). The hydrophobic

Table 4. Bond lengths (in Å), angles (in °) and selected torsion angles (in °) with standard deviations in L-Met and L-Val.

	L-Met(A)	L-Met(B)	L-Val(A)	L-Val(B)
Bond				
S(1)–C(4)	1.813(3)	1.810(3)		
S(1)–C(5)	1.794(4)	1.796(4)		
O(1)–C(1)	1.252(3)	1.264(3)	1.257(2)	1.266(2)
O(2)–C(1)	1.255(4)	1.246(4)	1.264(2)	1.250(2)
N(1)–C(2)	1.485(4)	1.483(4)	1.495(2)	1.497(2)
C(1)–C(2)	1.529(3)	1.535(3)	1.535(2)	1.542(2)
C(2)–C(3)	1.536(3)	1.538(4)	1.547(2)	1.545(2)
C(3)–C(4)	1.513(4)	1.516(4)	1.531(3)	1.528(2)
C(3)–C(5)			1.532(2)	1.529(3)
Angle				
C(4)–S(1)–C(5)	99.1(2)	100.1(2)		
S(1)–C(4)–C(3)	110.5(2)	114.9(2)		
O(1)–C(1)–O(2)	125.5(2)	125.9(2)	125.0(1)	126.0(2)
O(1)–C(1)–C(2)	117.6(3)	116.1(3)	118.0(2)	115.8(2)
O(2)–C(1)–C(2)	116.8(2)	118.0(2)	116.9(1)	118.2(1)
N(1)–C(2)–C(1)	109.5(2)	109.8(2)	109.3(1)	109.3(1)
N(1)–C(2)–C(3)	109.9(2)	107.9(3)	109.9(1)	109.4(2)
C(1)–C(2)–C(3)	112.2(2)	111.2(2)	112.7(1)	110.5(1)
C(2)–C(3)–C(4)	111.2(3)	114.4(3)	110.7(2)	111.9(1)
C(2)–C(3)–C(5)			112.3(1)	110.9(2)
C(4)–C(3)–C(5)			111.2(1)	109.8(1)
Torsion				
N(1)–C(2)–C(3)–C(4) [$\chi^1/\chi^{1,2}$]	–166.1(3)	–165.4(3)	–154.2(2)	–58.1(2)
N(1)–C(2)–C(3)–C(5) [$\chi^{1,1}$]			80.8(2)	179.0(2)
C(2)–C(3)–C(4)–S(1) [χ^2]	171.6(3)	71.5(3)		
C(3)–C(4)–S(1)–C(5) [χ^3]	–178.5(3)	72.4(3)		
O(1)–C(1)–C(2)–N(1) [ψ]	–16.3(2)	–32.4(2)	–17.4(2)	–42.8(2)

layers contain the unpolar side chains, while the hydrophilic layers are composed of the charged carboxylate and amino groups. The latter layer consists of two identical sheets, denoted Sheet 1 and Sheet 2 in Fig. 3, related by a two-fold screw axis.

The four amino hydrogen atoms (two each from molecules A and B) in *gauche*⁺ and *trans* positions relative to the carboxylate group form five hydrogen bonds in each sheet, three of which can be seen in Fig. 3. The two sheets are interconnected through hydrogen bonds formed by the two hydrogen atoms in position *gauche*[–]. Two of these bonds are indicated by dotted lines in Fig. 3.

Geometric parameters for hydrogen bonds in both structures are listed in Table 5. From this table the similarities in the hydrogen bond pattern for these two crystals are apparent. Except for the H(3)A···O(2)B hydrogen bond, the differences in bond lengths between corresponding hydrogen bonds in the two structures do not exceed 0.05 Å. The differences between the two structures in the symmetry operations for the acceptor groups in Table 5 are due to unit cell definition. By reversing the direction for the *b*-axis and *c*-axis for L-Val one obtains an unconventional unit cell with $\beta = 89.43^\circ$, for which the symmetry operations in the table would coincide.

Table 5. Hydrogen bond lengths (in Å) and angles (in °) in L-Val/L-Met.^a

D	H	A	<i>d</i> (H···A)	\angle (D–H···A)	\angle (H···A–C)	Symmetry ^b
N(1)A	H(1)A	O(2)A	1.846/1.813	171.9/177.1	127.4/124.2	I(010)/I(070)
	H(2)A	O(1)B	1.741/1.716	177.3/167.1	116.4/119.1	I(000)/I(070)
	H(3)A	O(1)B	2.028/2.000	136.5/138.8	135.2/137.3	II(111)/II(171)
	H(3)A	O(2)B	2.407/2.550	128.7/131.0	136.1/128.8	II(101)/II(121)
N(1)B	H(1)B	O(2)B	1.858/1.846	166.4/162.9	133.7/128.7	I(010)/I(070)
	H(2)B	O(1)A	2.376/2.318	125.5/122.9	75.4/74.4	I(110)/I(100)
	H(2)B	O(2)A	1.880/1.830	165.7/164.1	97.1/95.7	I(110)/I(100)
	H(3)B	O(1)A	1.743/1.735	174.0/173.7	121.0/122.8	II(101)/II(101)
C(1)B	H(4)B	O(1)A	2.304/2.255	152.0/152.6	131.1/128.1	I(110)/I(110)

^a N–H normalized¹⁶ to 1.03 Å, C–H normalized to 1.10 Å. D=donor, A=acceptor. ^b Roman numerals I and II denote the following operations: (I) *x*, *y*, *z*, (II) $-x$, $y+1/2$, $-z$. Negative numbers are italicised.

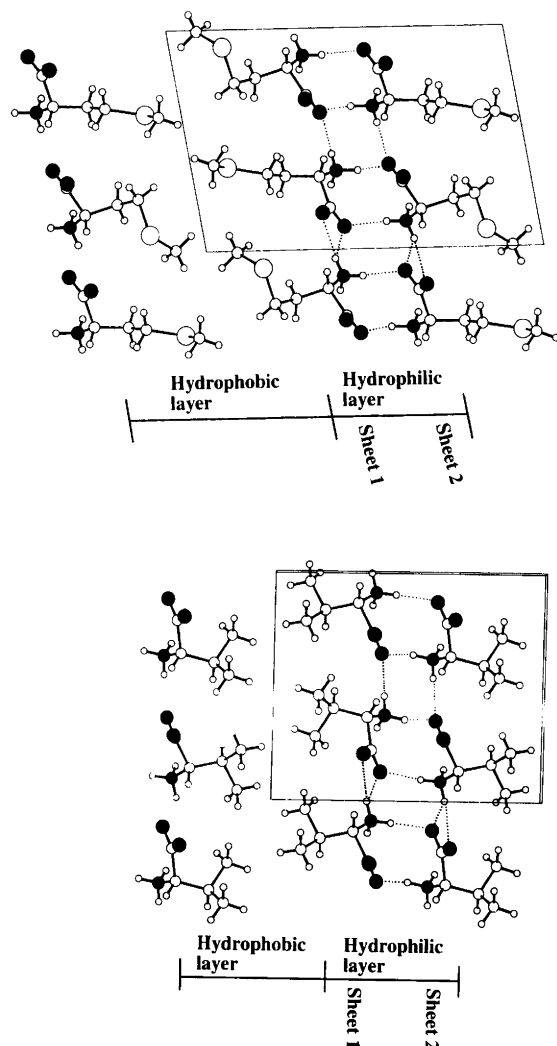


Fig. 3. PLUTO drawing of L-Met (upper) and L-Val (lower) viewed along the *b*-axis displaying the bilayer structure. O and N atoms black, C and H atoms white. Dotted lines indicate hydrogen bonds.

In addition to the short C–H...O contacts listed in Table 5, there is an unusual short methyl–C–H...O contact in L-Val with $d[\text{H}(10)\text{A}\cdots\text{O}(2)\text{A}] = 2.38 \text{ \AA}$.

Acknowledgement. The structure of L-Val was presented as a poster at the 15th Nordic Structural Chemistry Meeting at Røros, Norway, in January 1995 thanks to financial support from *Acta Chemica Scandinavica*.

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Received September 25, 1995.