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Interaction of Zn^{2+} with *N*-(2-pyridyl)-3-phenyl-2-propene amide, a model in lignin biosynthesis inhibition by cinnamides. Crystal and molecular structure of $[Zn(O–N)_2(CH_3OH)_2](CF_3SO_3)_2$

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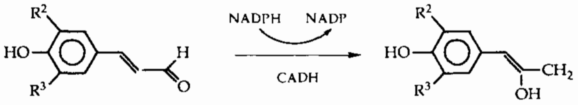
Abstract

Reacting $Zn(CF_3SO_3)_2$ with the title ligand (O–N) yields a 1:2 complex which precipitates from methanol as the $[Zn(O–N)_2(CH_3OH)_2](CF_3SO_3)_2$ salt. The crystal structure of this complex ($P1_1/c$, $a = 13.711(2)$, $b = 10.401(2)$, $c = 16.358(2)$ Å, $\beta = 124.27(1)°$, $R = 0.059$, 1918 observed reflections) reveals the presence of a centrosymmetric, nearly octahedral, complex cation. The all-*trans* configuration about Zn^{2+} is achieved by two methanol hydroxyl groups and two bidentate ligands bonded via their pyridyl nitrogens and amide oxygens. The amide group nitrogen is not coordinated to the metal, but it forms an N–H....O hydrogen bond to the $CF_3SO_3^-$ counterions. The influence of the amide substituent on the structure is discussed on the basis of comparisons with the $[Zn\{N\text{-(2-pyridyl)acetamide}\}_2(H_2O)_2]^{2+}$ ion containing a similar amidopyridine chelate ring.

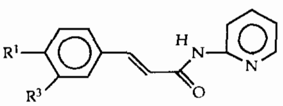
Introduction

Coniferyl alcohol dehydrogenase CADH is an enzyme which, when activated by the coenzyme NADPH, catalyzes the biosynthesis of the lignin monomer in plants [1, 2] (Scheme 1). The presence of divalent zinc is known to be required for the catalytic reaction to occur, but the precise role of zinc in the process is not fully understood as yet. Two contributions to the mechanism are commonly proposed, which both involve aldehyde activation: (i) polarization of the CO group by coordination of zinc to oxygen, favouring subsequent attack at carbon, (ii) acidity enhancement of a bonded water molecule, generating a hydroxyl group able to act as a proton acceptor and ionize the oxygen atom to O^-.



Scheme 1.

Because of a potentially considerable impact on the economy, important research efforts are being devoted to developing methods for inhibiting lignin biosynthesis. One such method consists of inactivating the enzyme by complexing the Zn^{2+} center with tailor-made molecules that would be better ligands than CADH. The following molecules **1** and **1'** are suitable for this purpose [3–5].



$R^1 = H$; $R^3 = H$ (O-N) 1
$R^1 = OH$; $R^3 = OMe$ (O-N)' 1'

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Moreover, comparison of **1** and **1′** will allow further evaluation of the complexing ability of the amide (ON) and phenol (OH) functions, respectively.

It has been shown that complexation of (O–N) with $ZnBr_2$ in ether results in $Zn(O–N)Br_2$ and $Zn(O–N)_2Br_2$ complexes that have been characterized by electronic spectroscopy. The stability constants determined for these species ($K_1 = 2 \times 10^4$ and $K_2 = 2.2 \times 10^4$ M^{-1}, respectively) confirm the good affinity of (O–N) for the Zn^{2+} center [6].

We report here the isolation and X-ray structure determination of the $[Zn(ON)_2(MeOH)_2]^{2+}$ cation, which precipitates as a crystalline compound when $CF_3SO_3^-$ is used as counteranion. The Zn^{2+} center is found to be stabilized in an octahedral arrangement. Although zinc complexes are mostly tetrahedral or pentacoordinate in biological systems [7, 8], the essential features of the ligand to zinc binding mode are clearly established from this six-coordinate compound. Octahedral coordination is not as widespread for Zn^{2+} as for first-row transition ions, especially with mixed oxygen–nitrogen donor ligands. To our knowledge, the only crystallographic work on a related complex deals with $[Zn(aapH)_2(H_2O)_2]^{2+}$, which possesses a similar amidopyridyl chelating ligand [9]. Comparison of the two structures could provide information on the effect of the carbonyl substituent (phenylpropene in **2** versus CH_3 in **3**), which has been found to be important for biological applications [2].

Experimental

Preparation of the complex

In a typical run, the ligand (0.22 g; 1 mmol) dissolved in 10 ml THF was added to a solution of $Zn(CF_3SO_3)_2$ (Aldrich) (0.2 g; 0.5 mmol) in acetonitrile (10 ml). The white powder precipitating immediately was stirred overnight. After filtration, it was washed with acetonitrile and THF, and dried *in vacuo*. Recrystallization from hot methanol gave colorless crystals of **1**. Yield 72%. *Anal.* Calc. for $C_{32}H_{32}F_6N_4O_{10}S_2Zn$: H 3.68; C 43.87; N 6.39. Found: H 3.02; C 44.56; N 6.78%.

Crystal data

$C_{32}H_{32}F_6N_4O_{10}S_2Zn$, $FW = 876.12$, monoclinic, $P2_1/c$, $a = 13.711(2)$, $b = 10.401(2)$, $c = 16.358(2)$ Å, $\beta = 124.27(1)°$, $V = 1927.7(5)$ Å^3, $Z = 2$, $D_c = 1.509$ g cm^{-3}, μ(Mo Kα) = 8.4 cm^{-1}, (Mo Kα) = 0.71069 Å, $T = 240$ K.

Crystallographic measurements and structure determination

Crystals suitable for X-ray work were obtained from methanol. The specimen used has the following dimensions (mm) between the indicated pairs of faces: 0.08 (102–102) × 0.16 (010–010) × 0.18 (100–100). The reduced unit cell was determined from 25 centered reflections ($20 < 2\theta < 25°$) found by the automatic search procedure of the Enraf-Nonius CAD-4 diffractometer. The auto-indexing routine indicated a primitive monoclinic cell, which was checked with oscillation photographs about each axis. The Niggli parameters were not consistent with a lattice of higher symmetry. Space group $P2_1/c$ was uniquely defined from the systematic absences ($h0l$, $l \neq 2n$; $0k0$, $k \neq 2n$) noted in the full data set. The intensity of the hkl and $hk\bar{l}$ data ($2\theta_{max} = 50°$) were collected with graphite monochromatized Mo Kα radiation by the ω scan technique, over the range $\Delta\omega = (0.80 + 0.35 \tan\theta)$. Orientation was monitored every 200 measurements. Intensity was checked every hour by means of 4 standard reflections, which showed fluctuation within ±1.2%. A set of 3388 independent reflections was collected at 240 K, of which 1918 with $I \geqslant 3.0\ \sigma(I)$ were retained for structure determination and refinement. The data were corrected for the effect of Lorentz and polarization. An absorption correction was deemed unnecessary.

The Zn atom and most of the non-hydrogen atoms were located by the direct methods of the SHELXS-86 package [10]. The remaining atoms were found from difference Fourier syntheses calculated with the SHELX-76 program [11]. The structure was refined on F by full-matrix least-squares. Large thermal motion indicated disorder in the $CF_3SO_3^-$ ion. A second set of weaker peaks was found in the difference Fourier map for an alternate orientation of the anion. A common isotropic temperature of 6.0 Å^2 was assigned to all atoms in this second individual and an overall occupancy factor was refined for each of the two individuals. The refined occupancies were normalized to 0.75 and 0.25 and fixed for the rest of the refinement. All non-hydrogen atoms were refined anisotropically. Hydrogens initially placed at idealized positions were isotropically refined in the last cycles.

The final residuals were $R = \Sigma||F_0| - |F_c||/\Sigma|F_0| = 0.059$ and $R_w = [\Sigma w(|F_0| - |F_c|)^2/\Sigma w|F_0|^2]^{1/2} = 0.053$ (weights derived from the counting statistics). The goodness-of-fit ratio was 2.38 for 387 refined parameters. The final difference Fourier synthesis showed five peaks of 0.34–0.28 e/Å^3 within 1.60 Å from Zn and a general background below ±0.25 e/Å^3. The scattering curves were from standard sources [12, 13]. Anomalous dispersion was included

TABLE 1. Refined atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors ($Å^2 \times 10^3$)

Atom	x	y	z	U_{eq}
Zn	0	0	0	46
S(20)[a]	2373(2)	1303(2)	7424(2)	53
S(20′)[b]	2544(4)	1458(6)	7296(4)	35
F(21)[a]	4045(5)	776(7)	9171(4)	130
F(22)[a]	2286(6)	428(7)	8787(5)	151
F(23)[a]	3006(6)	2339(6)	9063(4)	130
F(21)′)[b]	3936(15)	848(17)	9333(12)	99
F(22′)[b]	2196(14)	1087(19)	8867(11)	103
F(23′)[b]	3028(15)	2771(17)	8834(13)	108
O(8)	−483(3)	−1732(4)	252(3)	52
O(21)[a]	1201(4)	1780(6)	6971(4)	65
O(22)[a]	3205(5)	2161(7)	7393(5)	101
O(23)[a]	2471(6)	−38(6)	7242(5)	118
O(21′)[b]	1215(11)	1766(15)	6715(10)	48
O(22′)[b]	3167(14)	2410(14)	7235(11)	54
O(23′)[b]	2588(13)	225(16)	7052(11)	59
O(30)	214(3)	864(4)	1272(3)	59
N(1)	1774(4)	−708(4)	900(3)	48
N(7)	1284(4)	−2809(4)	1127(4)	52
C(2)	2633(5)	140(6)	1097(5)	67
C(3)	3811(5)	−186(7)	1645(5)	76
C(4)	4139(5)	−1408(7)	2016(5)	74
C(5)	3295(5)	−2270(6)	1848(5)	66
C(6)	2110(5)	−1879(6)	1281(4)	50
C(8)	87(5)	−2732(6)	649(4)	48
C(9)	−457(5)	−3927(6)	666(4)	48
C(10)	−1629(5)	−4023(6)	188(4)	51
C(11)	−2279(5)	−5146(6)	182(4)	52
C(12)	−1732(5)	−6270(6)	682(5)	59
C(13)	−2370(6)	−7285(7)	702(6)	81
C(14)	−3591(7)	−7172(7)	200(6)	96
C(15)	−4159(6)	−6081(7)	−325(6)	95
C(16)	−3514(5)	−5058(7)	−338(5)	76
C(20)[a]	2966(9)	1210(9)	8709(7)	89
C(20′)[b]	2853(19)	1478(21)	8563(13)	37
C(30)	642(7)	188(8)	2187(5)	86

Occupancy factors: [a]0.75, [b]0.25

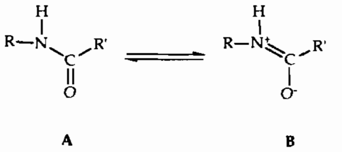
in structure factor calculation for Zn and S [14]. The final coordinates are listed in Table 1.

Results and discussion

Adding the ligand dissolved in THF to an acetonitrile solution of $Zn(CF_3SO_3)_2$ in a 2/1 ratio immediately affords a white material, which when recrystallized from hot methanol, gives a nearly quantitative yield of colorless crystals, analyzing as the methanol adduct $Zn(O{-}N)_2(MeOH)_2(CF_3SO_3)_2$ (**2**). The complex is air and light stable.

Its IR spectrum (nujol mull) exhibits a ν(CO) stretching frequency at 1667 cm^{-1} (free ligand: $\nu(CO) = 1694$ cm^{-1}) indicating metal coordination of the amide CO group.

As previously reported, such a low frequency shift of ν(CO), which corresponds to the stabilization of resonance form **B** (Scheme 2), is a good qualitative diagnostic for the coordination of the amide oxygen to a metal center [15].



Scheme 2.

Coordination of the pyridyl ring, which is characterized by a shift to higher frequency of the deformation band at about 621 cm^{-1}, is not observed on the IR spectrum because of the presence of a strong vibration of the triflate anion at 633 cm^{-1}.

Crystal structure

The structure of complex **2** was determined by single-crystal X-ray diffraction methods. The unit cell contains two dipositive cations and four triflate anions. Figure 1 shows a labelled ORTEP drawing of the cation. The bond distances and angles between the non-hydrogen atoms are listed in Table 2.

The Zn atom exhibits an approximately octahedral coordination in the cation. The equatorial plane is occupied by two (O–N) molecules acting as bidentate ligands via the amide oxygen and the pyridyl nitrogen. Since the N–H proton is retained in the formally neutral ligand, the amide nitrogen cannot coordinate and remains well separated from any metal atom. The two axial positions in the octahedron are occupied by methanol molecules. A similar all-*trans* octahedral arrangement has been observed in the $[Zn(aapH)_2(H_2O)_2]^{2+}$ complex (**3**) containing the related ligand *N*-(2pyridyl)acetamide (aapH).

Departure from octahedral geometry is significant, but relatively small. Since the Zn^{2+} center has a spherical d^{10} shell, these distortions have to originate from electronic and/or steric effects of the ligands. With the metal sitting on a crystallographic inversion center, the angle between each pair of *trans* bonds is exactly 180° and the four bonds defining each principal plane are strictly coplanar. Between *cis* bonds, the angles (Table 2) deviate at most by 4° from the ideal 90° value. The distortion can also be evaluated starting from the three principal planes, which would be orthogonal in a regular octahedron. The dihedral angles (range: 86.0–89.5°)* further indicate a small distortion, similar to that of the (pyridyl)acetamine complex (range: 87.0–89.3°).

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*Dihedral angles: [Zn–O(8)–N(1)]/[Zn–O(8)–O(30)] = 89.5°, [Zn–O(8)–N(1)]/[Zn–N(1)–O(30)] = 86.7°, [Zn–N(1)–O(30)]/[Zn–O(8)–O(30)] = 86.0°.

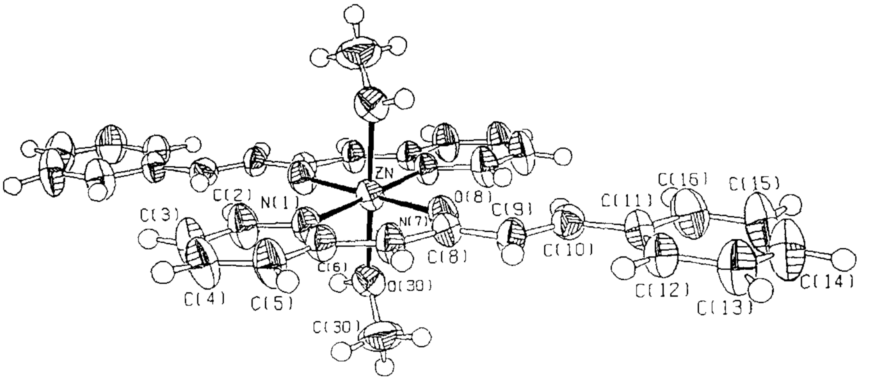
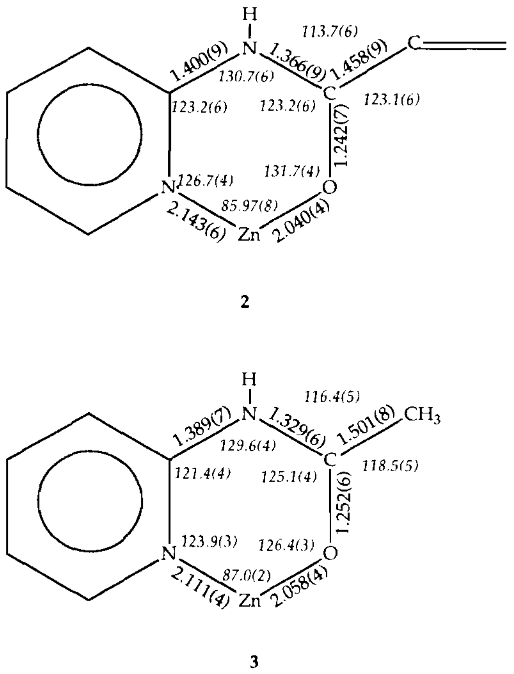


Fig. 1. ORTEP drawing and numbering scheme in the complex cation. Ellipsoids correspond to 50% probability.

TABLE 2. Geometry of the complex cation

Distances (Å)			
Zn–O(8)			
Zn–O(30)	2.040(4)	C(8)–O(8)	1.242(7)
Zn–N(1)	2.130(4)	C(8)–C(9)	1.458(9)
N(1)–C(2)	2.143(6)	C(9)–C(10)	1.337(11)
C(2)–C(3)	1.357(10)	C(10)–C(11)	1.466(10)
	1.377(12)	C(11)–C(12)	1.381(9)
C(3)–C(4)	1.371(10)	C(12)–C(13)	1.383(11)
C(4)–C(5)	1.364(11)	C(13)–C(14)	1.394(14)
C(5)–C(6)	1.403(10)	C(14)–C(15)	1.371(11)
C(6)–N(1)	1.327(8)	C(15)–C(16)	1.391(12)
C(6)–N(7)	1.400(9)	C(16)–C(11)	1.406(11)
N(7)–C(8)	1.366(9)		
Angles (°)			
O(8)–Zn–O(30)	93.3(2)	C(5)–C(6)–N(7)	115.9(6)
O(8)–Zn–N(1)	86.0(2)	N(1)–C(6)–N(7)	121.2(6)
O(8)–Zn–O(30)[a]	86.7(2)	C(6)–N(7)–C(8)	130.7(6)
O(30)–Zn–N(1)	89.7(2)	N(7)–C(8)–O(8)	123.2(6)
O(30)–Zn–N(1)[a]	90.3(2)	N(7)–C(8)–C(9)	113.7(6)
O(8)–Zn–N(1)[a]	94.0(2)	O(8)–C(8)–C(9)	123.1(6)
Zn–O(8)–C(8)	131.7(4)	C(8)–C(9)–C(10)	120.8(6)
Zn–O(30)–C(30)	124.0(4)	C(9)–C(10)–C(11)	126.1(6)
Zn–N(1)–C(2)	115.9(4)	C(10)–C(11)–C(12)	123.0(6)
Zn–N(1)–C(6)	126.7(4)	C(10)–C(11)–C(16)	118.2(6)
C(2)–N(1)–C(6)	117.4(6)	C(12)–C(11)–C(16)	118.7(6)
N(1)–C(2)–C(3)	122.5(7)	C(11)–C(12)–C(13)	121.4(7)
C(2)–C(3)–C(4)	119.2(7)	C(12)–C(13)–C(14)	119.2(8)
C(3)–C(4)–C(5)	119.4(7)	C(13)–C(14)–C(15)	120.6(8)
C(4)–C(5)–C(6)	118.6(7)	C(14)–C(15)–C(16)	120.1(8)
C(5)–C(6)–N(1)	122.9(6)	C(15)–C(16)–C(11)	120.0(7)

[a] $-x$, $-y$, $-z$



Scheme 3.

There are small differences in Zn–ligand bond lengths compared with those of the (pyridyl)acetamide complex (Scheme 3). The Zn–O(amide) distance here (2.040(4) Å) is slightly less than in **3** (2.058(4) Å), whereas the opposite effect is found for the Zn–N bonds (2.143(6) Å in **2**, 2.111(4) Å in **3**). This could be ascribed to replacing the compact methyl group of **3** by the more polarizable conjugated phenylpropene substituent, which presumably affects the donor basicities. However, nonbonded contacts could also contribute to inducing these rather small differences: for instance, the Zn–N versus Zn–O balance could be perturbed by the short H(2)...O(8) intramolecular contact of 2.34(7) Å which in turn varies with a change of the dihedral angle between the ligand plane and the equatorial plane. As to the Zn–O(30) distance of 2.130(4) Å to the methanol ligand, it is somewhat greater than those found in a Zn(β-diketonate)(MeOH)$_2$ molecule (2.080(4) Å), where the methanol ligands occupy *cis* position in the octahedron [16].

The geometry of the amide group is not expected to be sensitive to the presence of the coordinated metal [17]. The pattern observed for the non-deprotonated aapH ring in the Zn^{2+} and Ni^{2+} complexes is also found here for most of the distances and angles in the ligand (Table 2). Differences of -1.9, -2.9 and $+4.6°$ on N(7)−C(8)−O(8), N(7)−C(8)−C(9) and O(8)−C(8)−C(9), respectively, are due to conjugation with the external C(9)−C(10) double bond. The N(1)−C(6)−N(7)−C(8)−O(8) was found to be planar in the $Pd(aap)_2$ complex, where the amide N–H group is deprotonated, but an envelope conformation with N(7) lying 0.16 Å from the plane of the other four atoms was noted for the neutral ligands in the Zn^{2+} and Ni^{2+} compounds. In the present case, departure from planarity is significant, as expected for a non-deprotonated ring, but the puckering is different, the atom-to-plane distances being: N(1), 0.013(5); C(6), −0.026(6); N(7), 0.005(5); C(8), 0.016(6); O(8), −0.007(4) Å. The Zn atom is found at 0.15 Å from the latter plane, corresponding to a dihedral angle of 5.4° between the ligand and the ZnO_2N_2 plane. The corresponding angle in $[Zn(appH)_2]^{2+}$ is 18.5°.

The ligand as a whole can be described as four individually planar sub-units connected by a uninterrupted system of π electrons (isomer **B**, Scheme 2). The largest departure from planarity occurs for the phenyl ring, which is rotated by ~5° about the C(10)–C(11) bond from the coplanar orientation. The dihedral angles between the other subunits are: pyridyl–chelate = 2.6°, chelate–olefin = 3.5°, pyridyl–olefin = 1.9°.

A stereoview of the unit cell is given in Fig. 2. The structure consists of layers centered on the *bc* face and separated by normal van der Waals distances. Within these layers, the equatorial planes of the complex cations, containing the two chelating ligands, are roughly perpendicular to the *bc* face. The planes in adjacent cations (separated by $(b+c)/2$) make a 44° dihedral angle, creating a wedge-shaped region containing the $CF_3SO_3^-$ ions and the axial methanol ligands. These anions are disordered over two orientations, only one of which is shown in Fig. 2. In both orientations, they form moderately strong hydrogen bonds via two of their oxygen atoms: with the methanol proton (O(30)–H...O(21) = 2.720(7) Å (major component), 2.71(2) Å (minor)) and the amide N–H group (N(7)–H...O(23) = 2.765(8) Å (major), 2.96(2) Å (minor)). See also 'Supplementary material'.

Conclusions

The first conclusion to be drawn from this work is that complexation of Zn^{2+} with the (O–N) ligand occurs readily. It leads to an octahedral complex containing two coplanar chelating ligands and two axial methanol molecules. Therefore, in terms of basicity and availability of properly oriented donor atoms, this ligand forms stable compounds with Zn^{2+} ions in the free state. This is an important first step toward a better understanding of the inhibitory role of the amide function in lignin biosynthesis. The ligand likely retains the same mode of attachment to zinc in biological systems, even if the metal has a lower coordination. The uninterrupted π system in the ligand generates a flat elongated van der Waals profile which should perturb the behavior of the zinc ion and its environment in the biological system. However, further discussion on the relation between the structure of the complex and its biological activity must await the study of other model compounds and a better knowledge of the structure and processes taking place at the active center.

Supplementary material

Temperature factors, hydrogen coordinates, distances and angles involving the hydrogen atoms and

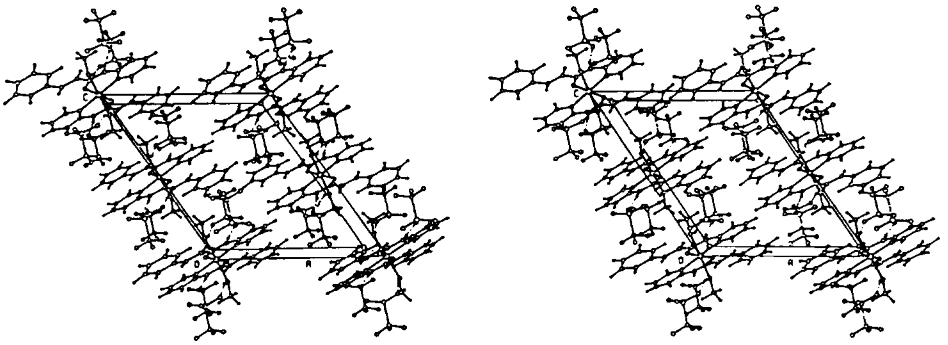


Fig. 2. Stereoview of the unit cell. The atoms are shown as spheres of arbitrary sizes. The major orientation is represented for the disordered $CF_3SO_3^-$ ion.

the triflate ions, geometry of the hydrogen bonds, weighted least-squares planes and structure factor amplitudes (21 pages) may be obtained upon request from author A.L.B.

Acknowledgements

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