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Two *N*-*ortho*-nitrobenzenesulfonyl *α*,*α*-disubstituted amino acid adducts

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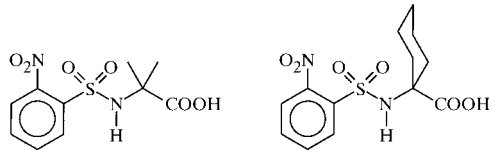
The carboxy group of 2-methyl-*N*-[(2-nitrophenyl)sulfonyl]-alanine, $C_{10}H_{12}N_2O_6S$, forms centrosymmetric hydrogen-bonded dimers with an O···O distance of 2.629 (2) Å and an intramolecular N—H···O(nitro) hydrogen bond N···O distance of 2.823 (2) Å. 1-[(2-Nitrophenyl)sulfonylamino]-cyclohexanecarboxylic acid, $C_{13}H_{16}N_2O_6S$, has $Z' = 2$ and forms similar interactions.

Comment

The incorporation of *α*,*α*-disubstituted amino acids into short peptide segments can dramatically increase the helical propensity of sequences as short as ten residues (Prasad & Balaram, 1984; Marshall *et al.*, 1990). This effect has been of recent interest in the development of novel amphipathic helical peptides, designed to exhibit antimicrobial activity under physiological conditions (Wysong *et al.*, 1997; Yokum *et al.*, 1996). However, the incorporation of some *α*,*α*-disubstituted amino acids into peptide sequences has proven to be difficult during solid-phase peptide synthesis (SPPS) by the use of the Fmoc-acid fluoride (Fmoc = 9-fluorenylmethoxycarbonyl) conditions set forth by Wenschuh *et al.* (1994). As part of an effort to increase the overall efficacy of the couplings, we have probed the utilization of the acid chloride analogues of several commonly used *α*,*α*-disubstituted amino acids, two of which are described here, namely Aib (2-aminoisobutyric acid) and Cyh (1-amino-1-cyclohexanecarboxylic acid). Because the use of acid chlorides greatly increases the propensity of oxazolone formation under SPPS conditions (Carpino *et al.*, 1991), we experimented with the use of the *ortho*-nitrobenzenesulfonyl protecting group as an alternative to the Fmoc protecting group. The *ortho*-nitrobenzenesulfonyl group is readily cleaved by nucleophilic displacement (Fukuyama *et al.*, 1995). It is, however, stable under acidic conditions and is thus orthogonal to the Boc chemistry (Boc is *tert*-butyloxycarbonyl) required for side-group protection of several amino acids during SPPS. In addition, due to the lower nucleophilicity of the sulfonyl group, oxazolone formation by intramolecular cyclization is minimized (Miller & Scanlan, 1998). The incorporation of the *ortho*-nitrobenzenesulfonyl group has the added advantage of introducing a greater propensity towards crystallization of the amino acid derivatives. We herein report the first crystallographic data of the *o*-nitrobenzenesulfonyl derivatives of these *α*,*α*-disubstituted amino acids, *i.e.* *o*NBS-Aib, (I), and *o*NBS-Cyh, (II).



(I) (II)

*o*NBS-Aib has $Z' = 1$, while *o*NBS-Cyh has $Z' = 2$. The conformations of the molecules are described by five torsion angles: that about the C—NO_2 bond and the four in the C—S—N—C—C(carboxy) chain. The conformations of *o*NBS-Aib (Fig. 1) and the two independent molecules of *o*NBS-Cyh (Fig. 2) are quite similar. In all three cases, the NO_2 group is rotated out of the plane of its attached phenyl group by 38.5 (2)–47.1 (3)°, as measured by the magnitudes of the O5—N2—C8—C3 torsion angles. This is similar to, but slightly smaller than, the value of 52.4 (6)° seen in *N*,*N*-dimethyl-*o*-nitrobenzenesulfonamide (Ruostesuo *et al.*, 1989). The four torsion angles about the C—S—N—C—C(carboxy) chain show good agreement between the two molecules of *o*NBS-Cyh (mean difference 4.6°), and also between *o*NBS-Aib and *o*NBS-Cyh (mean differences 4.3° with the unprimed molecule and 6.1° with the primed molecule). This conformation is different, however, from the conformation seen in *N*-*p*-toluenesulfonyl-*α*-aminoisobutyric acid (Crisma *et al.*, 1999), which differs from *o*NBS-Aib only by having a *p*-tosyl substituent on S rather than *o*-nitrophenyl. In that *p*-tosyl compound, torsion angles along the C—S—N—C—C(carboxy) chain are, respectively, 52.5 (2), 84.1 (3), 80.1 (3), and 33.7 (4)°. While the N—C—C—O torsion angle of the *p*-tosyl compound agrees well with those seen in *o*NBS-Aib and *o*NBS-Cyh; the other three torsion angles differ by 20–30°.

The likely cause of this conformational difference is hydrogen bonding by the N—H group. In the *p*-tosyl compound (Crisma *et al.*, 1999), the N—H group forms a

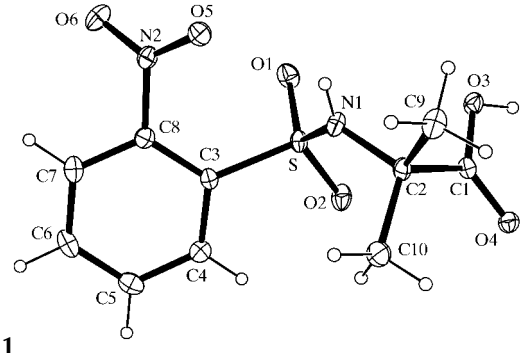


Figure 1
The molecular structure of *o*NBS-Aib shown with 50% probability displacement ellipsoids.

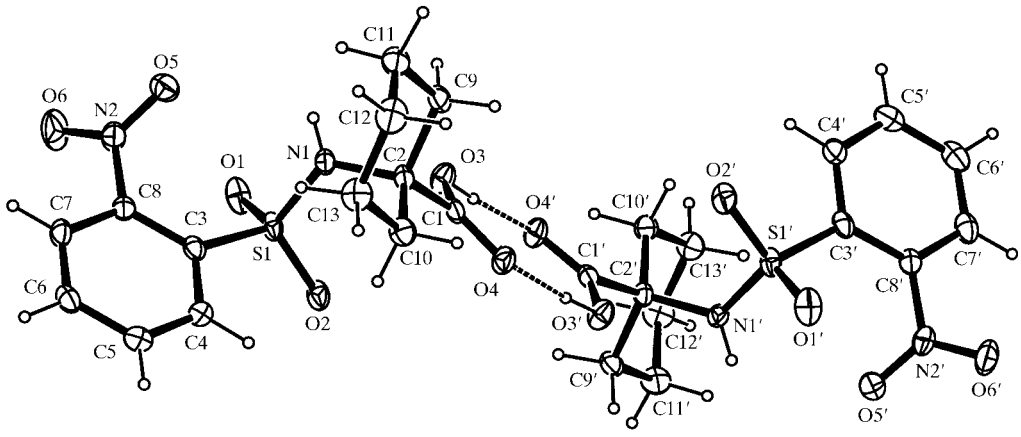


Figure 2
The two independent molecules of *o*NBS-Cyh shown with 50% probability displacement ellipsoids.

nearly linear intermolecular hydrogen bond of N···O length 2.893 (3) Å to a sulfonyl O atom. In both *o*NBS-Aib and *o*NBS-Cyh, all N—H groups form non-linear intramolecular contacts to nitro O atoms, and longer more linear intermolecular interactions to nitro or carboxy O atoms. The COOH group of *o*NBS-Aib forms a centrosymmetric hydrogen-bonded dimer with an O···O distance of 2.629 (2) Å. The two independent molecules of *o*NBS-Cyh form a hydrogen-bonded dimer about a pseudo-center near $(\frac{1}{4}, \frac{3}{4}, \frac{1}{2})$, with O···O distances of 2.619 (2) and 2.705 (2) Å.

The difference in the environments of the primed and unprimed molecules may be seen in the hydrogen bonding by the N—H group. That of the primed molecule forms a nearly linear intermolecular contact to the nitro O5^{i} atom [symmetry code: (i) $x, \frac{3}{2} - y, \frac{1}{2} + z$; see Table 2], while the nearest distance to the unprimed N—H group is somewhat longer, at 3.767 (2) Å to the sulfonyl O1′ atom at $(x, \frac{3}{2} - y, z - \frac{1}{2})$, and somewhat less linear, with an N—H···O angle of 152 (2)°.

The cyclohexyl group of *o*NBS-Cyh is in the chair conformation, having endocyclic torsion-angle magnitudes in the range 53.9 (2)–57.3 (2)°, in good agreement with the mean value of 54.6° observed in 1-aminocyclohexane-1-carboxylic acid and six of its derivatives (Valle *et al.*, 1988).

We have isolated a second polymorph of *o*NBS-Cyh having $Z' = 1$ from the same crystallization, but have not obtained crystals of sufficient quality to report the full structure here. That polymorph has space group $P\overline{1}$, with cell dimensions a = 8.48 (2), b = 8.52 (2), c = 11.44 (3) Å, α = 97.2 (2), β = 102.8 (2), γ = 106.1 (2)° and V = 759 (3) Å^3 at 297 K (R = 0.090). Its conformation is quite similar to that of the $Z' = 2$ polymorph described here.

Experimental

Compounds (I) and (II) were prepared by reacting the corresponding amino acid (1 equivalent) with chlorotrimethylsilane (1.85 equivalents), diisopropylethylamine (2.3 equivalents) and *ortho*-nitrobenzenesulfonyl chloride (0.9 equivalents) in anhydrous dichloromethane over 12 h (273 K to reflux), followed by aqueous work-up and extraction. Both amino acid derivatives were crystallized by dissolving the crude material in a hot ethanol solution, followed by slow cooling to room temperature.

Compound (I)

Crystal data

$C_{10}H_{12}N_2O_6S$	D_x = 1.572 Mg m^{-3}
M_r = 288.28	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 25 reflections
a = 11.665 (3) Å	θ = 14.8–21.1°
b = 10.614 (2) Å	μ = 0.292 mm^{-1}
c = 11.121 (4) Å	T = 100 K
β = 117.80 (2)°	Prism, colorless
V = 1217.9 (6) Å^3	0.45 × 0.43 × 0.20 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer (with Oxford Cryostream cooler)	2710 reflections with $I > 2\sigma(I)$
	R_{int} = 0.035
	θ_{max} = 30.0°
ω–2θ scans	$h = -16 \rightarrow 14$
Absorption correction: ψ scan (North *et al.*, 1968)	$k = -14 \rightarrow 8$
T_{min} = 0.880, T_{max} = 0.944	$l = 0 \rightarrow 15$
4282 measured reflections	3 standard reflections
3536 independent reflections	frequency: 60 min
	intensity decay: 5.0%

Table 1
Selected geometric parameters (Å, °) for (I).

S—O1	1.4338 (13)	S—C3	1.7832 (18)
S—O2	1.4376 (13)	O3—C1	1.314 (2)
S—N1	1.6096 (16)	O4—C1	1.224 (2)
C10—C2—C9	110.50 (15)		
C3—S—N1—C2	108.97 (15)	N1—S—C3—C8	77.28 (16)
S—N1—C2—C1	55.80 (19)	O5—N2—C8—C3	−38.5 (2)
O3—C1—C2—N1	38.50 (19)		

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3O···O4^{i}	0.90 (3)	1.74 (3)	2.629 (2)	171 (3)
N1—H1N···O5	0.78 (3)	2.32 (3)	2.823 (2)	123 (2)
N1—H1N···O4^{ii}	0.78 (3)	2.58 (3)	3.342 (2)	165 (2)

Symmetry codes: (i) $2 - x, 2 - y, 2 - z$; (ii) $2 - x, y - \frac{1}{2}, \frac{3}{2} - z$.

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0437P)^2 + 0.4249P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.042$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.109$	$\Delta\rho_{max} = 0.46$ e Å^{-3}
$S = 1.031$	$\Delta\rho_{min} = -0.37$ e Å^{-3}
3536 reflections	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
183 parameters	Extinction coefficient: 0.0105 (14)
H atoms: see below	

Compound (II)

Crystal data

$C_{13}H_{16}N_2O_6S$	$D_x = 1.479$ Mg m^{-3}
$M_r = 328.34$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 25 reflections
$a = 15.9780$ (12) Å	$\theta = 10.6$–$21.2°$
$b = 14.9840$ (11) Å	$\mu = 0.251$ mm^{-1}
$c = 13.4360$ (10) Å	$T = 100$ K
$\beta = 113.568$ (6)°	Fragment, colorless
$V = 2948.4$ (4) Å^3	0.55 × 0.42 × 0.35 mm
$Z = 8$	

Data collection

Enraf–Nonius CAD-4 diffractometer (with Oxford Cryostream cooler)	5772 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.033$
ω–2θ scans	$\theta_{max} = 29.0°$
Absorption correction: ψ scan (North *et al.*, 1968)	$h = 0 \rightarrow 21$
	$k = -20 \rightarrow 20$
$T_{min} = 0.887$, $T_{max} = 0.916$	$l = -18 \rightarrow 16$
9183 measured reflections	3 standard reflections
7815 independent reflections	frequency: 60 min
	intensity decay: 2.7%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0311P)^2 + 2.1884P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.043$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.116$	$\Delta\rho_{max} = 0.63$ e Å^{-3}
$S = 1.093$	$\Delta\rho_{min} = -0.61$ e Å^{-3}
7815 reflections	
413 parameters	
H atoms: see below	

Carboxy and amino H atoms were located in difference maps and were refined individually. Other H atoms were placed in calculated positions with C—H bond distances of 0.95 Å for phenyl and 0.98 Å for methyl, and thereafter treated as riding. $U_{iso} = 1.2U_{eq}$ of the attached C atom (1.5 for methyl). A torsional parameter was refined for each methyl group.

Table 3
Selected geometric parameters (Å, °) for (II).

S1—O1	1.4287 (16)	S1′—O1′	1.4290 (15)
S1—O2	1.4397 (15)	S1′—O2′	1.4363 (15)
S1—N1	1.6134 (17)	S1′—N1′	1.6041 (17)
S1—C3	1.778 (2)	S1′—C3′	1.781 (2)
O3—C1	1.319 (2)	O3′—C1′	1.314 (2)
O4—C1	1.224 (2)	O4′—C1′	1.223 (2)
C10—C2—C9	109.44 (16)	C10′—C2′—C9′	109.17 (16)
C3—S1—N1—C2	108.84 (16)	C3′—S1′—N1′—C2′	−103.64 (17)
S1—N1—C2—C1	56.7 (2)	S1′—N1′—C2′—C1′	−59.4 (2)
O3—C1—C2—N1	39.1 (2)	O3′—C1′—C2′—N1′	−30.4 (2)
N1—S1—C3—C8	87.61 (18)	N1′—S1′—C3′—C8′	−83.36 (18)
O5—N2—C8—C3	−47.1 (3)	O5′—N2′—C8′—C3′	45.1 (3)
C10—C2—C9—C11	−55.4 (2)	C10′—C2′—C9′—C11′	54.2 (2)
C9—C2—C10—C13	56.6 (2)	C9′—C2′—C10′—C13′	−55.2 (2)
C2—C9—C11—C12	54.6 (2)	C2′—C9′—C11′—C12′	−55.5 (2)
C9—C11—C12—C13	−53.9 (2)	C9′—C11′—C12′—C13′	55.3 (2)
C11—C12—C13—C10	55.3 (3)	C11′—C12′—C13′—C10′	−55.7 (2)
C2—C10—C13—C12	−57.3 (2)	C2′—C10′—C13′—C12′	56.9 (2)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3O···O4′	0.85 (3)	1.77 (3)	2.619 (2)	175 (3)
N1—H1N···O5	0.83 (3)	2.61 (3)	3.050 (2)	115 (2)
O3′—H3O′···O4	0.89 (3)	1.82 (3)	2.705 (2)	172 (3)
N1′—H1N′···O5′	0.83 (3)	2.53 (3)	2.999 (2)	117 (2)
N1′—H1N′···O5^{i}	0.83 (3)	2.40 (3)	3.214 (2)	168 (3)

Symmetry code: (i) $x, \frac{3}{2} - y, \frac{1}{2} + z$.

For both compounds, data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995) for compound (I), *MAXUS* (Mackay *et al.*, 1999) for compound (II); program used to solve structure: *SHELXS*97 (Sheldrick, 1997) for compound (I), *SIR*92 (Altomare *et al.*, 1993) for compound (II); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999) for compound (I), *SHELXL*97 for compound (II).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1155). Services for accessing these data are described at the back of the journal.

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