The First X-Ray Crystal Structure of an *O*-Alkyl Aminosulfoxonium Salt: Conclusive Evidence for *O*-Alkylation of Sulfinamides and Planarity of Nitrogen

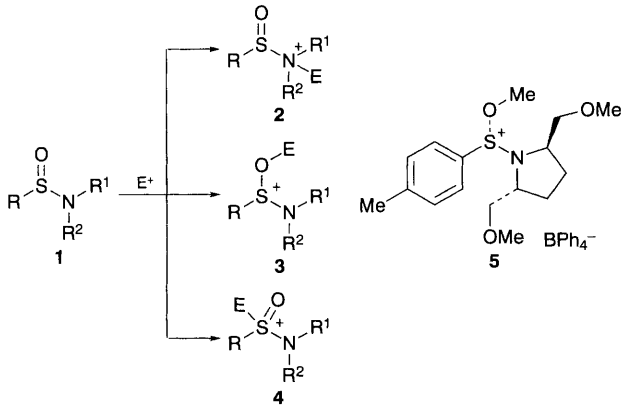
I. Fraser Pickersgill,[a] Allan P. Marchington,[b] Mark Thornton-Pett[a] and Christopher M. Rayner*[a]

[a] *School of Chemistry, University of Leeds, Leeds, UK LS2 9JT*
[b] *Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, UK CT13 9NJ*

The X-ray crystal structure of *O*-methyl (2*R*,5*R*)-bis(methoxymethyl)pyrrolidin-1-yl-(*S*)-*p*-tolylaminosulfoxonium tetraphenylborate **5** is reported: this is the first X-ray crystal structure of an *O*-alkyl aminosulfoxonium salt, and provides conclusive evidence that alkylation of sulfinamides occurs on oxygen.

Homochiral sulfinamides **1** and related compounds[1] are useful synthetic intermediates, allowing access to enantiomerically pure sulfoxides[2–4] and β-ketosulfoxides,[3,4] sulfinate esters,[4,5] other sulfinamides,[4] and unusual amino acids.[6] We have recently reported the use of alkylated sulfinamides (aminosulfoxonium salts) as electrophiles for the formation of C–C bonds when reacted with β-ketoester enolates.[7] Previously such salts have been used to prepare ammonium and sulfonium salts.[8,9] Sulfinamides, along with sulfonamides, have also been incorporated into peptides and investigated as transition state mimics for amide hydrolysis, with potential application as peptidase inhibitors.[10]

The alkylation of a sulfinamide can theoretically occur at any one of three sites (Scheme 1). It has generally been assumed that the protonation site of a sulfinamide is nitrogen **2**,[1,11] although from comparison with sulfoxides and carboxylic acid amides, *O*-protonation might realistically be expected. Recently, ^{14}N NMR studies have led to the conclusion that protonation actually occurs on oxygen **3**.[12] Minato *et al.* have reported[8,9] that the alkylation of a simple sulfinamide with methyl triflate gave the *O*-methylated species as the sole product. Their assignment of the alkylation site was based purely on the chemical shift of the methyl singlet as observed by ^1H NMR, and hence was not conclusive.[9] Although considerable structural information regarding sulfinamides is available, including X-ray crystal structures (*vide infra*), the corresponding aminosulfoxonium salts are less well investigated. It was of crucial importance for our own studies, *viz.* the rational design of sulfinamide-based asymmetric alkylating agents, that we had conclusive proof of the structure of the aminosulfoxonium salts we were dealing with.



Scheme 1

The aminosulfoxonium salt **5**† was prepared by methylation (CF_3SO_3Me) and anion exchange ($NaBPh_4$),[7–9] of the corresponding sulfinamide, which was prepared from commercially available (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine and (1*R*,2*S*,5*R*)-menthyl (*S*)-(−)-toluene-*p*-sulfinate using a modified Anderson procedure.[2,13] Recrystallisation from CH_2Cl_2–Et_2O gave crystals of **5** of suitable quality for X-ray crystal structure determination (Fig. 1).‡ This clearly shows that alkylation occurred at oxygen. Whilst the N *vs.* O selectivity may vary depending on the particular substrate and electrophile, and in this case steric hindrance around the nitrogen and relatively large electrophile (*e.g.* CF_3SO_3Me *vs.* H^+) may disfavour *N*-alkylation, we believe that, coupled with other recent results,[12] alkylation and protonation of sulfinamides occurs at oxygen.

Previous X-ray studies on sulfinamides[14] have shown that the lone pair on the nitrogen is heavily delocalised into the d orbital of the adjacent sulfur atom hence shortening the S–N bond and introducing a degree of sp^2 hybridisation at the nitrogen. For example 1-phenylsulfinyl-2,2,6,6-tetramethyl-4-oxopiperidine is reported[15] to have a S–N bond length§ of 1.652 Å with the nitrogen distorted out of plane by 0.144 Å. As would be expected, on formation of the *O*-methyl aminosulfoxonium salt (Fig. 1), we observe the S–N bond length is now considerably shorter [1.588(3) Å] and the distortion from planarity at nitrogen reduced to 0.082 Å, both consistent with more extensive delocalisation of the nitrogen lone pair.

One other structural feature which may have important consequences in this particular case, is the close proximity of the aminosulfoxonium *O*-methyl group to one of the methyl ether units on the pyrrolidine. Although the X-ray results relate to the solid state, we have observed that salts such as **5** are considerably less reactive as electrophiles in our alkylation reactions than simple aminosulfoxonium salts.[7] This may be explained by the salt adopting a similar conformation predominantly in solution, and the resultant steric hindrance slowing the rate of reaction.

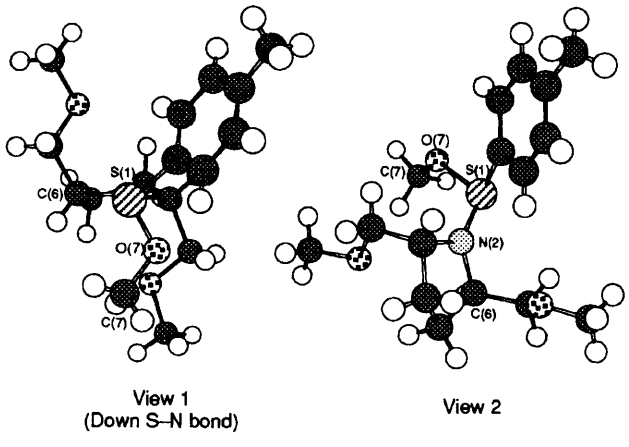


Fig. 1 X-Ray crystal structure of **5** (BPh_4^- counter ion omitted for clarity). Selected bond lengths (Å) and angles (°): S(1)–N(2) 1.588(3), S(1)–O(7) 1.606(2), N(2)–C(3) 1.506(4), N(2)–C(6) 1.499(4), O(7)–C(7) 1.452(4), N(2)–S(1)–O(7) 111.54(12), C(6)–N(2)–S(1) 127.6(2), C(7)–O(7)–S(1) 114.8(2), N(2)–S(1)–C(81) 105.55(14).

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Footnotes

† *Selected data* for **5**: Colourless prisms; mp 129.0–130.0 °C (CH_2Cl_2–Et_2O); $[\alpha]_D^{25}$ +52 (*c* 0.1; acetone); IR (film) ν 1700 cm^{-1} (br); ^1H NMR (300 MHz, [$^2H_6$]acetone) δ 7.83 (d, *J* 8.4 Hz, 2H), 7.62 (d, *J* 8.4 Hz, 2H), 7.34 (br s, 8H), 6.95 (t, *J* 2.3 Hz, 8H), 6.76 (t, *J* 7.2 Hz, 4H), 4.36 (s, 3H), 4.26–4.16 (m, 2H), 3.73 (dd, *J* 4.7, 7.2 Hz, 2H), 3.63 (dd, *J* 7.0, 10.8 Hz, 2H), 3.35 (s, 6H), 2.48 (s, 3H), 2.37–2.18 (m, 2H), 2.16–1.80 (m, 2H).

‡ *Crystal data* for **5**: $C_{40}H_{46}BNO_3S$, *M* = 631.65, orthorhombic, space group $P2_12_12_1$, *a* = 10.0744(3), *b* = 18.622(5), *c* = 18.712(4) Å, *U* = 3510(2) $Å^3$, D_c = 1.195 Mg m^{-3}, *Z* = 4, *F*(000) = 1352, λ = 1.54184 Å; μ (Mo-Kα) = 1.108 mm^{-1}, *T* = 200 K. 5642 Data collected (one octant and its Friedel opposites) to 2θ = 130° on a Stoe STADI4 diffractometer operating in the ω–θ scan mode using graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å) at 200 K. The structure was solved by direct methods (SHELXS-86[16]) and refined anisotropically by full-matrix least-squares based on all unique F^2 (SHELXL-93).[16] Hydrogen atoms constrained to idealised positions with fixed isotropic displacement parameters of nU_{eq} of the parent carbon atom (*n* = 1.5 for methyl, 1.2 for all others). The weighting scheme was $w = [\sigma^2(F_o^2) + 0.0637(P)^2]^{-1}$, $P = (F_o^2 + 2F_c^2)/3$. The absolute configuration was confirmed by refinement of a 'Flack' enantiopole parameter[17] to 0.01(2). Final $wR(F^2)$ for all 5642 reflections was 0.1135 with a conventional $R(F)$ of 0.0441 [for 3910 reflections with $I > 2.0\sigma(I)$] for 419 parameters. Structure has been transferred to Chem3D Plus™ for display purposes. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ The calculated single N–S bond length for a sulfinamide is reported to be 1.730 Å, derived from the conventional radii and the electronegativity correction by Schomaker and Stevenson.[15]

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