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ORIGINAL PAPER

Intermolecular Hydrogen Bonds and the Supramolecular Structure of *N*,*N*′-Bis(*p*-tolylsulfonyl)diethylenetriamine

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Abstract The title compound *N*,*N*′-bis(*p*-tolylsulfonyl) diethylenetriamine (**1**) was synthesized and its crystal structure determined by X-ray diffraction. Adjacent molecules of **1**, symmetrically related through a *c*-glide, are linked by alternating hydrogen bonds that form molecular chains along [0 0 1]. Two molecular chains occur in each unit cell and pack to form alternating layers in a three-dimensional supramolecular structure. The compound crystallizes in the $Pca2_1$ space group stabilized by the inclusion of solvent dichloromethane molecules in structural voids between molecules of **1**. The dichloromethane molecules are related through a twofold screw rotation axis and are not disordered.

Keywords Sulfonamide · Hydrogen-bonding · Supramolecular · Graph set analysis

Introduction

Conversion of amines into *N*-substituted sulfonamides has enjoyed several uses in analytical and synthetic organic chemistry. For example, the Hinsberg test exploits the reaction of amines in general with substituted benzene sulfonyl chloride derivatives to isolate the sulfonamides of amine mixtures, relying upon the different solubilities of the resultant sulfonamides in aqueous solution for distinguishing primary, secondary, and tertiary amines [1]. Sulfonamides played a crucial role in the synthesis of macrocyclic polyamines, which are the cyclization products of a condensation reaction between the sodium sulfonamide salt and the glycol derivatives under Richman–Atkins conditions [2]. The rich chemistry of macrocyclic-based metal complexes has seen these being investigated for their possible use as imaging agents or biosensors for an ever increasing array of biologically significant molecules or ions [3–5]. Acyclic chelates have, however, retained their importance due to their equally robust coordination chemistry and metal complexes based upon acyclic chelates have been approved for commercial use [6]. Designing synthetic pathways for asymmetrically substituted macrocyclic and acyclic chelating systems [7] potentially leads to significant improvements of presently used metal complexes in clinical applications. The synthetic successes surrounding asymmetrically substituted azamacrocylic compounds and their acyclic analogues, is attributed to the steric characteristics [8] imposed upon sulfonamides in which tosyl groups, in particular, are protecting groups that mask the nucleophilicity of the nitrogen atom.

Isolating convenient sulfonamide-based synthetic building blocks for designing new chelating systems remains an important endeavor for bioinorganic and organic chemists alike. Our interest in synthesizing asymmetric diethylenetriamine-based chelates led to the synthesis of the title compound so as to determine the solid state structure and investigate the influence hydrogen-bonding arrays may have on the geometry surrounding the sulfonamide moiety.

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Experimental Section

Solvents and Chemicals

All chemical solvents were distilled and dried prior to use in synthetic procedures. Diethanolamine, 1,2-diaminoethane,

and *p*-toluenesulfonyl chloride were purchased from Aldrich and used as received.

Physical Measurements

The ^{1}H and ^{13}C NMR spectra were obtained with a Bruker 300 MHz spectrometer in deuterated chloroform.

A crystal of dimensions 0.50 × 0.37 × 0.25 mm^3 of (**1**) was used for collection of intensity data on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA) using the APEX 2 [9] data collection software. The collection method involved ω-scans of width 0.5° and 512 × 512 bit data frames. Data reduction was carried out using the program *SAINT-NT* [10].

The crystal structure was solved by direct methods using *SHELXTL* [11]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Hydrogen atoms involved in hydrogen-bonding were located in the difference map and refined freely. Diagrams and publication material were generated using *SHELXTL*, *PLATON* [12], and *ORTEP-3* [13]. Details of the data collection are given in Table 1.

Starting Materials

N-*p*-Tolylsulfonylethylenediamine [14] and *N*-*p*-tolylsulfonylaziridine [15, 16] were prepared according to literature procedures and used for synthesizing compound **1** via a modified procedure [16].

Synthesis of *N*,*N*′-Bis(*p*-tolylsulfonyl) diethylenetriamine (**1**) (Scheme 1)

N-*p*-Tolylsulfonylethylenediamine (1.0 g, 4.67 mmol) was dissolved in CH_3CN and heated to reflux under argon. A CH_3CN solution (11 mL) of *N*-*p*-tolylsulfonylaziridine (0.92 g, 4.67 mmol) was added dropwise over a period of 3 h and the mixture was allowed to further reflux for 12 h. This was then cooled to room temperature affording a pale yellow oil after removal of the solvent under reduced pressure. The compound was crystallized from dichloromethane/diethyl ether (50:50) to give (**1**) as a crystalline solid. Yield: 70%. $\delta_H(CDCl_3)$: 2.418 (6H; Ts-C*H*$_3$), 2.606 (4H; C*H*$_2$NC*H*$_2$), 2.948 (4H; Ts-NC*H*$_2$), 7.285 (4H; CH_3CH *Ar*), 7.734 (4H; C*H*C-SO_2 *Ar*). $\delta_C(CDCl_3)$: 21.921 (Ts-*C*H$_3$), 42.962 (*C*H$_2$N*C*H$_2$), 48.152 (Ts-N*C*H$_2$), 127.615, 130.075, 137.146, 143.812 (Ts-*C*H; Ts-*C*-).

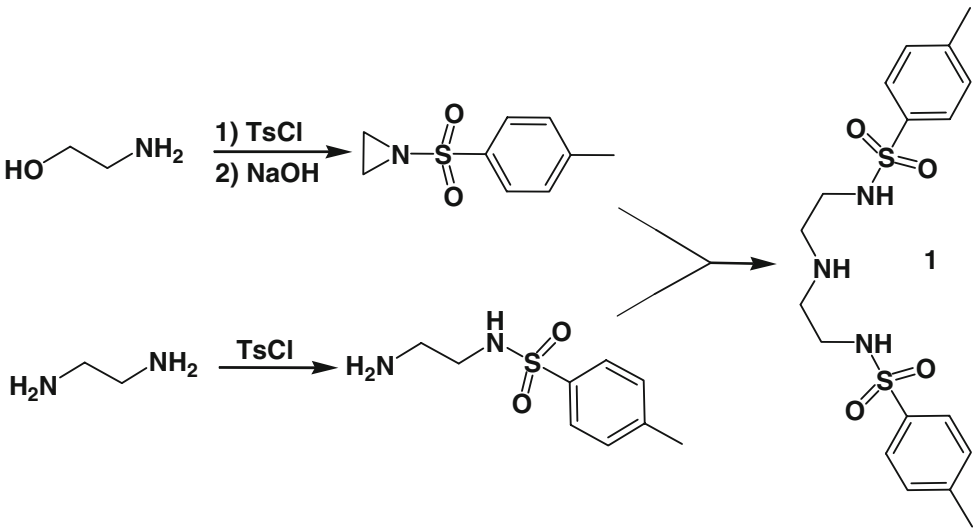
Table 1 Crystal data and structure refinement for the title compound

CCDC deposit no.	CCDC 662299
Empirical formula	$C_{19}H_{27}Cl_2N_3O_4S_2$
Chemical formula	$C_{18}H_{25}N_3O_4S_2CH_2Cl_2$
Formula weight	496.46
Color/shape	Colorless needles
Temperature (K)	172(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$Pca2_1$
Unit cell dimensions	$a = 25.4644(4)$ Å
	$b = 11.2639(2)$ Å
	$c = 8.10410(10)$ Å
	$\alpha = 90°$
	$\beta = 90°$
	$\gamma = 90°$
Volume $(Å)^3$	2324.49(6)
Z	4
Density (calculated) (g cm^{-3})	1.419
Absorption coefficient (mm^{-1})	0.489
$F(000)$	1040
Crystal size (mm^3)	0.50 × 0.37 × 0.25
θ range for data collection (°)	1.60–28.00
Limiting indices	$-33 < h < 31$, $-14 < k < 14$, $-9 < l < 10$
Reflections measured	23,941
Independent/observed reflections	5,474
R_{int}	0.0311
Completeness to $\theta = 28.00°$	100.0%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5474/4/285
Goodness of fit F^2	1.046
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0471$, wR2 = 0.1173
R indices (all data)	$R1 = 0.0563$, wR2 = 0.1232
Absolute structure parameter	0.05(7)
Largest differential peak and hole (e $Å^{-3}$)	0.388 and −0.384

Results and Discussion

The use of *p*-toluenesulphonyl groups as protecting groups in the synthesis of macrocyclic compounds is not uncommon and it is therefore surprising that relatively few structures of diethylenetriamine derivatives bearing tosyl groups have been reported. Compound **1** has been synthesized as outlined in Scheme 1 with the specific aim of protecting the terminal nitrogen atoms. Further substitution at the central nitrogen affords C_2 symmetry to related acyclic chelating systems using **1** as a convenient synthetic precursor [17].

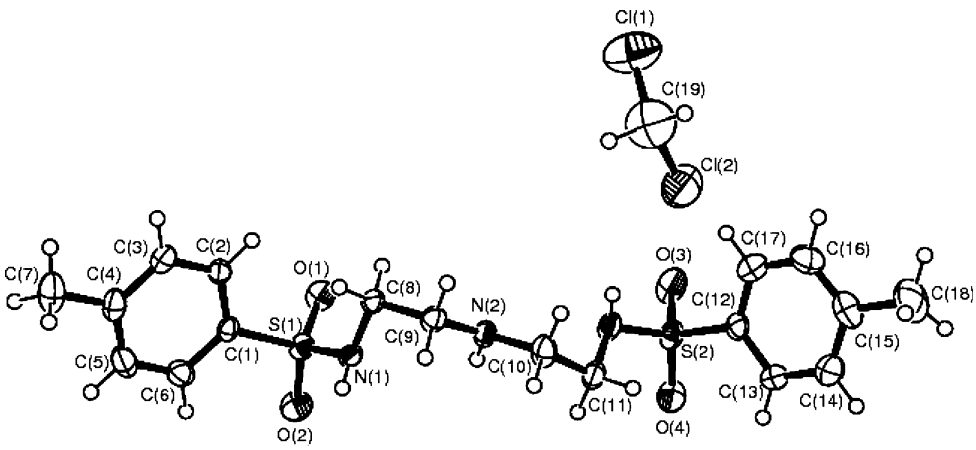
Scheme 1 Synthetic outline of compound **1**



The asymmetric unit consists of a single molecule of compound **1** and the inclusion of a dichloromethane solvent molecule as indicated in the ORTEP diagram shown in Fig. 1. The inclusion of this volatile solvent in crystal lattices is not uncommon. Inclusion of dichloromethane is reported [18] to be the most frequent amongst structures of metalloorganic compounds and second only to methanol in structures of organic compounds. Host–guest interactions [19] have previously been reported for calixarenes in which the dichloromethane inclusion is facilitated by participation in hydrogen-bonding networks. No disorder is associated with the dichloromethane solvent molecule, often the result of intermolecular non-bonding interactions. The distance between the chlorine atoms of the dichloromethane and the *p*-toluenesulphonyl groups, in excess of 5 Å, excludes the feasibility of any C–H···Cl interactions between these entities. Intermolecular CH···O interactions, in which the dichloromethane molecule acts as a donor via the C–H bonds to oxygen atoms of sulphonyl moieties, are identified on 361 occasions in the CCDC database. These interactions have an average H···O distance of 2.57 Å, which is shorter than the observed H···O distances for analogous interactions in the solvate structure of **1**. The significance of these weak CH···O interactions between the dichloromethane molecule and the *p*-toluenesulphonyl groups, and their contribution towards aligning molecules of **1** within the crystal lattice, previously reported for aromatic compounds [20] is unclear. The donor–acceptor (D···A) proximity in these CH···O interactions is misleading and may be rationalized by their inherent D–H···A angle defined by the location of the hydrogen atom. The proximity of the donor carbon in the dichloromethane to the oxygen acceptor of the sulphonyl moiety in this structure is underlined by a D–H···A angle of 163°. It is clear, however, that the dichloromethane molecules occupy cavities between the larger solute molecules (Fig. 2) of compound **1**, a phenomenon reported to be crucial in stabilizing structures and facilitating crystallization [18]. Adjacent solvent molecules are symmetrically related through a twofold screw axis at $y = ½$ and run parallel to the [0 0 1] direction between molecular chains of **1**.

The unit cell contains two molecular chains of compound **1** formed via an intricate hydrogen-bonding array

Fig. 1 ORTEP drawing of title compound (50% probability ellipsoids)



consisting of N–H···N and N–H···O intermolecular interactions (Table 2). The molecular chains are symmetrically equivalent through a twofold screw axis at (½, ½, 0) and

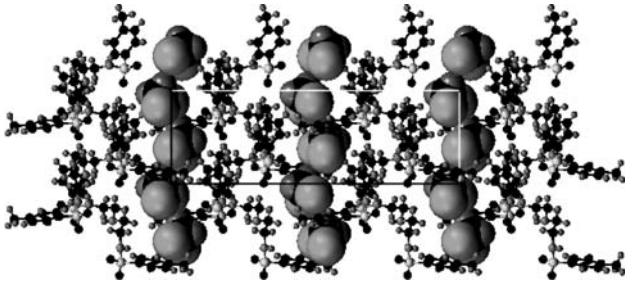


Fig. 2 Spacefill diagram of included DCM molecules (solid shading) viewed along [0 1 0]

Table 2 Hydrogen bonds for **1** (Å) and (°)

D–H···A	D–H	H···A	D···A	π(DHA)
N(1)–H(1H)···N(2)^{i}	0.80(2)	2.19(2)	2.994(3)	174(3)
N(3)–H(3H)···O(2)^{ii}	0.79(2)	2.60(3)	3.307(4)	150(3)

Note: Symmetry codes: $i = (1½ - x, y, z + ½)$; $ii = (1½ - x, y, z - ½)$

are parallel to [0 0 1]. Adjacent molecules in each chain are related via a *c*-glide at $a = ¼$ that oscillates hydrogen-bonding motifs (Fig. 3) along [0 0 1].

A C(5) chain motif [21] is defined by an intermolecular N–H···N hydrogen bond in which the terminal tosylated nitrogen N(1) acts as a donor via H(1H) to the central amino atom N(2) at (1½ − x, y, z + ½). Tosylated nitrogen atom N(3) acts as a hydrogen donor via H(3H) to oxygen O(2) in the sulfonyl group at (1½ − x, y, z − ½) completing a N–H···O intermolecular interaction that defines a C(10) chain. The described C(5) and C(10) chains, parallel to [0 0 1], constitute the basic unitary graph set. A basic binary graph set includes a $C_2^2(15)$ descriptor when combining N–H···N and N–H···O interactions via translation along [0 0 1]. The binary graph set is elaborated by a *c*-glide at $a = ¼$ with a glide component ½/*c*/ that further combines these intermolecular interactions to describe a ring motif $R_2^2(9)$ (Fig. 3).

The graphs sets describing the hydrogen-bonding array in compound **1** are comparable to that observed for a structurally similar triazaheptane derivative [7]. In the structure of di-*p*-toluenesulfonyl-2,6-di(methylethyl)-1,4,7-triazaheptane (**2**, Chart 1) N–H···O intermolecular

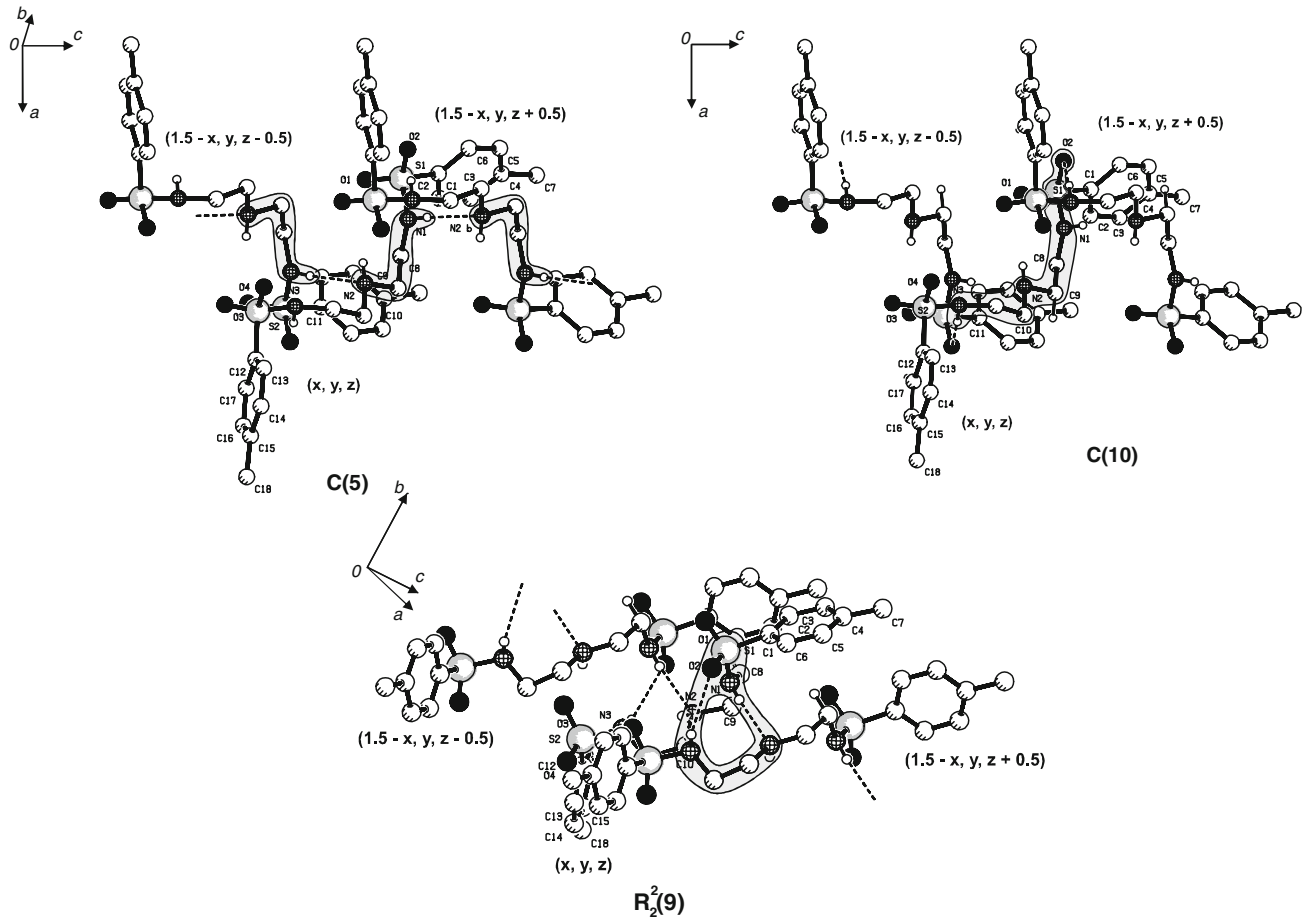
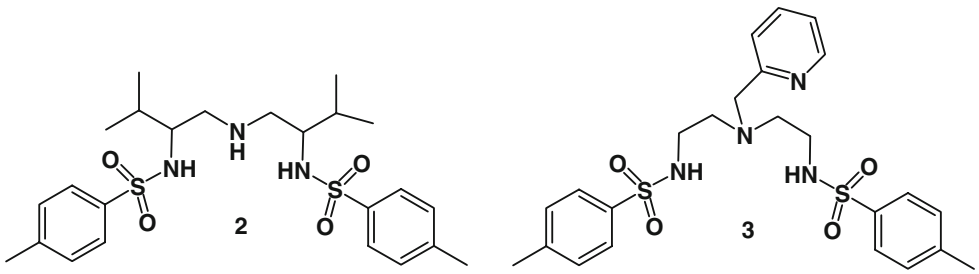


Fig. 3 Graph sets for N–H···O and N–H···N interactions along [0 0 1]. Hydrogen atoms removed for clarity

Chart 1 Compounds discussed: REFCODE **2** (LAHKIP); **3** (IFECUR)



interactions are the only interactions present, where nitrogen atoms in amino groups acts as donors to the oxygen atoms of sulfonyl moieties. The C(10) chain motifs and a chain of rings $C_2^2(20)$ $R_2^2(8)$ motifs describe the basic unitary and basic binary graph set along [1 0 0], respectively. Expected distorted tetrahedral geometries occur at the sulfur atom in the *p*-toluenesulfonyl groups (Table 3). The imposed restriction to rotation [8] about bonds to amine nitrogens protected by bulky *p*-toluenesulfonyl groups, predisposing these compounds toward cyclization products, becomes evident from the structures of **1** and **2**. The diethylenetriamine backbone in both structures does not assume an orientation typical of primary alkylamines [22]. The diethylenetriamine backbone in bis((*p*-toluenesulfonylamido)ethyl)-2-(aminomethyl) pyridine) [17] (**3**, Chart 1) adopts a conformation that more closely resembles that observed in azamacrocycles.

Dihedral angles in the structure of **3** for *cis* configurations between O=S bonds, in *p*-toluenesulfonyl groups, and N–H bonds, of the amine moieties they are protecting, range between 35 and 42°. In compound **3** two crystallographically independent molecules occupy the asymmetric unit and N–H···O and O–H···N intermolecular interactions occur only with included ethanol solvent molecules. Several discrete, D(2), interactions describe the hydrogen-bonding pattern with the solvent molecule in which the ethanolic oxygen acts as a donor to the pyridine nitrogen or as an acceptor for the interaction with the amine nitrogen atom. On a binary level these interactions result in $R_2^2(10)$ motifs. A $R_1^2(10)$ motif describes the hydrogen-bonding pattern for the N–H···O intermolecular interactions between two amine nitrogen atoms in the diethylenetriamine backbone and the oxygen of the same ethanol molecule. Larger variations occur for analogous dihedral angles in **1** and **2** where N–H···O interactions involve the oxygen atom of the sulfonyl moieties. The dihedral angle $O_2S_1N_1H_{1H} = 44.2(1)$ in **1** and $O_3S_2N_3H_{37} = 41.3(1)$ in **2** compare with the dihedral angles observed in the structure of **3**. Anomalies are $O_2S_1N_1H_{35} = 2.4(1)$ in **2**, that places the sulfonyl oxygen and amino hydrogen atom in a pseudo-eclipsed position, and $O_3S_2N_3H_{3H} = 62.2(1)$ in **1**, where the sulfonyl moiety does not participate in the hydrogen-bonding array. Given the above crystallographic data a convincing argument cannot be advanced for *p*-toluenesulfonyl groups masking the nucleophilicity of nitrogen atoms through steric control in diethylenetriamine derivatives. The discussion alluding to the minimal loss of internal entropy that favors cyclization products perhaps affords a more plausible explanation.

Table 3 Selected bond angles (°) for **1**

O(1)–S(1)–O(2)	119.59(14)
O(1)–S(1)–N(1)	108.67(13)
O(2)–S(1)–N(1)	105.58(13)
O(1)–S(1)–C(1)	108.03(13)
O(2)–S(1)–C(1)	107.65(13)
N(1)–S(1)–C(1)	106.64(12)
O(3)–S(2)–O(4)	120.07(16)
O(3)–S(2)–N(3)	105.97(13)
O(4)–S(2)–N(3)	107.12(15)
O(3)–S(2)–C(12)	107.87(16)
O(4)–S(2)–C(12)	107.49(13)
N(3)–S(2)–C(12)	107.80(14)

Supplementary Material

CCDC 662299 contains the supplementary crystallographic data for this paper. Copies may be obtained free of charge from the Director, CDC, 12 Union Road, Cambridge, CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

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