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Experimental demonstration of anomeric effect and structure: X-ray conformational and configurational analysis of *N*-2-(1,4-dioxane)-*N′*-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea

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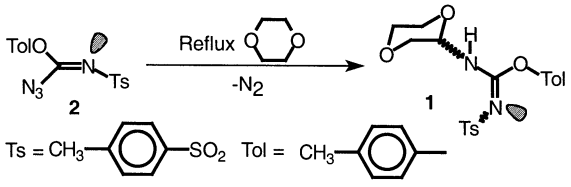
Abstract—The conformational, configurational behavior and the structure of *N*-2-(1,4-dioxane)-*N′*-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea (**1**) has been studied using X-ray crystallographic analysis. The *endo*-anomeric effect controls the population of dioxane ring conformers or anomers but not the configuration interconversion of the imine of the imidoyl moiety. X-Ray analysis of **1** demonstrates that the dioxane ring adopts the chair conformation, that the imidoyl amino group prefers axial conformation and that the tosyl and tolyl groups about the C=N bond retain the *E* configuration. Isourea (**1**) was synthesized by the thermal decomposition of *N′*-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) imidoyl azide in refluxing dioxane.

1. Introduction

In recent years, an increasing number of investigations have been concerned with the anomeric effect and the conformational analysis of tetrahydropyrans, 1,3-dioxanes, glycosides and other cyclohexane derivatives.[1–29] Salzner revisited the origin of the anomeric effect and concluded that anomeric effects are due to charge back donation from lone pairs rather than dipole repulsions.[30] There have been comparatively fewer reports on 1,4-dioxane and its substituted analogs.[25–29,34] The major area of interest has been pharmaceutical activities of 1,4-dioxanes.[25–29] The anomeric effect is well recognized as an important factor in defining the predominant conformational state of many cyclic heteroatom-containing compounds. The geometry of the conformations of the transition state and/or of the intermediate is documented to pre-establish the selectivity of the chemical reactions and/or the stereochemistry of the adducts.[31–33] Since it is entirely conceivable that the pharmaceutical activity is related to the physicochemical properties of the dioxanes, a thorough investigation of 1,4-dioxane derivatives was initiated many years ago.[17,18,22,25–29,34] Recently, dynamic conformational analysis and X-ray crystallography of 9,10-bisbromomethyl-1,4,5,8-tetraoxadecalin (4a,8a-bisbromomethyl-hexahydro-*p*-dioxino)[2,3-*b*]-*p*-dioxane was undertaken by Fuchs and co-workers.[34a] They proved that this tetraoxadecaline has *cis* configuration and adopts double chair conformation.

The purpose of the present paper is to provide evidence, which will serve to establish that the large imidoylamino group [(*p*-CH_3–C_6H_4–O–C=N–SO_2–C_6H_4–CH_3-*p*)–NH–] adopts an axial position (the anomeric effect). Additional aims of this report are to investigate the factors that contribute to this axial preference and to study the conformations and configurations of **1**, Scheme 1.



Scheme 1.

We believe, this system allows us to shed more light on the phenomenon known as the anomeric effect.

We synthesized *N*-2-(1,4-dioxane)-*N′*-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea (**1**) and characterized it by ^1H, ^{13}C NMR, mass spectral analysis, IR and elemental analysis. Second, we studied the structure,

Keywords: anomeric effect; conformational analysis; configurational analysis.
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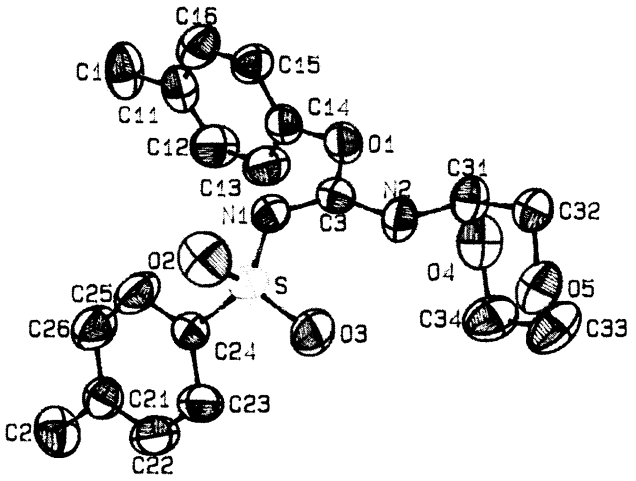
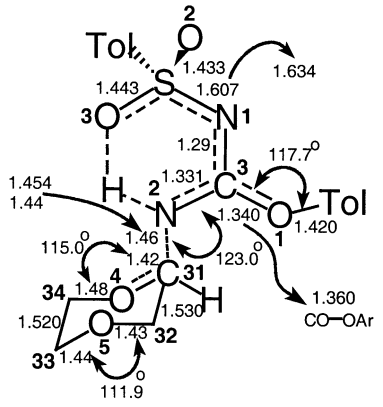


Figure 1. Molecular structure of **1** from X-ray crystallographic analysis.



Scheme 2.

conformation of 1,4-dioxane, configuration of the imine group of the imidoyl moiety and the anomeric effect using X-ray crystallographic analysis.

2. Results and discussion

2.1. Synthesis

N-2-(1,4-Dioxane)-*N*′-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea (**1**) was synthesized by the thermal decomposition of N′-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) imidoyl azide (**2**) in refluxing dioxane, Scheme 1.

2.2. X-Ray crystallographic analysis

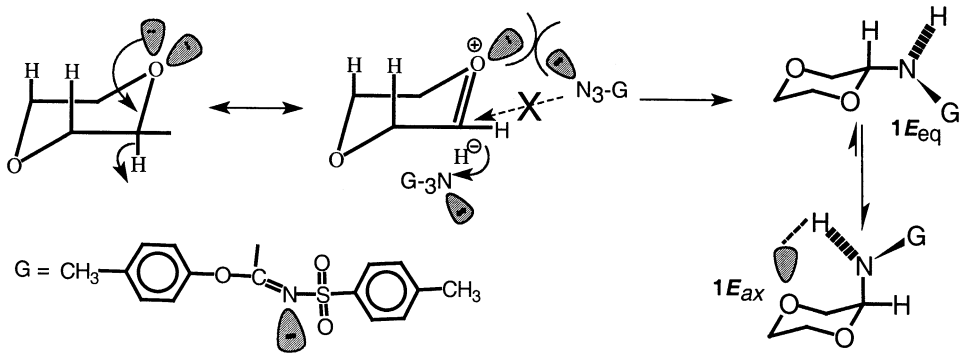
The molecular structure of **1** was analyzed by X-ray crystallography, Fig. 1 and Scheme 2. Selected bond angle, bond length and torsion angle are summarized in Tables 1–3. The following observations are made based on the X-ray analysis of **1**. (a) The dioxane ring retains the chair conformation. (b) The imidoyl amino group (HN–G, G=*p*-Me–C_6H_4–O–C=N–SO_2–C_6H_4–Me-*p*) prefer the axial position. (c) The tosyl and tolyl groups about the C=N bond (N1–C3) are in *trans* position (i.e. *E* isomer). (d) The S=O3 and the Tol–O (O1–C14) bonds holds the *s-cis* conformation with the C=N bond (the torsion angle is almost equal to zero). (e) There is a relatively strong intramolecular hydrogen bond between the N–H and the oxygen of S=O3, Fig. 1, Scheme 2, Tables 1–3. The S=O3 bond length (1.433 Å) is longer than S=O2 (1.34 Å). The S–N1 bond length (1.607 Å) is shorter than a normal S–N bond (1.634 Å).[35,36] The N2–C3 bond length (1.331 Å) is approximately equal to N(sp^2)–C(sp^2).[35] The C3–N2–C31 bond angle is equal to 120° which indicates sp^2 hybridization for the nitrogen atom. The *s-cis* conformation of S=O3, N1–C3 bonds and the S=O3···H–N hydrogen bond helps the formation of a stable six-membered ring. The C14–O1–C3 bond angle (117.7 Å) indicates the sp^2 hybridization for O1. The C3–O1 bond length (1.340 Å) is somewhat shorter than C14–O1 bond (1.420 Å) and typical ArO–CO-bonds (1.360 Å).[35] This indicates the C3–O1 bond has double bond character.

The *endo*-anomeric effect[29] in **1** is demonstrated by the following observations. The O4–C31 bond length (1.420 Å) is shorter than O4–C34 (1.480 Å) and O–C of tetrahydropyran (1.441 Å) bonds. The N2–C31 bond length (1.460 Å) is longer than C(sp^3)–N(sp^2) (1.454 Å) and typical –N–C–O– (1.440 Å) bonds.[37–39] The C34–O4–C31 bond angle (115°) is longer than C33–O5–C32 (111.9°). The torsion angle (α) O4–C31–C32–O5 (54.34°) is smaller than (β) O4–C34–C33–O5 (57.04°). The torsion angle in the 1,4-dioxane ring is 57°.[40,41]

The repulsion between the hydrogen of the H–N–G group and the axial hydrogen at C34 (1,3-repulsion) distorts the

Table 1. Selected bond angle (degrees) calculated by X-ray crystallographic analysis

Atom 1	Atom 2	Atom 3	Bond angle	Atom 1	Atom 2	Atom 3	Bond angle
C24	S	N1	101.9 (3)	N2	C3	N1	127.4 (7)
C24	S	O3	108.8 (4)	N2	C3	O1	114.2 (6)
C24	S	O2	108.5 (4)	N1	C3	O1	118.2 (6)
N1	S	O3	113.6 (3)	C32	O5	C33	111.9 (6)
N1	S	O2	107.0 (4)	O5	C32	C31	108.4 (6)
O3	S	O2	116.0 (4)	C31	O4	C34	115. 0 (6)
C3	N2	C31	123.0 (6)	O5	C33	C34	108.7 (7)
S	N24	C23	118.7 (6)	N2	C31	C32	108.2 (6)
S	N1	C3	124.5 (5)	N2	C31	O4	109.5 (6)
C14	O1	C3	117.7 (6)	C32	C31	O4	110.9 (7)
O1	C14	C15	118.0 (7)	O4	C34	C33	107.6 (7)



Scheme 3.

Table 2. Selected bond length (Å) calculated by X-ray crystallographic analysis

Atom 1	Atom 2	Bond length	Atom 1	Atom 2	Bond length
S	N1	1.607 (7)	O1	C14	1.420 (9)
S	O3	1.447 (5)	O1	C3	1.340 (9)
S	O2	1.433 (6)	O5	C32	1.430 (1)
N2	C3	1.331 (9)	O5	C33	1.440 (1)
N2	C31	1.460 (1)	O4	C31	1.420 (1)
N1	C3	1.290 (1)	O4	C34	1.48 (1)

Table 3. Selected torsion angle (°) calculated by X-ray crystallographic analysis

Atom 1	Atom 2	Atom 3	Atom 4	Angle
N1	S	C24	C23	133.32 (0.65)
N1	S	C24	C25	−48.50 (0.76)
O3	S	C24	C23	13.08 (0.75)
O3	S	C24	C25	−168.74 (0.68)
O2	S	C24	C23	−114.12 (0.67)
O2	S	C24	C25	64.06 (0.77)
C24	S	N1	C3	−123.93 (0.68)
O3	S	N1	C3	−7.03 (0.81)
O2	S	N1	C3	122.32 (0.68)
C31	N2	C3	N1	174.09 (0.74)
C31	N2	C3	O1	−11.17 (1.0)
C3	N2	C31	C32	156.9 (0.68)
C3	N2	C31	O4	−82.32 (0.85)
S	C24	C23	C22	177.97 (0.66)
S	C24	C25	C26	−178.52 (0.75)
S	N1	C3	N2	−12.56 (1.17)
S	N1	C3	O1	172.88 (0.53)
C3	O1	C14	C15	105.27 (0.81)
C3	O1	C14	C13	−78.91 (0.90)
C14	O1	C3	N2	169.91 (0.62)
C14	O1	C3	N1	−14.81 (0.97)
O1	C14	C15	C16	177.11 (0.69)
O1	C14	C13	C12	−176.59 (0.77)
C33	O5	C32	C31	61.66 (0.84)
C32	O5	C33	C34	−64.55 (0.91)
O5	C32	C31	N2	65.70 (0.79)
O5	C32	C31	O4	−54.34 (0.84)
C34	O4	C31	N2	−65.78 (0.83)
C34	O4	C31	C32	53.30 (0.88)
C31	O4	C34	C33	−54.32 (0.94)
O5	C33	C34	O4	57.04 (0.94)

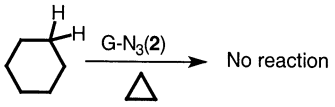
torsion angle of the CH_2–CHNG bond to a nearly planar position, Fig. 1, Scheme 2.

There is major evidence for hydrogen bonding. The X-ray structure of **1** indicates that there is a positive interaction between the lone pair of dioxane (O5) and the hydrogen of the NH group. The distance between the NH with O5 of the dioxane ring is 2.72 Å. The repulsion between the axial C34–H and the NH is too small to prevent the axial preference, Fig. 1.

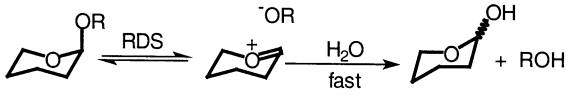
The next step was to address the major force(s) that influence the preference for the axial N-amination (via imidoyl azide) of 1,4-dioxane, Schemes 1 and 3.

2.3. Evaluation of hyperconjugation effect

Generally the imidoyl azide of type (2) does not react with C–H bonds, Scheme 4. Jones and Kirby have used increasing electron demand on oxygen as a probe to test the relationship between bond length and reactivity in tetrahydropyranyl acetates and phosphate monoester dianions, Scheme 5.[42–44] In the case of **1**, hyperconjugation of the oxygen lone pairs of 1,4-dioxane increases the reactivity of the C–H bond forcing dioxane into a co-planar conformation, Scheme 3. This would allow the azide to add from the axial side producing conformer $\mathbf{1}E_{ax}$. The formation of conformer $\mathbf{1}E_{eq}$ is blocked by electronic repulsion, Scheme 3. The axial conformer $\mathbf{1}E_{ax}$ is favored in the solid phase or in non-polar solvents ($CDCl_3$). In other words, the *endo*-anomeric effect of the oxygen of dioxane and the intramolecular hydrogen bonds (between the N–H with oxygen (O3) of S=O (–N–H···O=S–) of tosyl and the NH and oxygen (O4) lone pairs of dioxane) push the G–NH– to take the axial position. The steric hindrance of the imidoyl group (G) does not influence this axial preference, Fig. 1, Scheme 3.



Scheme 4.



Scheme 5.

3. Conclusion

The anomeric effect (hyperconjugative effect) plays a major role and other electronic effects (resonance, induction, hydrogen-bonding, steric hindrance) play a minor role in the axial preference of the imidoyl amino group (HN–G, G=*p*-Me–C_6H_4–O–C═N–SO_2–C_6H_4–Me-*p*). Steric hindrance does not influence the axial preference. The dioxane ring retains the chair conformation. The tosyl and tolyl groups about the C═N bond (N1–C3) hold *trans* positions (i.e. *E* isomer). The S═O3 and the Tol–O (O1–C14) bonds hold *s-cis* conformation with the C═N bond (e.g. the torsion angle is almost equal to zero). There is a relatively strong intramolecular hydrogen bond between the N–H and the oxygen of S═O3.

4. Experimental

^{1}H and ^{13}C NMR were recorded by VARIAN EM390 (90 MHz). The IR spectra were obtained on a SHIMADZU ZU-435. Mass spectra were analyzed by FISON TRIO 1000 instruments (70 eV). Melting points were taken by the GALLEN KAMP melting point apparatus and are uncorrected. Elemental analysis was performed using Heraeus CHN–O-Rapid analyzer by Tarbiat Modaress University, Science Research Center, Tehran, Iran. All starting materials and solvents were purified with the proper purification techniques before use.

4.1. X-Ray crystallographic analysis

Diffraction data collections were made on an Enraf–Nonius CAD4 (MULTAN 80) with Mo Kα radiation (λ=0.707 Å) at room temperature (CCDC deposition No. 177106).

4.1.1. Synthesis of *N′*-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy)imidoyl azide (2). This was reported earlier.[45–47]

4.1.2. Synthesis of *N*-2-(1,4-dioxane)-*N′*-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylpheny) isourea (1).[45,48] A solution of (0.33 g, 1 mmol) of azide **2** and dry-peroxide free dioxane (19.5 cc, 225 mmol) was heated in an oil bath (96±1°C) under an atmosphere of nitrogen (dry, oxygen free). At the end of thermolysis (5 h, confirmed by TLC analysis), excess dioxane was removed under reduced pressure to give a white solid. Crystallization from ethanol gave 0.35 g (90% yield) of **1**, mp 139–141°C. IR (KBr, cm^{-1}) 3300, 3050–2850, 1640, 1400, 1310–1200,1150, 1120–1060, 910–810. ^{1}H NMR (δ ppm, $CDCl_3$) 2.4 (s, 3H), 2.45 (s, 3H), 3.55–4.12 (m, 6H), 5.23–5.5 (m, 1H), 7.0 (d, *J*=9 Hz, 2H), 7.22 (d, *J*=9 Hz, 2H), 7.35 (d, *J*=7.8 Hz, 2H), 7.73 (d, *J*=7.8 Hz, 2H), 8.5 (d, *J*=8.0 Hz, br, 1H). ^{13}C NMR (δ ppm, $CDCl_3$, 1-Hdecl.) 21.8, 22.4, 63.7, 67.4, 69.7, 76.6, 122.1, 127.1, 130.2, 130.2, 136.7, 140.2, 143.8, 149.7, 157.6. Elemental analysis calcd for $C_{19}H_{22}N_2O_5S$: C, 58.44; H, 5.67; N, 7.17. Found, C, 58.40; H, 5.60; N, 7.30. Mass spectrum (70 eV): 261 (50), Ts–NH–Tol; 197 (6.9), Ts–N═C═O; 106 (41), TsNH; 0.87 (69.7), $[dioxane]^+$; 43 (20), HN═C═O.

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