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Dynamic ^{1}H-NMR demonstration of anomeric effect and structure: conformational and configurational analysis of *N*-2-(1,4-dioxane)-*N*′-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea

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The conformational and configurational behavior and the structure of *N*-2-(1,4-dioxane)-*N*′-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea (**1**) were studied using dynamic NMR. The *endo*-anomeric effect, hydrogen bonding, temperature, and polarity of solvent control the population of dioxane ring conformers or anomers but not the configuration interconversion of the imine of the imidoyl moiety. Dynamic ^{1}H-NMR, ΔH°, ΔS°, ΔG°, and $\Delta G^\ddagger$ 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.

Key Words: Anomeric effect, dynamic NMR, conformational analysis, configurational analysis, hydrogen bonds, dioxane, aminoimidoyl.

Introduction

The anomeric effect is well recognized as an important factor in defining the predominant conformational state of many cyclic heteroatom-containing compounds. The major area of interest has been the 1,4-dioxanes pharmaceutical activities.[1] The geometry of the conformations of the transition state and/or of the intermediate

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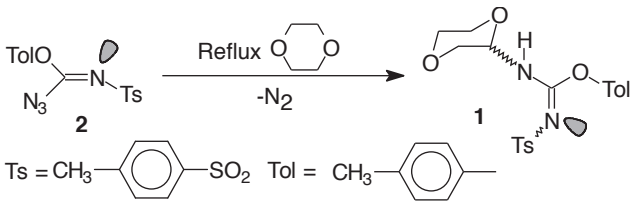
is documented to pre-establish the selectivity of the chemical reactions and/or the stereochemistry of the adducts.[2–4] Since it is entirely conceivable that the pharmaceutical activity is related to the physicochemical properties of the dioxanes, thorough investigation of 1,4-dioxane derivatives was initiated many years ago.[1]

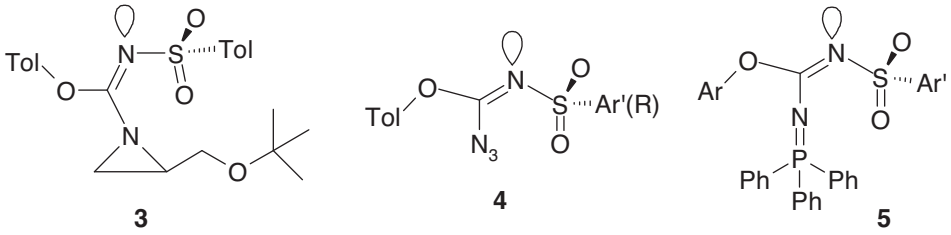
Summerbell and co-workers initiated an investigation of the stereochemistry of 1,4-dioxane derivatives.[5] Hariss and Spragg reported that the NMR spectrum of 1,4-dioxane is apparently temperature-independent and suggested that the barrier for ring inversion of this compound should be lower than that of cyclohexane.[6] Anet and Sandstrom investigated the NMR spectra of 2 diastereomers of hexa-deuteriated dioxane in CCl_2F-CCl_2F at -116 °C and observed 2 well-resolved lines for the chair-chair ring inversion ($\Delta G^{\ddagger}$ = 9.7 kcal/mol).[7] Lemieux et al. reported that the chair-chair equilibrium for 2,6-*cis*-dimethoxy-1,4-dioxane in water favors the diaxial conformer (57%) to a much greater extent than do carbon disulfide (7%) or pyridine (12%).[8] Dynamic conformational and 3-dimensional X-ray analysis of 9,10-bisbromomethyl-1,4,5,8-tetraoxadecalin (4a,8a-bisbromomethylhexahydro-*p*-dioxino)[2,3-b]-*p*-dioxane was undertaken by Fuchs and co-workers. They proved that this tetraoxadecaline has a *cis* configuration and adopts a double chair conformation.[9] Jensen and Neese reported the ring (chair ⇆ twist) inversion barriers ($\Delta G^{\ddagger}$ = 9.2 kcal/mol at –86.0 °C) for *cis*-2,3-dimethyl-1,4-dioxane.[10] Fuchs and co-workers discussed the structure, conformation, gauche, and anomeric effect of the *cis*- and *trans*-2,3-difluoro-1,4-dioxane.[11] They found that trimethylsilyloxy- and *tert*-butoxy-substituted 1,4-dioxanes (in contrast to CH_3O, PhO, and AcO substituents) alleviate the anomeric effect.[12] Dauphin and co-workers studied the conformation and structure of 2- and 8-functionalized 1,4,7,10-tetraoxaspiro[5.5]undecanes and gave the definite structural characterization of *E,E, Z,E,* and *E, Z* isomers.[13] Caminati and co-workers assigned the free jet millimeter wave spectra of the 1:1 complex between 1,4-dioxane and 4 isotopomers of water.[14] They concluded that the water molecule lies in the plane of symmetry of 1,4-dioxane, the water hydrogen involved in the hydrogen bond is axial with respect to the ring, while the "free" hydrogen is *entgegen* to the ring. We synthesized *N*-2-(1,4-dioxane)-*N*'-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea (**1**) and characterized it by ^{1}H-NMR, ^{13}C-NMR, mass spectral analysis, IR, and elemental analysis (Scheme 1).[1] We then studied the structure, conformation of 1,4-dioxane, configuration of the imine group of the imidoyl moiety, and the anomeric effect using X-ray crystallographic analysis.[1] We also reported the dynamic ^{1}H-NMR (500 MHz) study of 2-(*tert-b*utoxymethyl)-1-[N'-(4-methylbenzenesulfonyl) (4-methylphenoxy) imidoyl] aziridine **3** (Scheme 2).[15] The free energy of activations ($\Delta G^{\ddagger}$) is 11.11 kcal/mol (T_c = 238 K) and 11.30 kcal/mol (T_c = 242 K) in acetone-d_6 and chloroform-d, respectively, and is attributed to nitrogen inversion of aziridine ring nitrogen.



Scheme 1

Recently, we initiated the dynamic ^{1}H-NMR (500 MHz) investigation of 4-methylphenoxyimidoyl azides **2** and **4** (4-CH_3-C_6H_4-O-C=N-Y)-N_3, Y = 4-CH_3-C_6H_4-SO_2 (Schemes 1 and 2), 4-Br-C_6H_4-SO_2, C_6H_4-SO_2, CH_3-SO_2, CN, [16,17] and imidoyl iminophosphoranes **5** [18] in acetone-d_6 at a temperature range of

183-298 K. The observed free energy barrier (almost 12 kcal/mol) is attributed to conformational isomerization about the N-S bond for **4** and **5**, and (almost 14 kcal/mol) to configurational isomerization (E/Z) about the C=N bond for Y = CN in **4**.



Scheme 2

The purpose of the present study was to provide evidence that will serve to establish that large imidoyl amino [(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 were to investigate the factors (resonance, hyperconjugation, steric hindrance, hydrogen bonding, polarity of solvent, and temperature) that contribute to this axial preference and the conformations and/or configurations of **1** (Scheme 1). We studied the effect of polarity of solvent and temperature (dynamic ^{1}H-NMR) on the anomeric effect, conformation(s) of 1,4-dioxane, and configuration(s) of the imine group of the imidoyl moiety of **1**. Furthermore, we calculated the standard free energy (ΔG°), enthalpy (ΔH°), the entropy (ΔS°), and free energy of activation ($\Delta G^\ddagger$). We think that this system allows us to shed more light on the phenomenon known as the anomeric effect.

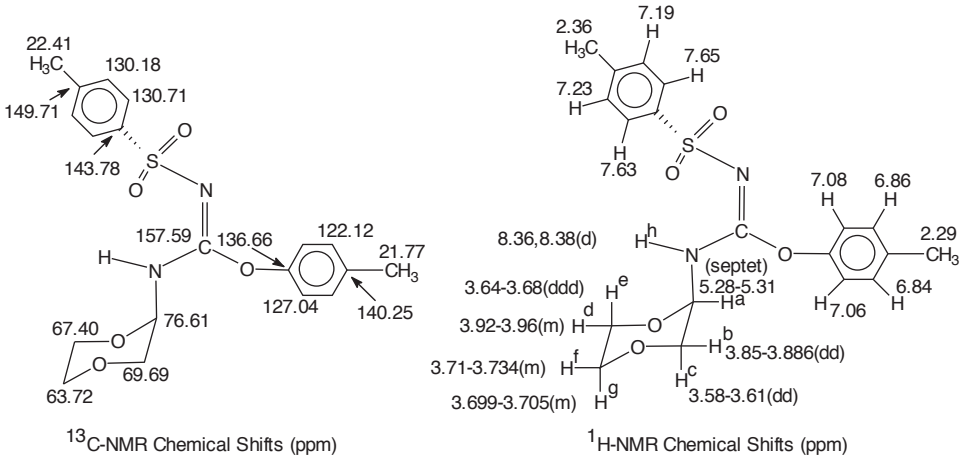
Results and discussion

^{13}C-NMR and ^{1}H-NMR spectroscopic analysis. The exact chemical shift (ppm) (^{13}C-NMR and ^{1}H-NMR) for each nucleus is placed on an appropriate atom of structure **1**. The chemical shift of the dioxane protons was assigned using coupling constants, the COSY-NMR, and the proton decoupling experiments (Scheme 3, Figures 1 and 2).

Dynamic NMR. X-ray established the conformational and configurational analysis of **1** in solid phase.[1] The question raised here is this, what are the effects of solvent polarity and temperature on anomeric effect, conformation, and configuration of **1**? There are 3 major observable movements that should be considered for **1**. The inversion of the dioxane ring and rotations about the N-S and the C=N bonds. The N-S rotation is restricted by strong hydrogen bonding of the O3 with the HN- bond. This energy barrier is almost 12 kcal/mol for the imidoyl azide **2**, **4**, and imidoyl iminophosphoranes **5**. The strong C=N of the amino imidoyl group [with a higher energy barrier similar to aziridine **3**, ($\Delta G^\ddagger > 24$ kcal/mol), Scheme 2] shows less tendency to isomerize.[1,15–18]

The axial-equatorial interconversion of dioxane is what we observe by ^{1}H-NMR. In fact, in solution and/or at higher temperatures both isomers are in equilibrium. Similar behavior was observed for 2,5-di-*tert*-butoxy-1,4-dioxane. In this case, X-ray shows 100% diaxial but in chloroform-d 23% equatorial conformer was calculated by NMR.[12] Generally, all 6 member heterocyclic compounds including the dioxane derivatives were

reported to have a chair conformation.[12,19−25] Generally the chair conformation is confirmed in solid phase by X-ray but in solution by R value.[26,27] The R value can be calculated using coupling constants (J) (Eq. 1) or dihedral angles (Eq. 2).



$J_{ah} = 8.5, J_{ab} = J_{ba} \cong 4.8, J_{bc} = J_{gem} = 11.6, J_{ca} = J_{ac} = 2.5,$

$J_{de} = J_{gem} = 11.3, J_{dg} = J_{gd} = 3.5, J_{df} = J_{fd} = 5.6, J_{ef} = J_{fe} = 3.7$

Scheme 3

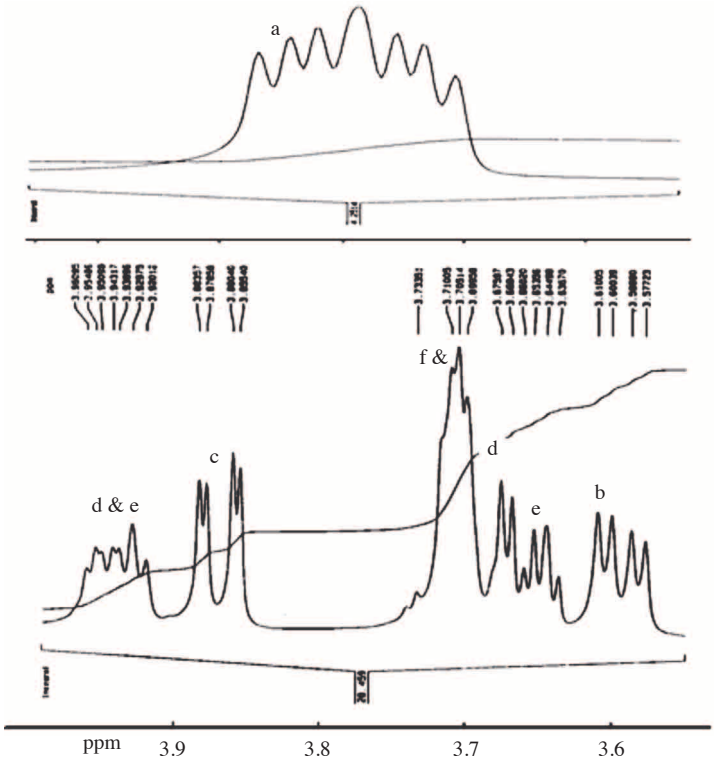


Figure 1. Dioxane portion (for peak assignment see Scheme 3) of ^{1}H-NMR (500 MHz) spectra of **1** in $CDCl_3$ at 300 K.

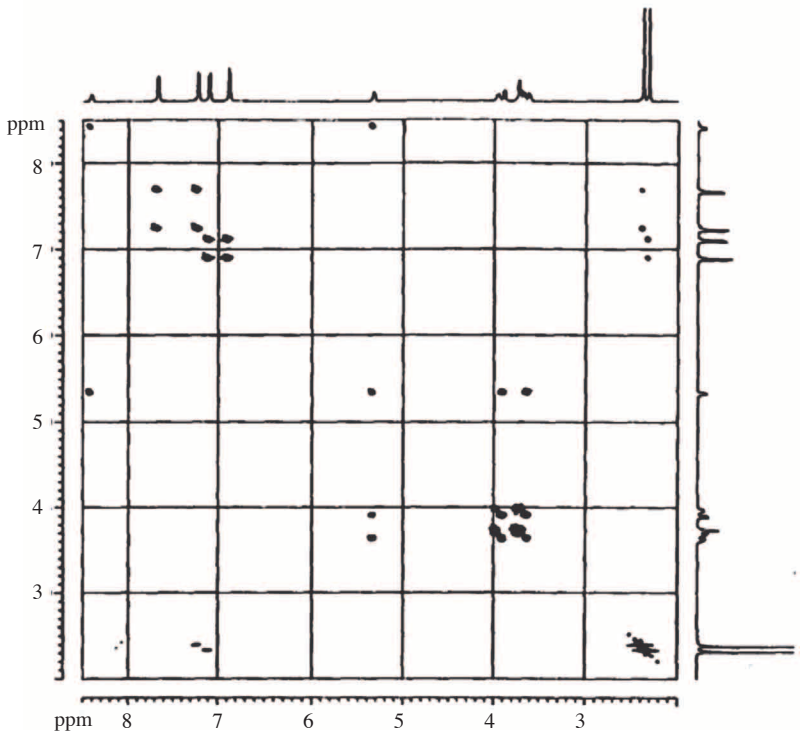


Figure 2. The COSY-NMR (500 MHz) spectrum of **1** in $CDCl_3$ at 300 K.

$$R = J_{\text{trans}}/J_{cis} = 1/2(J_{aa} + J_{ee})/1/2(J_{ae} + J_{ea}) = (J_{aa} + J_{ee})/2J_{ae} \tag{1}$$

$$\cos\psi = (3/2 + 4R)^{1/2} \tag{2}$$

A typical chair conformation has an R value equal to 1.9-2.2. R values less than 1.8 indicate a flattened chair, R values larger than 2.3 indicate a puckered chair.[11,12,19,26–29] In this investigation, the R-value was calculated using coupling constants ($^3J_{HH}$) (^{1}H-NMR in chloroform-d at room temperature (Figure 1) Eqs. 3 and 4). The ^{1}H-NMR signals for dioxane protons overlap in DMSO-d_6 and acetone-d_6 (Figures 4 and 5). This is acceptable because in more polar solvents the rate of axial-equatorial interconversion is faster.

The calculated R value and dihedral angles for –CH_2-CHNHG- are equal to 1.934 and 56.3°, respectively (Eqs. 1 and 2). This confirms the chair conformation for 1,4-dioxane of **1** in solution.[11,12,19,20,26–29]

$$J_{ab} = J_{\text{trans}} = X_{ax.ax}J_{ax.ax} + (1 - X_{ax.ax})J_{eq.eq} = 4.8Hz \tag{3}$$

$$J_{ac} = J_{cis} = X_{ax.eq}J_{ax.eq} + (1 - X_{ax.eq})J_{eq.ax} = 2.5Hz \tag{4}$$

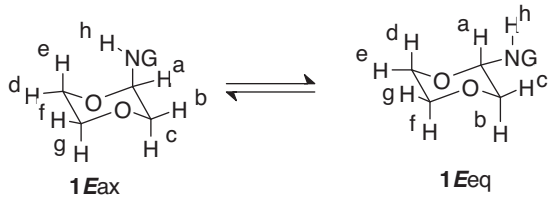
Chemical shifts and coupling constants in ^{1}H- and ^{13}C-NMR spectra have been used extensively to detect the axial/equatorial location of protons and substituents in cyclohexanes and heterocycles and also the anomeric effect.[8–36]

The ^{13}C-NMR (125 MHz) and ^{1}H-NMR (500 MHz) spectra of **1** show only 1 set of peaks per carbon. This means that either 2 isomers equilibrate very fast (related to the time scale of NMR) or there is only 1 isomer.

The coupling constants $^3J_{HH}$ (see below) proved that the former is true. In both saturated and unsaturated systems a decrease in the vicinal coupling is observed when an electronegative substituent is introduced at the H-C-C-H moiety.[31−36] For example $^3J_{HH}$ in the CH_2-CH-NHG fragment of **1** should be less than $^3J_{HH}$ in the CH_2-CH_2 fragment. As observed the coupling constants ($^3J_{HH}$) 5.6 Hz and 3.5 Hz in the CH_2-CH_2 fragment are larger than 4.8 Hz and 2.5 Hz in the CH_2-CH-NHG fragment.

Furthermore, the steric orientation of the substituent in the H-C-C-H moiety is also of significance. It has been provided in cyclohexanes and heterocycles that if 1 of the 2 coupled protons is antiperiplanar to electronegative atoms or groups such as the halogen or –OR group the coupling constant is diminished by 1-2 Hz below the normal value.[30−36] Then when 1 of the 2 protons of CH_2 in the CH_2-CH-NHG fragment is antiperiplanar to NHG the coupling constant should be about 1-2 Hz less than the same one in the CH_2-CH_2 fragment.

Now, if we assume that only the axial conformer $\mathbf{1}\boldsymbol{E}_{ax}$ exists in chloroform, then the $J_{ab} = J_{eqeq}$ should be near 1-2 Hz and the $J_{ac} = J_{eqax}$ should be less than the normal value of 2-3 (e.g. 1-2 Hz), because H^c holds an anti position to the HNG- group.[30−36] In other words, the axial conformer ($\mathbf{1}\boldsymbol{E}_{ax}$) co-exists in solution with equatorial (i.e. $J_{cis} = 2.5$ Hz and $J_{trans} = 4.8$ Hz, Eqs. 3 and 4 (Scheme 4)).



Scheme 4

Now, let us assume that only the $\mathbf{1}\boldsymbol{E}_{eq}$ exists in chloroform; then the $J_{ab} = J_{axax}$ should be equal to 7-12 Hz, but such a coupling constant was not observed. This again indicates that both conformers are in equilibrium ($\mathbf{1}\boldsymbol{E}_{ax} \leftrightarrows \mathbf{1}\boldsymbol{E}_{eq}$). With the same conclusion we have $J_{trans} = 5.6$ Hz and $J_{cis} = 3.5$ Hz for CH_2-CH_2 protons. Similar coupling constants have been reported for tetrahydropyrans and 1,4-dioxanes.[8,12,19,20−25,37−47] We would not observe these coupling constants if **1** assumed a nonchair confromation.

Calculation of ΔG°, ΔH°, and ΔS° for the ring inversion of 1. If we assume that the conformational energy barrier of **1** is similar to 2-alkoxy-1,4-dioxane,[12,19,25,28] then using the coupling constants $J_{eqeq} = 1.2$ Hz and $J_{axax} = 7.7$ Hz (for the –CH_2-CHOR) and having the J_{trans} at different temperatures for **1** the molar fraction of each conformer can be calculated using Eqs. 3 (Table 1) (assuming that J_{eqeq} and J_{axax} do not change at different temperatures).[12,19] The equilibrium constant and the free energy change can be calculated from the molar fraction. The slope of the line of the plot of ΔG° versus temperature gives ΔS° = 2.42 ± 0.56 cal/mol K. Extrapolation of the line gives ΔH° = 602 ± 167 cal/mol (Figure 3 and Table 1). The conclusion, concerning a dominant change in entropy with little change in enthalpy, reflected specific solvation effects.

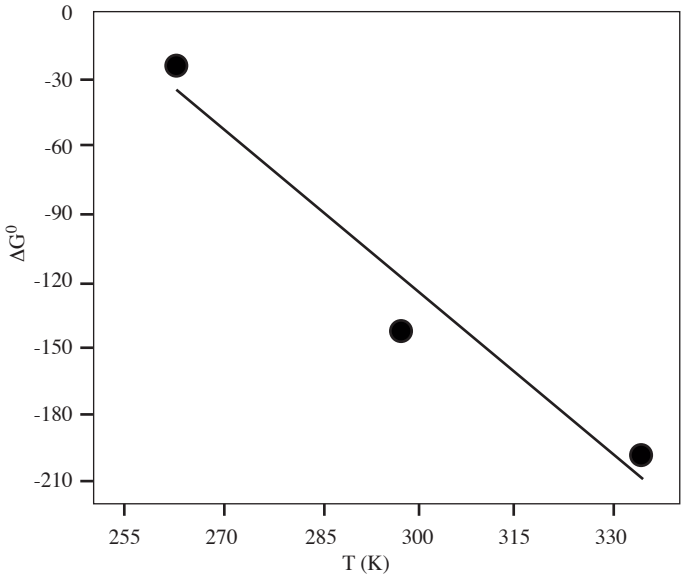


Figure 3. Plot of ΔG° vs. temperature for isourea **1** in chloroform-d (r = 0.99).

Table 1. Coupling constants (J_{trans})^a, molar Fraction (X), equilibrium constants (K), the free energy change for (**1***E*$_{ax}$ $\leftrightarrows$ **1***E*$_{eq}$) in chloroform-d.

T (K)	J_{trans}	X_{eq}	X_{ax}	$K(X_{eq}/X_{ax})$	ΔG^o (cal/mol)
263	4.52	0.51	0.49	1.05	-23.01
298	4.84	0.56	0.44	1.27	-142.87
335	4.93	0.57	0.43	1.35	-198.18

^{a} Calculated by ^{1}H-NMR (500 MHz)

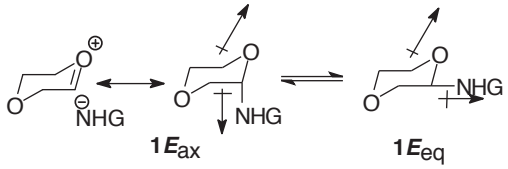
In cyclic systems, entropy of axial isomer usually is about 2.18 cal mol^{-1}k^{-1} less than that of equatorial isomer because a number of equatorial isomers are 3 times axial isomers ($\Delta S^o = RLn3$). This value is equal to the experimental value. As a result, the solvation effect of $CHCl_3$ must be equal in the 2 isomers (see next section).

Conformational analysis of **1** was studied by AM1, PM3, and DFT.[48] The most stable isomer was the same as the X-ray and it was 5.3 kcal mol^{-1} more stable than the equatorial. This indicates that the solvation effect of $CHCl_3$ must be equal for the 2 isomers (see next section).

These values complement the X-ray findings[1] and demonstrate that the *endo*-anomeric effect is more important than the *exo*-anomeric effect.[30] The intramolecular hydrogen bonding makes N2-C3 bond more sp^2. Therefore, the imidoyl group (GNH) acts as an electron-withdrawing group (Scheme 5). Similarly, with compounds such as 2-methylaminotetrahydropyran,[21,30,44] 2-aminotetrahydropyran,[49] and 2,5-diisopropylamino-1,4-dioxane[50] the *exo*-anomeric effect is more important due to the electron donating ability of the amino group.

Solvent effect. The ^{1}H-NMR of **1** was studied in 3 solvents (chloroform-d, acetone–d_6 and dimethyl sulfoxide-d_6). The effect of solvent polarity on chemical shifts and the coupling constants of the protons of

the dioxane ring are depicted in Figures 4 and 5. The aromatic region of **1** is not affected by the polarity of solvent at the temperature range (200-360 K). Therefore, the rotations of the S-N and C=N bond in solution are restricted in a way similar to the solid phase (X-ray). In other words, the configuration of the imidoyl group (*E*-isomer) does not inter-convert with *Z*-isomer.



Scheme 5

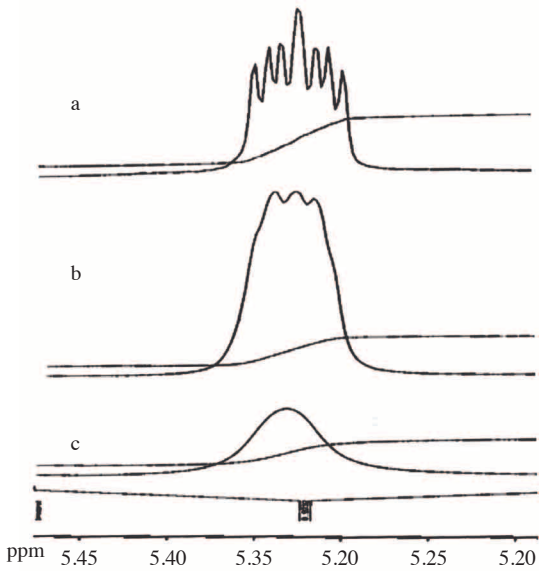


Figure 4. The effect of solvent polarity (a) chloroform-d (b) acetone-d_6 (c) dimethyl sulfoxide-d_6 on the coupling constants of anomeric CH of **1** at room temperature.

Generally, the equatorial conformers of the heterocyclic compounds have higher dipole moments than the axial conformer; therefore, the former conformer population is higher in hydrogen bonding solvents ($CHCl_3$) or polar ones (Scheme 5). The dioxane ring protons, GNH chemical shifts, and the coupling constants of **1** were broadened in dimethyl sulfoxide or acetone as discussed earlier. The experimental and theoretical values for ΔS° are similar in chloroform-d. The experimental ΔH^o is much lower than the theoretical values.[48] This indicates that the axial and equatorial conformers must solvate equally in chloroform-d. However, when the dipole moment for both conformers was the same, the direction of equilibrium would shift. This means that the more polar solvent favors the axial conformer, i.e. polar solvents actually enhance the *endo*-anomeric effect as one could expect from resonance structures $\mathbf{1}_{ax-1} \leftrightarrow \mathbf{1}_{ax-2}$ (Scheme 6).[25] The average dipole moments for axial conformer (6.204 D) calculated by AM1 is almost equal to the equatorial value (6.265 D).[48] There is stronger hydrogen bonding between chloroform and the negative charge on the nitrogen of $\mathbf{1}_{ax-1}$ than the charge on the oxygen of $\mathbf{1}_{eq}$, which should favor the axial conformer (this is observed by NMR) (Scheme 6 and Figure 6).

This is why the experimental ΔH° value is much lower than the theoretical value. On the other hand, entropy of equatorial isomer must decrease ($\Delta\Delta S^\circ < 0$, when releasing the solvent) at the time the equatorial isomer passes to the axial form. Indeed, since the endo-anomeric effect is not operating for the equatorial isomer ($\mathbf{1}_{eq}$), the endocyclic oxygen should be especially electron-rich and prone to solvation by hydrogen bonding solvents. However, chloroform forms a stronger hydrogen bond with the negative charge on the nitrogen of $\mathbf{1}_{ax-1}$, which could solvate equatorial-axial isomers equally. This is why theoretical and experimental $\Delta\Delta S^\circ$ values are equal.

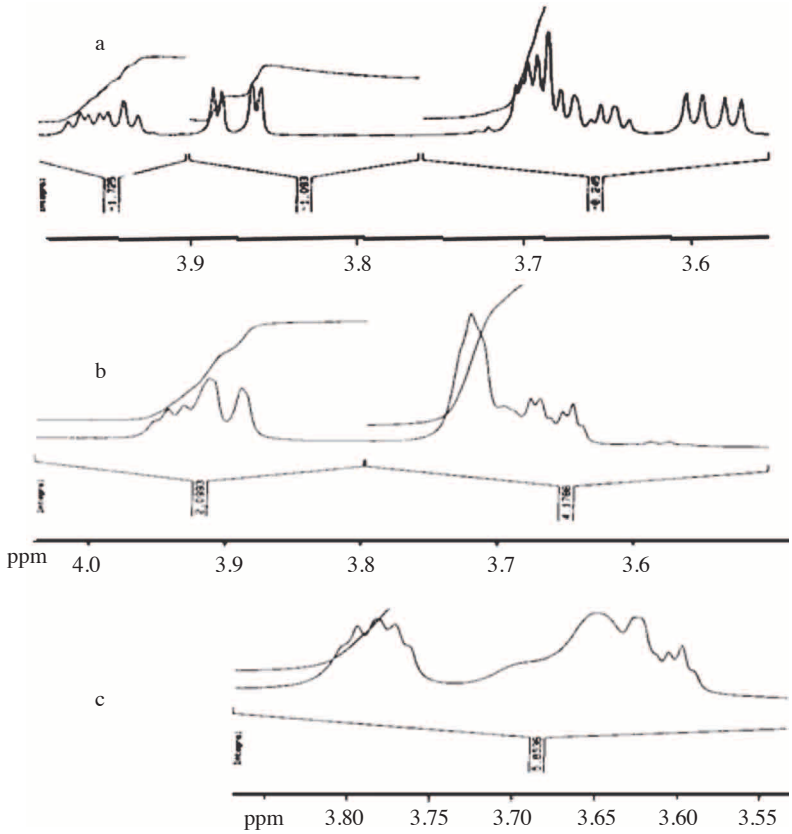
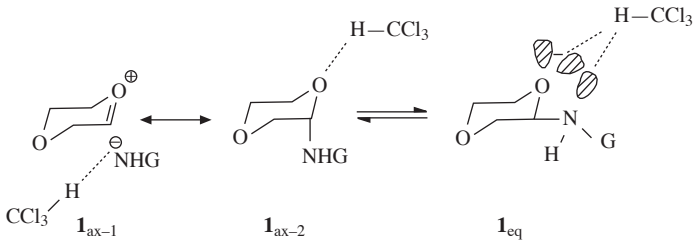


Figure 5. The effect of solvent polarity (a) chloroform-d (b) acetone-d$_6$ (c) dimethyl sulfoxide-d$_6$ on the chemical shifts and coupling constants of the dioxane protons of **1** at room temperature.



Scheme 6

Evaluation of temperature effect. The next step was to investigate the effect of temperature on conformations of dioxane ring and configuration of imine of the imidoyl group of **1** by ^{1}H-NMR in chloroform-d, acetone–d$_6$ (Figures 6), and dimethyl sulfoxide-d$_6$. In all 3 solvents, peak broadening of signals of the dioxane

ring and GNH protons were observed at decreasing temperatures. This could be due to slow interconversion of axial $\leftrightarrows$ equatorial and/or all other possible dioxane conformers (chair $\leftrightarrows$ half-chair $\leftrightarrows$ boat $\leftrightarrows$ twist-chair). In other words, at lower temperatures a combination of conformers is observed by NMR. The configuration of the imidoyl (E-isomer $\leftrightarrows Z-$isomer) of **1** did not inter-convert at the temperature range of this investigation (200-360 K).

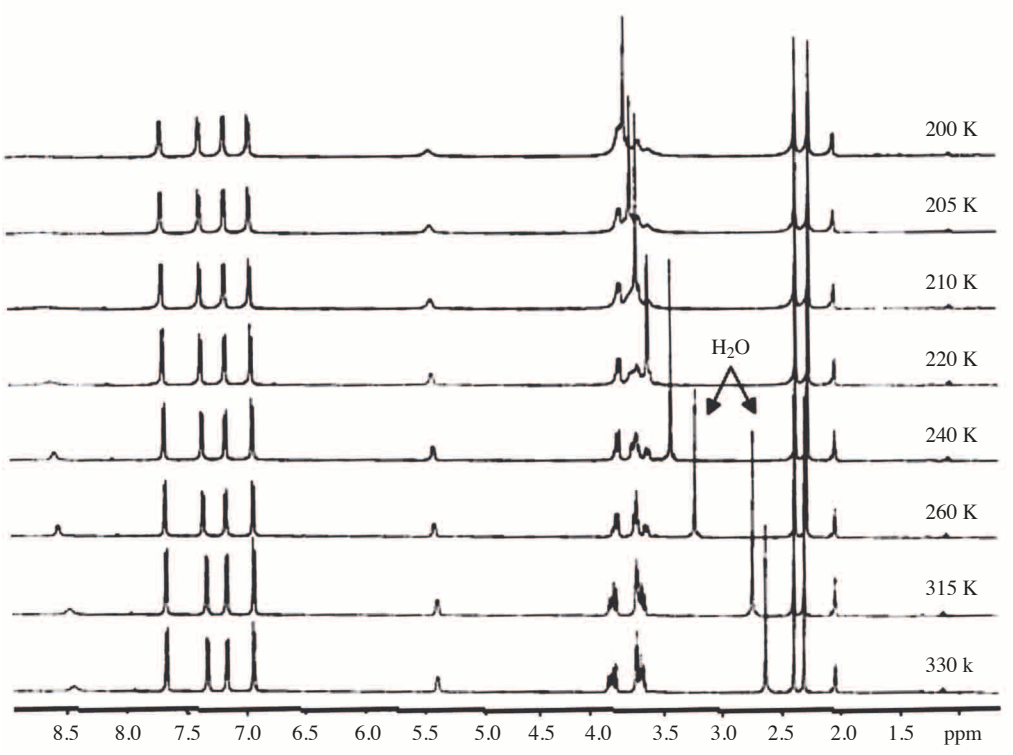


Figure 6. Temperature dependence of the ^{1}H-NMR (500 MHz) of **1** in acetone-d$_6$.

Calculation of $\Delta G^{\ddagger}$ for the dioxane ring inversion of 1. The energy of activation for the interconversion of conformational and/or configurational isomers could be calculated at coalescence temperature using Gutowsky-Holm and Eyring equations.[15−18] The coalescence temperature for **1** was much lower than anticipated due to the locked conformation and configuration as a result of the anomeric effect and hydrogen bonding. All attempts to reach the coalescence temperature failed at the temperature range 200-360 K. Dynamic NMR below 200 K could not be carried out due to the low solubility of **1** in proper NMR solvents.

The calculated free energy of activation for 1,4-dioxane ring inversion is reported to be 9.2-10.3 kcal/mol (e.g. $\Delta G^{\ddagger}$ = 9.7 kcal/mol).[7,10,11,48] It is also reported that the anomeric effect reduces this value by about 1.4-2.1 kcal/mol.[30] The energy for the ring inversion for substituted 1,4-dioxanes is anticipated to be near 8-9 kcal/mol. For example, *cis*-2,3-di-*tert*-butoxy-1,4-dioxane has $\Delta G^{\ddagger}$ equal to 9.15 kcal/mol (at 195 K).[12] On this account, the energy for the ring inversion of **1** is estimated to be 8-9 kcal/mol. However, the strong hydrogen bonds would stabilize the axial conformer (1 kcal/mol, calculated by AM1)[48] and therefore increase the energy for the ring inversion.

Conclusions

The anomeric effect (negative hypercojugative effect) plays the major role in the axial preference in solid phase or in non-polar solvent. The axial-chair conformation of the dioxane ring is preferred in solid phase or in chloroform. Other conformations compete in more polar solvents (dimethyl sulfoxide-d_6 and acetone-d_6) and/or at higher temperature. Temperature and solvent polarity influence the equilibrium between the axial and equatorial conformers and the interconversion of dioxane ring conformers. Similar trends are observed at lower temperatures and higher polarity of the solvents. The configuration of the imidoyl (E-isomer $\leftrightarrows Z-$isomer) did not interconvert in polar solvents and/or at the temperature range in our investigation (200-360 K). The steric hindrance plays a minor role in the reverse anomeric effect. The *endo*-anomeric effect and hydrogen bonding are responsible for the locked axial conformations and configurations of **1** in solid phase or in non-polar solvents.

Experimental section

Synthesis of N-2-(1,4-dioxane)-N'-(p-methylbenzenesulfonyl)-O-(p-methylpheny) isourea 1, N'-(p-methylbenzenesulfonyl)-O-(p-methylphenoxy)imidoyl azide **2** and **4**, 2-(*tert-b*utoxymethyl)-1-[N'-(4-methylbenzenesulfonyl) (4-methylphenoxy)imidoyl] aziridine **3**, and imidoyl iminophosphoranes **5** was reported earlier.[15–18]

Acknowledgements

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