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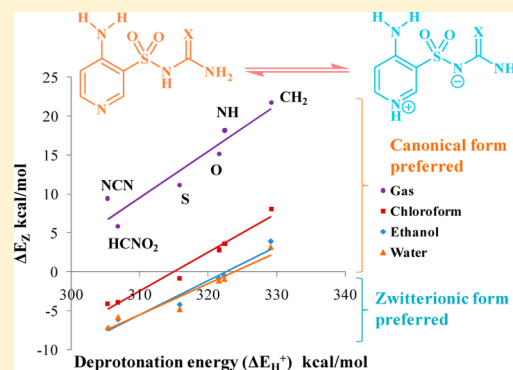
On the Stability of Zwitterions of Pyridine Sulfonylureas: The Effect of Isosterism, Acidity, and Microsolvation

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Supporting Information

ABSTRACT: Pyridine sulfonylureas (PSUs) are known to exist in zwitterionic form in the solid phase. For example, torsemide, a diuretic drug, exists in three polymorphic forms: two of them in the zwitterionic state and one in the “partial zwitterionic” state. Initial computational analysis showed that the energy difference between the canonical and the zwitterionic states of a model PSU is very large in the gas phase (~15 kcal/mol), thus disfavoring the zwitterionic state. In order to understand the apparent dichotomy on the preferred state of PSUs, extensive computational analysis using density functional theory was taken up on a few analogues of PSU. The zwitterionic isomer was less stable than the canonical form in the model PSU, 4-amino-pyridyl-3-sulfonylurea. However, under implicit polar solvent conditions, the zwitterionic and the canonical forms of the model PSU were nearly isoenergetic. Furthermore, microsolvation calculations showed that the zwitterionic model of torsemide is thermodynamically more favorable over the canonical form in the presence of seven water molecules. A combined microsolvation-continuum solvent model showed that the zwitterionic form starts to dominate the canonical form under the influence of four water molecules. Analysis on the intramolecular interactions, the partial atomic charges, the conformational and tautomeric preferences was also carried out, which enabled the rationalization of the formation of stable zwitterionic species in PSUs.



1. INTRODUCTION

Zwitterion is a charge-separated form of a molecule with a net zero formal charge. Molecules containing both acidic and basic functional groups tend to form zwitterions.^{1–3} Some molecules, such as the 12 π -electron quinonoid system and 1-methylpyridinium-3,5-dicarboxylic acid, are intrinsically stable in their zwitterionic form in the gas phase.^{4–7} Several experimental and theoretical studies have been conducted to improve the stability of zwitterions with the ultimate goal of applying the knowledge gained in biological studies.^{8–11} Most of the studies on the zwitterionic stabilization reported have been on amino acids. Apart from the amino acids, many drug molecules are known to exist in zwitterionic states, and in some cases, the origin of the drug action has been attributed to the zwitterionic character.^{12–14} Computational studies have been reported on the zwitterionic states of only a few therapeutically important species.^{15,16} In this article, we report quantum chemical studies on a therapeutically important scaffold of pyridine-3-sulfonylurea (PSU) to explore the origin of zwitterionic states in the PSU-based structural entities.

PSU and its derivatives are known for their extensive pharmaceutical applications,¹⁷ for example, torsemide (Figure 1), belongs to the class of loop diuretics.^{18,19} It is used in the management of hypertension and edema in patients with congestive heart failure, liver failure, and renal insufficiency.²⁰ Several derivatives of PSU with distinct therapeutic effects have

been reported (Figure 1).^{21–28} Dupont et al.²⁹ reported two different polymorphic crystal structures of torsemide and established their structural differences using X-ray diffraction. Both of these polymorphic forms adopted the zwitterionic arrangement (Scheme 1). A proton from the sulfonamide ($-\text{SO}_2\text{NH}-$) moiety of torsemide when transferred to the pyridine residue, leads to the formation of the corresponding zwitterion. Danilovski et al.³⁰ described a new polymorphic form of torsemide T–N, which was also reported to exist in the zwitterionic state, and that fact was reconfirmed by redetermining the crystal structure at low temperature.³¹ The crystal structures of several other PSU derivatives and their analogues (thio-, nitroethylene- and cyanoguanidine- bioisosteres) have also been reported, and the structures revealed that the pyridine unit in these systems is protonated.^{21,32–34} The foregoing observations indicate that the zwitterionic state is perhaps the preferred state of the PSUs in solid state. However, the gas phase quantum chemical analysis showed that the zwitterionic state is energetically less favorable than the canonical form in PSU by as much as 13.54 kcal/mol.³¹ Calculations in implicit solvent conditions, on the other hand, revealed a significant reduced energy difference between the

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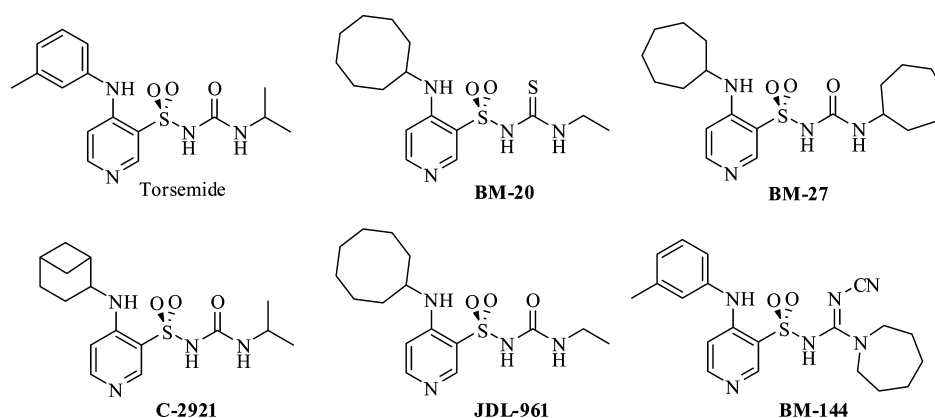
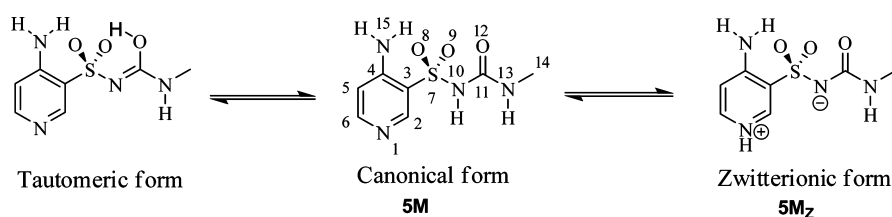


Figure 1. Several medicinally important pyridine-3-sulfonylurea derivatives.

Scheme 1. Prototropic Equilibrium in Model Pyridine Sulfonylurea (PSU)



isomers, and led to the conclusion that the zwitterionic state is probably stable in polar media as well as in the solid state.³¹

In the above studies, although the conformations of various Py-SO₂-NH-R and Py-SO₂-NH-C(X)-NH-R, (X = NH, O, S, HC-NO₂, N-CN) derivatives have been subjected to detailed analysis, the origin of the stability of the zwitterionic state of these species was not addressed. Our group has been involved in the estimation of conformational and tautomeric preferences of aminoguanidines,³⁵ biguanides,³⁶ guanylthiouraeas,³⁷ sulfonylureas,³⁸ benzimidazole carbamates,³⁹ nitroethenediamines,⁴⁰ bicalutamide,⁴¹ and so forth, and established the importance of the alternative states in explaining their therapeutic action. This current study is a continuation of our efforts in the direction of identifying the stable form of drugs/leads in nonconventional states. The specific questions addressed in this work are as follows: (i) Which structural features of the PSUs lead to the observed preference for the zwitterionic state? (ii) How does acidity of the PSU analogs get modulated as a function of substituents? (iii) What is the effect of microsolvation in stabilizing the zwitterionic state of a PSU? (iv) What are the conformational and tautomeric preferences of PSUs?

2. COMPUTATIONAL METHODS

Ab initio molecular orbital (MO)^{42,43} and density functional theory (DFT)^{44,45} calculations were carried out using the GAUSSIAN03⁴⁶ software package. Complete optimization, of various conformations, tautomers and zwitterionic states, was carried out using B3LYP (Becke3, Lee, Yang, Parr) and MP2 (Moller-Plesset perturbation) methods with 6-31+G(d,p) basis set. Further optimizations were performed at B3LYP/6-311+G(d,p) level of theory to see the effect of basis set on the geometries and energetics. For all the optimized structures, frequencies were computed analytically to characterize stationary points as minima or transition states, and also to estimate zero point vibrational energies (ZPE). To account for

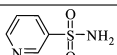
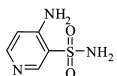
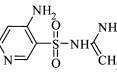
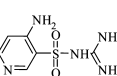
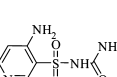
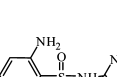
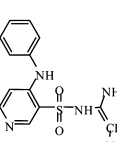
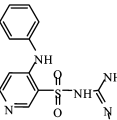
the “long-range” dispersion correction on the stabilities of the isomers, calculations were performed using ω B97XD functional.⁴⁷ In addition, calculations were also carried out using a new hybrid meta exchange-correlation functional M06-2X, which includes “medium-range” electron correlation.⁴⁸ The calculations based on M06-2X and ω B97XD methods were carried out using the GAUSSIAN09 software package. Proton affinities and deprotonation energies were estimated to confirm the basicity and acidity of the molecules. Solvent phase optimizations were carried out using the conductor-like polarizable continuum model⁴⁹ (CPCM, using RMIN = 0.5, OFAC = 0.8) at the B3LYP/6-31+G(d,p) level to understand the influence of the solvent medium. The default cavity was modified by adding individual spheres to all hydrogen atoms linked to nitrogen and oxygen atoms, using the keyword SPHEREONH. The NBO (natural bond orbital)^{50,51} analysis was employed to estimate the second-order interactions and partial atomic charges. The energy data and the geometric parameters reported were obtained at B3LYP/6-31+G(d,p), unless otherwise specifically mentioned.

3. RESULTS AND DISCUSSION

The results in this work are presented in three sections: (i) the neutral \rightleftharpoons zwitterion equilibrium in Py-SO₂NH-R and Py-SO₂-NH-C(X)-NH-R, (ii) the effect of microsolvation on the relative stabilities of the canonical and zwitterionic forms, and (iii) analysis of the conformational preferences and the ease of amide-iminol tautomerism in PSUs.

3.1. Neutral \rightleftharpoons Zwitterion Equilibrium. Compounds 1–8 (Table 1) are model systems of PSU and their medicinally important analogues. For example, 4-amino-pyridyl-3-sulfonylurea (5) is directly related to PSU, while compounds 1–4 are simpler analogues of 5 and compounds 6–8 are extended analogues of PSU that carry functional units of important lead compounds. Table 1 presents the ΔE_z values (energy difference between the canonical and the zwitterionic forms) estimated

Table 1. Different Analogues of Pyridine Sulfonylurea, Energy Difference of Corresponding Zwitterionic State with Normal Molecule (ΔE_Z) and Deprotonation Energy (ΔE_{H^+}) as well as Donor–Acceptor NBO along with Second-Order Energy ($E^{(2)}$) (in kcal/mol)^a

Structure	ΔE_Z								(ΔE_{H+})	Donor-acceptor NBO of zwitterion ^e	$E^{(2)}$
	Gas phase $\Delta E_Z(g)$					Solvent phase ^d					
	B3LYP ^b	B3LYP ^c	M06-2X ^c	ω B97XD ^c	MP2 ^b	$\Delta E_Z(w)$ Water	Ethanol	Chloroform			
1 	39.24	39.24	42.13	41.22	41.94	13.35	13.60	19.66	336.94	--	--
2 	27.63	27.43	29.97	29.26	30.45	7.10	8.19	12.58	336.61		
3 	21.75	21.76	23.82	23.38	24.12	3.13	3.93	8.04	329.16	$n_{N13} \rightarrow \pi^*_{CX}$	24.63
										$n_{N10} \rightarrow \sigma^*_{CX}$	9.27
4 	18.18	19.03	20.20	19.64	19.49	-0.94	-0.51	3.59	322.37	$n_{N13} \rightarrow \pi^*_{CX}$	30.89
										$n_{N10} \rightarrow \sigma^*_{CX}$	11.75
5 	15.16	15.28	16.21	15.99	16.50	-1.17	-0.86	2.37	321.57	$n_{N13} \rightarrow \pi^*_{CX}$	39.12
										$n_{N10} \rightarrow \sigma^*_{CX}$	12.70
6 	11.16	11.06	12.19	11.34	13.56	-4.82	-4.23	-0.83	315.84	$n_{N13} \rightarrow \pi^*_{C11-N10}$ $n_{N10} \rightarrow \sigma^*_{CX}$	62.60 13.38
7 	9.46	10.29	10.07	9.42	--	-7.18	-7.30	-4.05	305.34	$n_{N13} \rightarrow \pi^*_{CX}$	55.14
										$n_{N10} \rightarrow \pi^*_{CX}$	66.22
										$n_{N10} \rightarrow \sigma^*_{CX}$	9.20
										$n_{N10} \rightarrow \sigma^*_{S7-O8}$	10.84
										$n_{N10} \rightarrow \sigma^*_{S7-C3}$	18.87
8 	5.88	5.99	6.33	5.74	6.09	-5.82	-5.33	-2.96	306.81	$n_{N13} \rightarrow \pi^*_{CX}$	56.93
										$n_{N12} \rightarrow \pi^*_{C=N}$	19.12
										$n_{N=C} \rightarrow \pi^*_{C=N12}$	17.20
										$n_{N12} \rightarrow \sigma^*_{C11-N13}$	13.67
										$n_{N10} \rightarrow \sigma^*_{CX}$	10.75

^aAll energies (ΔE_Z and ΔE_{H^+}) are corrected for zero-point vibrational energy. ^bBasis set 6-31+G(d,p) is used for optimizations. ^cBasis set 6-311+G(d,p) is used for optimizations. ^dImplicit solvent analysis using CPCM method, and ϵ values are 78.35, 24.85, and 4.71 for water, ethanol and chloroform, respectively. ^eX = CH₂, NH, O, S, CH-NO₂, N-C≡N in 3, 4, 5, 6, 7 and 8, respectively.

for compounds 1–8 at various theoretical levels. As can be seen, in the gas phase, the ΔE_Z value for compound 5 is in the range of 15–17 kcal/mol, indicating lack of any preference for the zwitterion (SZ). The choice of the quantum chemical methods does not influence the ΔE_Z values. Under solvent conditions, the zwitterionic form is marginally more preferred in polar media (~1 kcal/mol); however, with a decrease in the dielectric constant of the medium, it gradually loses its prominence. The energy required for the loss of a proton (ΔE_{H^+}) in compound 5 is 321.57 kcal/mol, which indicates that PSUs are quite acidic at the N¹⁰ center, adjacent to the sulfur atom (the ΔE_{H^+} in 5 is lower than that of acetic acid, 332.66 kcal/mol). The proton affinity of the pyridine ring in compound 5 is 223.47 kcal/mol (see Supporting Information Table S1), which is greater than that of compound 1 (207.93 kcal/mol). This data indicates that the increased acidity at N¹⁰ center is noticeable in PSU analogues 1–8, and this factor facilitates the formation of zwitterions in PSUs (Figure 2). In

compounds 1–8, a gradual decrease in the ΔE_Z values is noted in both the gas and solvent phase conditions. The second order delocalization increases significantly in compounds 3–8, which facilitates a gradual increase in the acidity at the –SO₂NH– center in these systems. Introduction of an NH₂ group at the C⁴ position in 1 allows intramolecular hydrogen bond formation in the system, and decreases the ΔE_Z value, while at the same time causing an increase in the proton affinity at the pyridyl nitrogen center. Similarly, introduction of electron delocalization centers at the nitrogen atom of the –SO₂NH₂ group in compound 1 increases the acidity at the N¹⁰ atom and the electron delocalization from N atom, while decreasing ΔE_Z values, thus facilitating the formation of zwitterions. It should be noted that the energy differences ($\Delta E_Z(g)$) between the canonical and zwitterionic structures 3Z–6Z (21.75, 18.18, 15.16, and 11.16 kcal/mol, respectively) decrease with an increase in the electronic delocalization in these zwitterions. In 5, all the electronic factors are ideally suited to provide almost

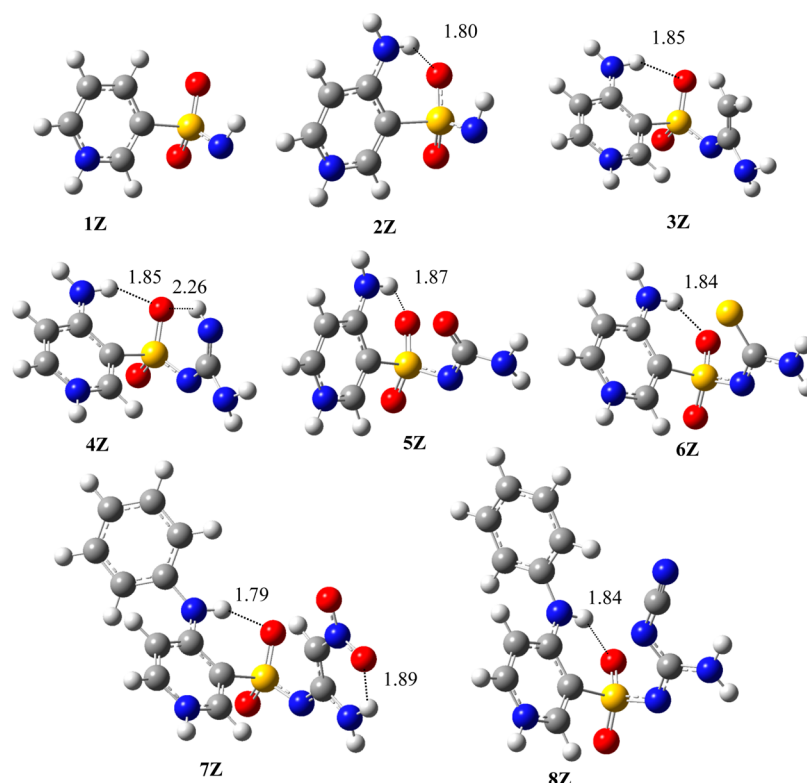


Figure 2. B3LYP/6-31+G(d,p) optimized geometries of 1Z to 8Z zwitterionic structures of 1–8. (Intramolecular hydrogen bonding distances (Å) are shown as dashed lines.)

isoenergetic status between the canonical and the zwitterionic forms under polar solvent conditions. Zwitterions (7Z and 8Z) are characterized by the presence of an extensive conjugation in these molecules, facilitating the formation of highly stable zwitterionic states in polar media. Analysis of this data reveals that the sulfonylurea moiety promotes extensive delocalization, and therefore $\Delta E_Z(g)$ decreases in the order $3 > 4 > 5 > 6$. In 7 and 8, the presence of electron withdrawing groups further increases delocalization, consequently making the $-\text{SO}_2\text{NH}-$ moiety sufficiently acidic to form stable zwitterions with ease.

None of the derivatives of compound 1 and 2 showed the presence of zwitterion in their related crystal structures (CSD refcode: VETVEV, WUYQAJ, WAMMUD, WAMNAK, etc.).^{52–55} However, in the crystal structures of derivatives of 4 and 5, the zwitterionic state is noted in the solid state (CSD refcode: TORSEM02, TORSEM03, TORSEM04, VOBNEF, QOVDUB, etc.). More importantly, all the crystal structures of derivatives of compounds 6, 7, and 8 clearly show the presence of only zwitterionic structure (WINWOF, GIQRUT, etc.).^{21,33,34} Thus, as moving from compound 1 to compound 8, the preference for the formation of a zwitterionic structure increases.

The proton affinity of the molecules at the pyridyl nitrogen center in compounds 2 to 8 is in the range of 219 to 223 kcal/mol, indicating that the proton accepting ability of these systems is not significantly different (see Supporting Information, Table S1). On the other hand, the deprotonation energies originating from $\text{N}^{10}-\text{H}$ bond vary between 305 and 337 kcal/mol (Table 1), and cause significant variations in acidity. An almost linear relationship between ΔE_Z and deprotonation energy (Figure 3) of PSU analogues is noted, and a similar trend is observed between the Gibbs free energy (ΔG_Z) and the deprotonation energy (Table S2). By contrast,

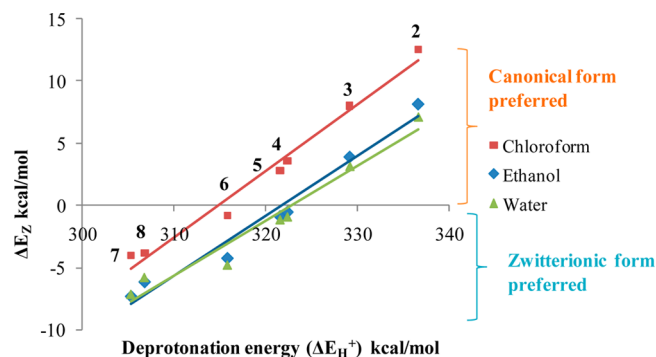


Figure 3. Energy level diagram between ΔE_Z and the deprotonation energy of PSU analogues.

the stability of amino acids zwitterions (with aliphatic side chain) is reported to depend strongly on the proton affinity at the nitrogen center; therefore, stability of zwitterions is nearly proportional to the amino acid proton affinity.^{10,56,57} In PSU analogues, the presence of an acidic site N^{10} near to a resonating moiety or electron withdrawing group facilitates greater acidity at this site. Therefore, lower deprotonation energy of N^{10} facilitates preferential proton release for binding with the pyridyl nitrogen, which further leads to the preferential stabilization of the zwitterionic form in 4Z–8Z.

3.2. Microsolvation Effect. Although the continuum solvent calculations can account for the overall environmental effect as the solute and the solvent interaction is represented through a dielectric continuum, they cannot account for the direct bonding interactions that affect the relative thermodynamic stability. The effect of discrete solvent molecules on the canonical and zwitterionic forms can be efficiently studied using

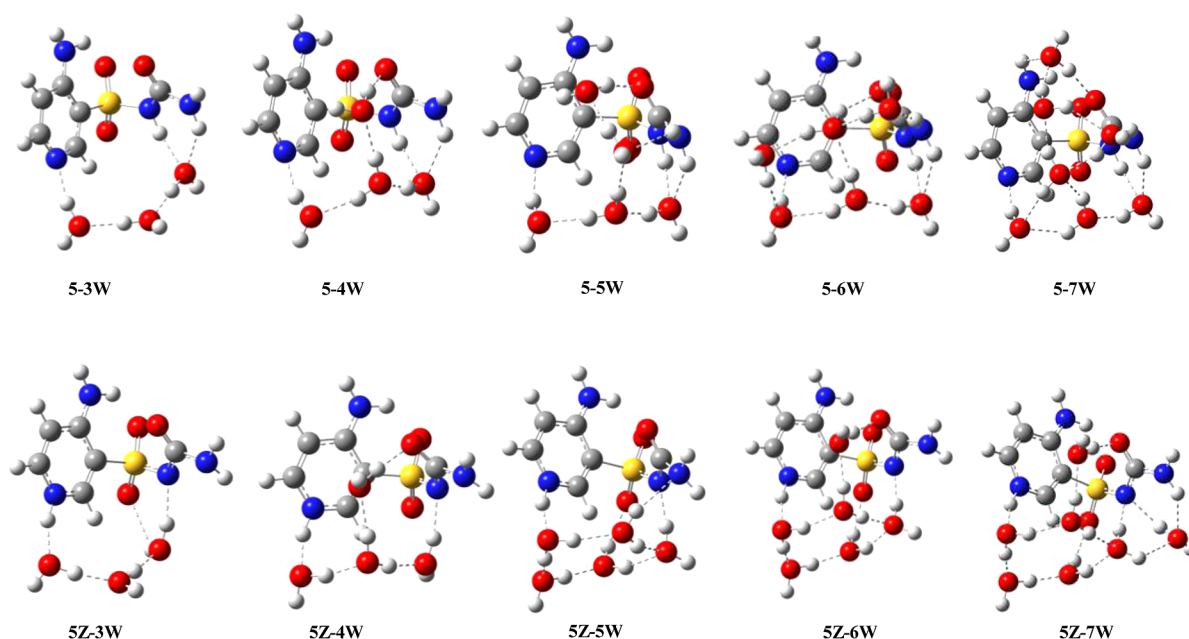


Figure 4. ω B97XD/6-311+G(d,p) optimized geometries of the lowest energy canonical and zwitterionic microsolvated clusters of **5** and **5Z**.

a microsolvation approach. Keeping this in view, several microsolvation studies have been carried out on various amino acids^{58–60} to know the number of water molecules required to make the two states (zwitterionic and non-zwitterionic states) isoenergetic. Spanning of water molecules in the form of a water chain/ring/cage, across oppositely charged/ionizable centers, stabilizes the zwitterionic form.^{58–60} PSUs have several polar functional groups such as pyridine, amine, and sulfonylurea, which can participate in hydrogen bonding with the water molecules. In the zwitterion of PSU, the N¹ (of pyridine) and the N¹⁰ (of sulfonylurea) are the positive and negative centers, respectively, which are separated by 4.6 Å. A chain or a ring of 3–5 water molecules can easily bridge these positive and negative centers. To understand the influence of the network of hydrogen bonds through water on the zwitterion of the PSU, microsolvation studies have been performed on **5**.

The relative stability of the canonical (**5**) and zwitterionic forms (**5Z**) of PSU has been determined as a function of the number of water molecules associated with them in microsolvation. About 40 different conformations of **5** and **5Z** were searched in the presence of 3–7 water molecules in order to find the lowest energy states, using B3LYP, M06-2X, and ω B97XD methods. The 3D structures of the lowest energy zwitterionic and canonical clusters are given in Figure 4, and the energy differences between the canonical and the zwitterionic forms, estimated at various levels of theory are listed in Table 2 [other alternative and higher energy conformations of **5** are given in the Supporting Information; (Figures S1 to S5 and Tables S4 to S8)]. The results obtained using ω B97XD functional are employed for discussion in this section.

The water clusters of **5** and **5Z** adopt various structures in their stable arrangements (Figure 4). In most cases, a chain of three water molecules (with a network of hydrogen bonds) is found between the amino groups of the urea moiety and the nitrogen atom of the pyridine residue. In the canonical form, this chain remains intact in all the water clusters (**5-3W** to **5-7W**) reported, additional water molecules forming bridges

Table 2. Relative Energy of the Most Stable Zwitterionic Conformation **5Z** in a Microsolvation Environment of 3–7 Water Molecules (in kcal/mol)^a

microsolvated structure	ΔE				
	microsolvation			microsolvation-continuum solvent ^d	
	$\epsilon = 1$			$\epsilon = 78.35$	
	B3LYP ^b	M06-2X ^c	ω B97XD ^c	M06-2X ^c	ω B97XD ^c
5Z ^e	15.16	16.21	15.99	2.11	1.43
5Z-3W	7.74	7.33	7.71	0.93	0.78
5Z-4W	4.25	6.41	5.40	−0.02	−1.05
5Z-5W	5.29	3.72	4.54	−0.47	−0.32
5Z-6W	2.65	2.06	1.31	−1.76	−3.37
5Z-7W	−0.14	−1.24	−0.73	..	−5.74

^aAll energies are corrected for zero-point vibrational energy. ^bBasis set 6-31+G(d,p) is used for optimizations. ^cBasis set 6-311+G(d,p) is used for optimizations. ^dImplicit solvent analysis, using CPCM method. ^eAll entries correspond to bare conformation **5Z**.

within various functional units of **5**. On the other hand, in the water clusters of zwitterion **5Z**, a chain of three water molecules is found in smaller clusters (containing 3–4 water molecules) and a ring of five water molecules is noticed in larger clusters, with 5–7 water molecules. For example, in **5-7W**, the chain of three water molecules is clearly found, whereas in **5Z-7W**, a ring of five water molecules with the extended water molecules can be seen in the zwitterionic cluster (Figure 4).

The energy difference between **5** and **5Z** gradually decreases with an increase in the number of water molecules employed in microsolvation (Table 2). A chain of three water molecules in **5-3W** and **5Z-3W** decreases their energy difference to 7.71 kcal/mol (from ~15 kcal/mol in the absence of water molecules). Additional water molecules decrease this energy gap further. When six water molecules are involved, **5-6W** and **5Z-6W** become almost competitive. Moreover, in the presence of seven water molecules, **5Z** becomes marginally more stable than **5**. From this data (Table 2), it can be concluded that the

Table 3. Relative Energies (in kcal/mol) of Various Conformational and Tautomeric Isomers of PSU^a

structure	structural description	gas phase					solvent phase ^d					
		B3LYP ^b	B3LYP ^c	M06-2X ^c	ω B97XD ^c	MP2 ^b	water	ethanol	chloroform	water	ethanol	chloroform
							B3LYP ^b			ω B97XD ^c		
PSU-1	global minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PSU-2	S ⁷ –N ¹⁰ rotamer of PSU-1	1.54	1.50	2.73	2.53	3.70	0.87	0.68	0.96	1.54	1.58	1.77
PSU-3	N ¹⁰ –C ¹¹ rotamer of PSU-2	3.40	3.40	3.08	4.03	4.03	0.42	0.86	1.64	1.07	1.17	1.88
PSU-4	N ¹⁰ –C ¹¹ rotamer of PSU-1	4.78	4.64	4.64	5.04	4.89	0.57	0.83	1.81	0.79	1.13	2.13
PSU-5	C ¹¹ –N ¹³ rotamer of PSU-4	5.80	5.81	5.97	5.93	6.88	2.22	2.34	3.29	1.75	1.88	2.94
PSU-t1	1,3-H shift tautomer of PSU-4	5.19	6.01	6.38	7.93	8.26	5.48	5.46	5.46	7.47	7.50	7.64
PSU-t2	S ⁷ –N ¹⁰ rotamer of PSU-t1	6.53	7.32	7.49	9.14	9.17	6.06	6.01	6.25	8.00	8.08	8.47
PSU-t3	N ¹⁰ –C ¹¹ rotamer of PSU-t1	7.31	7.86	8.09	9.45	9.60	7.05	7.05	7.36	8.26	8.32	8.57
PSU-t4	S ⁷ –N ¹⁰ rotamer of PSU-t3	8.40	8.87	8.81	10.55	10.52	7.51	7.46	7.83	8.79	8.89	9.40
PSU-t5	1,3-H shift of PSU-4 (N ¹³ –O ¹² H-shift)	18.60	--	--	--	18.50	20.50	20.21	19.91	--	--	--
PSU-t6	S ⁷ –N ¹⁰ rotamer of PSU-t5	20.50	--	--	--	22.41	20.85	21.10	21.46	--	--	--
PSU-t7	C ³ –S ⁷ rotamer of PSU-t3	16.04	--	--	--	18.59	11.87	11.84	13.15	--	--	--
PSU-t8	1,3-H shift of PSU-3 (N ¹⁰ –O ⁹ H-shift)	21.65	--	--	--	23.43	20.20	20.22	23.16	--	--	--

^aAll energies are corrected for zero-point vibrational energy. ^bBasis set 6-31+G(d,p) is used for optimizations. ^cBasis set 6-311+G(d,p) is used for optimizations. ^dImplicit solvent analysis, using CPCM method.

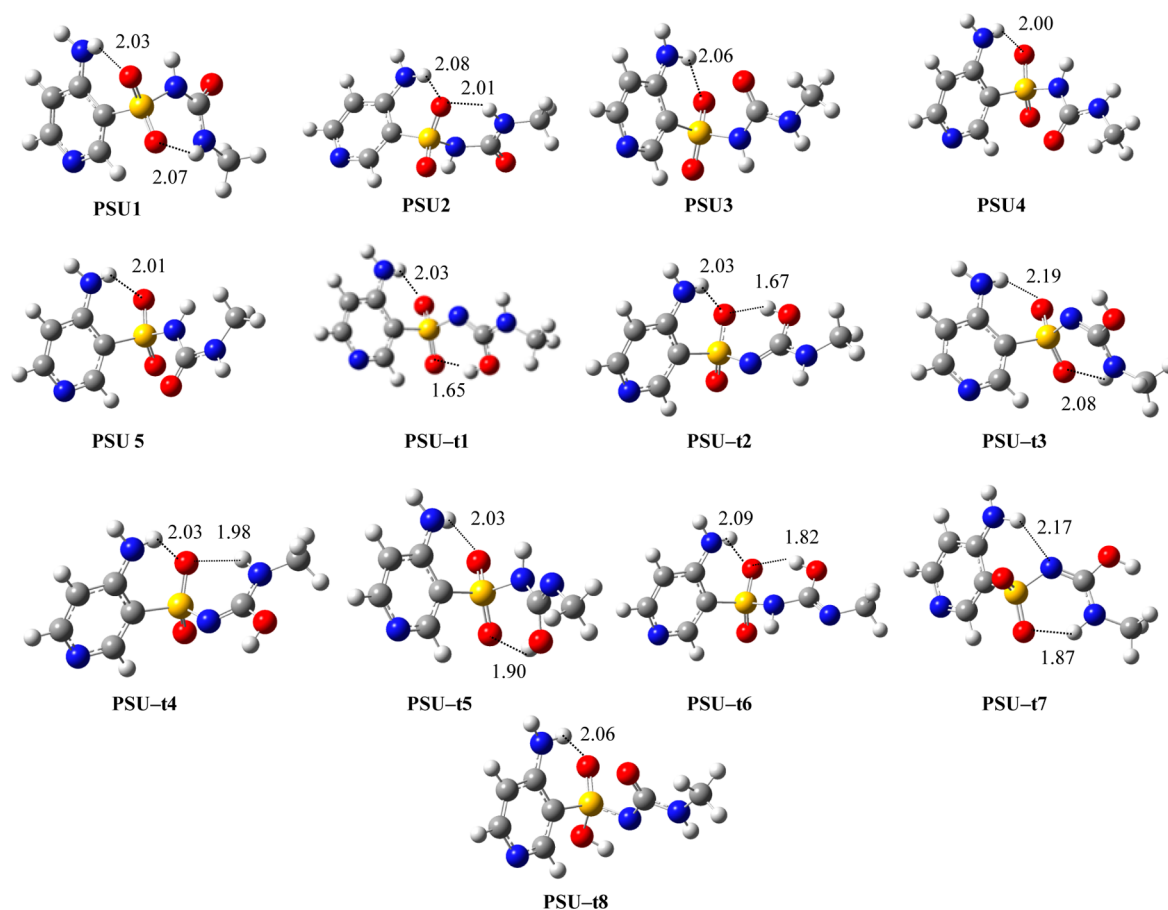


Figure 5. B3LYP/6-31+G(d,p) optimized geometries of conformational (PSU-1 to PSU-5) and tautomeric (PSU-t1 to PSU-t8) isomers of PSU (The intramolecular H-bonds distances (Å) are shown as a dashed line).

transition of the canonical conformation to the zwitterionic conformation starts in the presence of seven water molecules. When both explicit and the continuum methods are employed for modeling the solvent effect, it becomes clear that four water molecules are sufficient to stabilize the zwitterionic state.

Moreover, in the larger water clusters (containing 6 and 7 water molecules), the zwitterions are predominant by about 3.4 and 5.7 kcal/mol, respectively, in the CPCM solvent model. The strength of hydrogen bonding interactions in the zwitterionic clusters increases as the number of water molecules in these

Table 4. Relative Energies (in kcal/mol) of the Protonated Isomer of PSU-1 and the Tautomeric Forms of PSU^a

structure	gas phase					solvent phase ^d			
	B3LYP ^b	B3LYP ^c	M06-2X ^c	ω B97XD ^c	MP2 ^b	ethanol	chloroform	ethanol	chloroform
						B3LYP ^b	ω B97XD ^c	B3LYP ^b	ω B97XD ^c
HPSU-1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
HPSU-t1	−3.29	−2.32	−2.31	−0.67	−0.2	2.56	1.78	4.77	3.71
HPSU-t2	−1.92	−1.06	−0.83	0.63	1.16	3.46	2.67	6.09	4.76
HPSU-t3	−2.19	−1.44	−1.59	−0.02	0.41	3.94	3.24	5.56	4.55
HPSU-t4	−1.3	−0.6	−0.89	0.63	1.23	4.42	3.55	6.24	5.03
HPSU-t7	3.51	3.94	3.89	5.13	6.26	8.79	7.95	9.52	8.92

^aAll energies are corrected for zero-point vibrational energy. ^bBasis set 6-31+G(d,p) is used for optimizations. ^cBasis set 6-311+G(d,p) is used for optimizations. ^dImplicit solvent analysis, using CPCM method.

clusters increases. Therefore, in the larger water clusters, the zwitterionic structures are strongly stabilized as compared to their canonical counterpart. Quantum chemical calculations clearly indicate that the zwitterionic state (SZ) is stabilized more strongly due to its higher dipole moment compared to the canonical form (S) as the number of water molecules increases in microsolvation environment.

In the gas phase conditions, the influence of different DFT functionals and basis sets is insignificant on the relative energies of the bare canonical and zwitterionic forms (Table 1). However, the influence of DFT functionals is found to be significant in the microsolvation condition (see Tables S4 to S8). The B3LYP calculations indicated that at least seven water molecules are required to make the canonical and zwitterionic forms isoenergetic. However, the calculations using ω B97XD and M06-2X functionals indicated that the zwitterionic form dominates over the canonical form by 0.73 to 1.24 kcal/mol in the presence of seven water molecules. In addition, trends observed using ω B97XD and M06-2X functionals are quite comparable. This suggests that ω B97XD and M06-2X functionals are much better than the B3LYP functional in describing the relative stability of the zwitterionic and the canonical clusters in explicit water conditions since they capture even the weak “long-range” interactions.

3.3. Conformational Analysis of PSU. In this study, 3-(4-amino-3-pyridyl)-sulfonyl-1-methylurea, (SM, Scheme 1), has been taken as a model system for the diuretic therapeutic agents, PSU derivatives. All the possible conformers and tautomers on the potential energy surface (PES) were explored using quantum chemical methods. The B3LYP/6-31+G(d,p) calculations in different media (gas phase, water, ethanol, and chloroform) (Table 3) and the MP2/6-31+G(d,p), M06-2X/ ω B97XD/6-311+G(d,p) calculations in the gas phase, indicate that PSU-1 (Figure 5) is the most stable conformation. PSU-1 is characterized by two intramolecular H-bonds N¹⁵–H⁹ (2.03 Å) and N¹³–H⁸–O⁸ (2.07 Å) (Figure 5). PSU-2 is a rotational isomer (S⁷–N¹⁰) of PSU-1, which also shows the presence of two intramolecular H-bonds N–H⁹–O. PSU-3 to PSU-4 are the less stable isomers with relative energies ~3–5 kcal/mol in the gas phase, however, under implicit solvent conditions (water, ethanol, and chloroform), the energy differences are less pronounced.

Compounds PSU-t1 to PSU-t6 are the iminol tautomers of PSU-4 (Figure 5). The energy difference between the amide and the iminol tautomers (PSU-1 vs PSU-t1) is ~5–6 kcal/mol at B3LYP level and ~8 kcal/mol at MP2 level (Table 3). These values are much smaller than the energy difference, ΔE value of 12 kcal/mol between acetaldehyde and vinyl alcohol.⁶¹

The amide-iminol tautomers of acetamide⁶² and urea⁶³ are found to have ΔE of about ~13 and ~16 kcal/mol, respectively (Table S9). In comparison, the amide-iminol tautomerism in PSU is considerably a more favorable process with ΔE ~5–8 kcal/mol.

All the tautomeric structures are characterized by two intramolecular H-bonds either on one side or on opposite sides of the molecule (except PSU-t8). The tautomers in which both the oxygen atoms of the sulfonyl group are involved in intramolecular hydrogen bonds are energetically more preferred in comparison to tautomer with only the single hydrogen bond. The tautomers are interconvertible via a unimolecular 1,3-H shift processes or a bimolecular proton shift processes. The 1,3-H shift (N¹⁰–O¹² H-shift) in PSU-4 leads to the generation of the iminol tautomer PSU-t1, which is the most preferred tautomer under the gas phase and solvent phase conditions. The results in Table 3 indicate that the tautomeric preferences toward the iminol tautomers of PSU decrease in polar solvents. For example, the energy difference of PSU-4 with PSU-t1 is about 0.40 kcal/mol in the gas phase, but the tautomeric preference for PSU-t1 decreases with an increase in the polarity of the solvent [3.65 (chloroform) < 4.63 (ethanol) < 4.91 kcal/mol (water)]. PSU-t3 and PSU-t4 are the other competitive alternatives to the structures, PSU-t1 and PSU-t2, on the PES. The relative energies of other possible tautomers are also listed in Table 3. Data in Table 3 indicates that the tautomers generated from N¹⁰–O¹² H-shift are more preferred than those arising from N¹³–O¹² H-shift.

In addition to the pure crystalline forms, various salts of PSUs with nitrate and sulfate as counter-cations in which they do not exist as zwitterions have also been reported.^{32,64–67} It is intriguing to note the effect of protonation on tautomerism. Thus the B3LYP/6-31+G(d,p) calculations revealed that the tautomeric structures PSU-t1 to PSU-t4 become more stable than PSU-1 under protonated conditions (Table 4). Figure 6 shows the comparative tautomerization energies of PSU and HPSU. The tautomer PSU-t1 is less stable than PSU-1 by ~5 kcal/mol; however, tautomer HPSU-t1 is more stable than HPSU-1 by 3.29 kcal/mol. HPSU-t7 is less stable than HPSU-1 only by 3.51 kcal/mol, whereas PSU-t7 tautomer is highly unfavored by 16 kcal/mol in comparison to PSU-1. Similar results are found in solvent media also. All these factors indicate that in the protonated conditions (at the pyridyl nitrogen), PSU greatly favors the tautomeric states (Figure 6). The overall relative stabilization experienced in PSU-t1 upon protonation is 8.48 kcal/mol, whereas it is 12.53 kcal/mol in PSU-t7. The greater stabilization of the tautomers in the protonated state can be attributed to the increased intramolecular H-bond

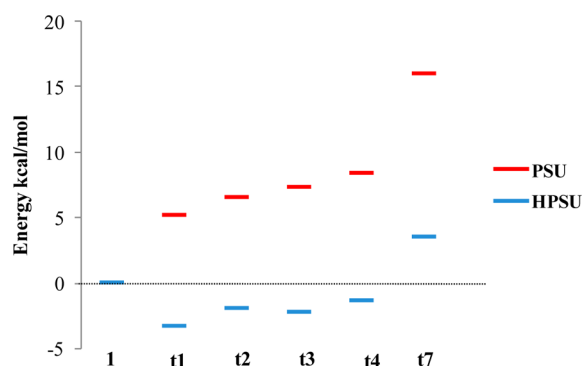


Figure 6. The comparative energy profile (B3LYP/6-31+G(d,p)) of neutral and protonated PSU in the gas phase.

strength in the tautomers in comparison to **HPSU-1**. In perspective, the results presented in this section indicate that the observed zwitterionic preferences in solid state, for the PSU derivatives can also be influenced by the tautomer preferences during solidification (especially in mild acidic condition).

4. CONCLUSIONS

Zwitterionic state of torsemide is about 15 kcal/mol higher in energy as compared to its canonical form in the gas phase, although, in the solid state, it (and the related PSU derivatives) is known to exist in the zwitterionic state. Extensive DFT studies were carried out on a series of PSU analogues to address this dilemma. The energy differences between the canonical and the zwitterionic states of 1–3 are very high and hence they cannot adopt zwitterionic form, this fact is also supported by the corresponding experimental data. The possibility of the zwitterionic form increases in 4–8, which can be attributed to the increased electron delocalization and increased acidity at the $-\text{SO}_2\text{NH}-$ center. $\Delta E_z(\text{g})$ value between the canonical and the zwitterionic forms, is low in the gas phase for the PSU analogues 7 and 8. Solvation plays a major role in stabilizing zwitterions, therefore, **6Z** to **8Z** even in chloroform and **5Z** to **8Z** in ethanol and water are more stable than the corresponding canonical forms in the CPCM continuum model. The number and strength of hydrogen bonding interactions of water with the zwitterions modulate their stability. In the presence of seven water molecules, the zwitterionic conformation, **5Z-7W**, is energetically comparable with the canonical form in the gas phase. Microsolvation-continuum approach indicates that the transition of the canonical form to the zwitterionic form starts under the influence of four water molecules. Gas and solvent phase calculations indicate the amide-iminol tautomeric potential of PSU model is in the order of 5 kcal/mol. Tautomer generation by 1,3-H shift from N^{10} is easier than the hydrogen shift from N^{13} . The iminol tautomers of PSU are characterized by the presence of two intramolecular H-bonds. Taken together, the results reported in the study indicate that (i) the electronic factors like improved electron delocalization, (ii) solvent effect (explicit and implicit), and (iii) tautomer preferences can induce gradual, quantitatively expressible differences in PSUs, which make the zwitterionic forms of these species more stable.

■ ASSOCIATED CONTENT

Supporting Information

Table S1 contains proton affinities of molecules 1–8. Tables S4 to S8 contain relative energies of the canonical and the

zwitterionic water clusters. Figures S1 to S5 have optimized geometries of the canonical and the zwitterionic configurations with 3–7 water molecules. Table S9 contains the absolute and the relative energies of acetaldehyde, acetamide, and urea, and their corresponding tautomers. Tables S2 and S10 to S12 contain relative Gibbs free energies of various geometries. Tables S13 to S14 list absolute energies of all the geometries under consideration. Tables S16 to S19 list the Cartesian coordinates of all the optimized structures. This Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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