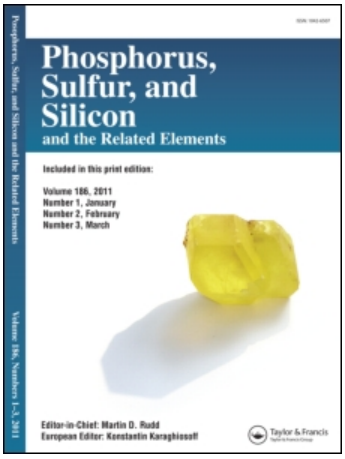

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THEORETICAL STUDY OF PHOSPHONAMIDATES, PHOSPHONAMIDES AND SULFONAMIDES AS TRANSITION STATE ISOSTERES OF HIV PROTEASE

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Abstract Ab-initio calculations at the RHF/6-31+G* level are performed on the N-methyl(methyl) conformers of phosphonamidates, phosphonamides, and sulfonamides. Sulfonamides and phosphonamidates are found to have very similar conformers and energies as potential transition state isosteres. Local minima in both are separated by a 2.0 kcal/mol barrier. The anti conformation and molecular dipole moments of phosphonamides play a role in the transition state isostere as was previously evidenced in the hydroxyethylene based mimics.

Key Words: Phosphonamidates, phosphonamides, sulfonamides, HIV protease mimics.

INTRODUCTION

HIV protease plays a major role in the life cycle of the HIV virus and provides an attractive therapeutic target for the treatment of AIDS.[1] Of the various types of proteases which have been classified according to their catalytic mechanisms, the aspartic proteases are the most significant here.[2] The activity of these enzymes originates from the structural and electronic complementarity of the active site to the transition state of the substrate (Figure 1). Protease inhibitors are transition state isosteres for the hydrolysis of the amide bond and behave as stable structures which both mimic the transition state of a catalyzed reaction and will be more tightly bound than the substrate.[3,4] Successful transition state isosteres which are similar to the aspartate tetrahedral intermediate (hereafter called TI) in geometry, electron density and the hydrolysis of amide bond include the phosphonamidates, sulfonamidates, and hydroxyethylenes.[5,6,7]

Phosphonamidates ($PO_2CH_3NHCH_3$) and other phosphorous analogs have been used with success to prepare HIV protease inhibitors.[8] A disadvantage of the phosphonamidate moiety is its lability under acidic conditions.[9] The sulfur containing transition state (T.S.) analog on the other hand, has been shown to fragment the systems at temperatures between 46-49°C[10] but the corresponding sulfinamides are less prone to this. The sulfonamides SO_2RNHR (hereafter called SO_2) were investigated experimentally as HIV inhibitors and found to be only partially efficient.[11] In contrast, phosphonamidates analogs[12] (hereafter called PO_2) have been used with success in preparation of both HIV protease inhibitors and thermolysin inhibitors.[13] The PO_2 derivatives however are unstable under acidic conditions[14] and this initiated experimental trials on the phosphonamidate esters, phosphinates and phosphonate esters.[15]

By minimizing unfavorable strain energy and favoring compounds whose conformations require the least reorganization on enzyme binding, the focus here is first on resolving all possible conformations of PO_2, SO_2 and phosphonamides (hereafter called POH). In spite of the fact that both SO_2 and PO_2 possess the required tetrahedral structure to mimic the transition state, the PO_2 moieties appear to be superior inhibitors to

the SO_2. Finally, we compare these two species to POH and to understand their ability to function as isosteres.

GAUSSIAN92 calculations at the RHF/6-31+G* level of theory were performed.[16]

RESULTS AND DISCUSSION

Figures 1,2,3,4 and Tables I, II summarize the conformational studies on TI, POH, SO_2, PO_2 respectively. Some of the interconversions routes of various minima on the TI, POH, PO_2 and SO_2 surfaces are presented in these figures numerically. In Figure 1, minimum **1** may overcome the 10.2 kcal/mol barrier, **2**, to convert to minimum **3** which lies 3 kcal/mol above the global minimum Table III summarizes the ChelpG charges on various atomic centers of the global minima of TI, SO_2, PO_2 and the two minima (**1, 3**) of POH. Table III also tabulates the net dipole moments of the global minima of all these species.

The relative energies of conformers of TI and POH are given in Table I.

TABLE I
Energies of Minima and Transition States TI and POH (Kcal/mol)

Conformation		Relative Energy		ZPE Energies		dipoles (Debyes)
		TI	POH	TI	POH	TI
minimum	1	0.0	0.0	0.0	0.0	3.4
transition state	2	10.2	2.3	9.9	1.9	4.9
minimum	3	3.0	0.1	3.0	0.1	5.0
transition state	4	2.2	1.3	2.1	0.9	4.2
minimum	5	0.8	0.4	0.9	0.4	2.5
transition state	6	6.7	4.0	6.6	4.0	2.7
transition state	7		1.3		0.9	

FIGURE 1 Minima and Transition States of the Tetrahedral Intermediate (RHF/6-31+G*)

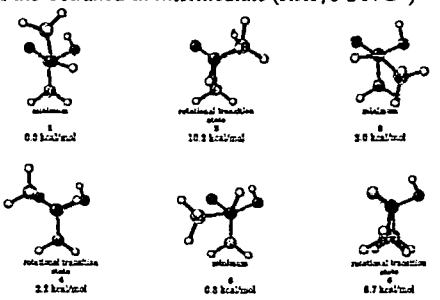
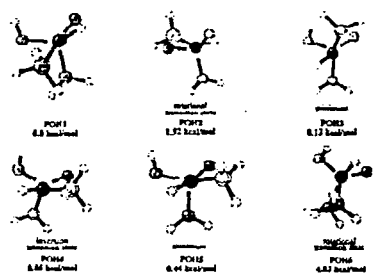


FIGURE 2 Minimum and Transition States of Phosphonamides (RHF/6-31+G*)



Figures 1 and 2 clearly show that a potential mimic for the global minimum of the tetrahedral intermediate is found in the POH local minimum 3. This conformer with the methyl groups anti to each other is only 0.12 kcal/mol above the global minimum of POH. Figure 2 also shows that the conversion from **1** to **3** on the POH surface only requires overcoming a 1.9 kcal/mol barrier, **2**, thus the POH provides a readily available transition state isostere. On the other hand, by comparing Figures 3 and 4 for the PO_2 and SO_2 to Figure 1 for TI, it is clear that no stable conformation with the methyl groups anti to each other exits. When the ability of any of the PO_2 or SO_2 conformers to rotate to the anti position is considered, preliminary results indicate that the sulfonamides are unable to match the anti configuration and are eliminated as potential transition state mimics. Phosphonamidates show a barrier of five kcal/mol in rotating to the preferred anti conformation and protonation of the phosphonamidates to match the isostere's configuration is currently under investigation.

Table I shows that the major difference between TI and POH is in the rotational barrier from **1** to **3**. In TI the barrier is 9.9 kcal/mol compared to a 1.9 kcal/mol barrier in POH. The facile conversion in POH explains its inhibitory effect as a transition state isostere and this may also facilitate the hydrolysis of the amide bond.

Molecular Dipole moments for all POH and TI conformers are given in Table I. While the conformational spaces of PO_2 and SO_2 are similar, their charge distributions differ significantly. The TI and PO_2 charges show some resemblances, indicating that PO_2 can mimic TI in hydrogen bonding and electrostatic interactions, while the SO_2 charges differs from both. Surprisingly, the global minima, **1**, on the POH and TI surfaces do not agree closely in individual charges or net dipole moment (Table 3).

TABLE II
Energies of Minima and Transition States of Sulfonamides and Phosphonamidates

conformation	PO_2 rel.	SO_2 energies	PO_2 zpe	SO_2 energies	POH ZPE	Comparison Energies	
minimum	1	0.0	0.0	0.0	0.0	0.0	0.0
transition state	2	1.5	1.5	0.9	0.8	1.3	0.9
minimum	3	1.1	1.3	1.0	1.1	0.1	0.1
transition state	4	6.7	7.5	6.4	7.0	2.3	1.9
transition state	5	8.1	9.6	8.1	9.6	4.0	4.0
minimum	6					0.4	0.4
transition state	7					1.3	0.9

TABLE III
ChelpG Charges for TI, SO_2, PO_2 AND POH

Structure		Central Atom 1	O2	O3	N	Net Dipole Debyes
TI	tetrahedral intermediate	1.27	-1.11	-0.86	-1.02	3.4
PO2	phosphonamidate	1.57	-0.99	-0.96	-0.91	5.3
SO2	sulfonamidate	1.33	-0.62	-0.66	-0.69	4.5
POH(1)	phosphonamide	1.35	-0.83	-0.74	-0.86	4.1
POH(3)	global minimum local minimum	1.49	-0.81	-0.78	-0.87	3.4

When charges in conformer **3**, the TI mimic on the POH surface, are compared to the TI global minima, there are some improvements at the O-H site while wide differences exist on the central atom. The net dipole moment of conformer **3** however, matches the tetrahedral intermediate exactly and uniquely. Global minima dipoles of PO_2 and SO_2 are higher than TI by over 1.0 Debye while the dipole moment of the POH global minimum, **1**, exceeds TI by 0.7 Debye. In SO_2 the conversion from **1** to **3** (Figure 3) appears similar to TI if it proceeds via transition state **5**.

FIGURE 3 Minima and Transition States of (N-Methyl) Methylphosphonamidate (RHF/6-31+G*)

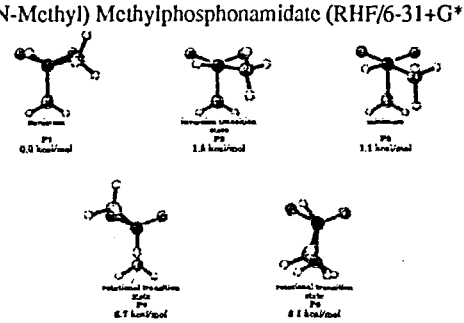
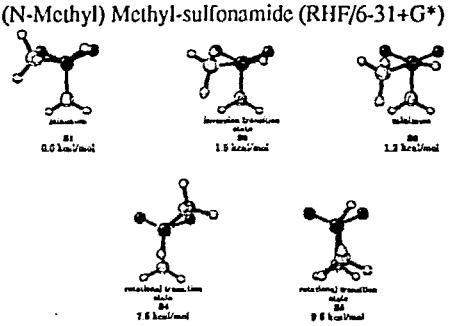


FIGURE 4 Minima and Transition States of (N-Methyl) Methyl-sulfonamide (RHF/6-31+G*)



It involves a high barrier of 7.5 kcal/mol compared to 9.6 kcal/mol in TI. The resulting conformations appear with the dihedral of about 60° for the methyl groups in SO_2 whereas on the TI surface they are anti and close to 180°. If a lower path is selected on the SO_2 surface (Figure 3), namely from **1** via **2** to **3**, the barrier heights resemble the POH values of less than 2 kcal/mol but again, the methyl groups in conformer 3 are not in the preferred anti conformation. In addition, the **1** to **3** conversion in SO_2 results in a dipole increase of 1.3 Debyes, whereas in the POH (conformer 3) the dipole moment reduces by 0.7 Debye to exactly match the dipole moment of **1** in TI. All these factors explain why the sulfonamides are less efficient transition state isosteres.

The phosphonamidate surface (Figure 4) resembles SO_2 essentially since the global and local minima are in gauche-like conformations. Again, the net dipoles of both stable conformers exceed the TI dipole by up to two Debye units.

The conformational specificity of the POH anti methyl groups combined with a precise net dipole moment succeeds in matching the tetrahedral intermediate and creates a favorable transition state isostere.

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