

# DFT Studies of the Ring Opening Mechanism of SB-3CT, a Potent Inhibitor of Matrix Metalloproteinase 2

*Peng Tao,<sup>†</sup> Jed F. Fisher,<sup>‡</sup> Shahriar Mobashery,<sup>‡</sup> and H. Bernhard Schlegel<sup>\*,†</sup>*

<sup>†</sup>Department of Chemistry, Wayne State University, 5101 Cass Ave Detroit, Michigan 48202

<sup>‡</sup>Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

hbs@chem.wayne.edu

## Table of Contents

Details of the computational methods .....	3
Table S1 .....	4
Table S2 .....	5
Table S3 .....	6
Figure S1 .....	7
Figure S2 .....	8
Full reference 9 .....	9

Molecular orbital calculations were carried out with the development version of the GAUSSIAN series of programs.<sup>1</sup> Hartree Fock (HF), density functional theory (DFT),<sup>2-4</sup> and second order Møller-Plesset perturbation theory (MP2)<sup>5</sup> were compared with benchmark CBS-QB3<sup>6,7</sup> calculations. The B3LYP hybrid exchange-correlation functional<sup>8-10</sup> was chosen for the DFT calculations. The 6-31+G(d) basis set was used for geometry optimization. Single point calculations with a 6-311+G(d,p) basis set were carried out using these optimized geometries. The reactant complex, transition state (TS), and product complex for the ring opening reaction and **1** and **2** were evaluated in the gas phase using level of theories above (see Table S1 and Figure S1). Relative to the CBS-QB3 results, B3LYP performs significantly better than HF and MP2, with an average difference of 2.4 kcal/mol, and was used for the remaining calculations.

To facilitate the comparison with experiment, the ring openings of the model systems were studied in methanol (dielectric constant  $\epsilon = 32.63$ ) and acetonitrile ( $\epsilon = 36.64$ ) using the integral-equation-formalism of the polarizable continuum model (IEF-PCM).<sup>11</sup> Geometries were optimized at the B3LYP/6-31+G(d,p) level of theory with IEF-PCM solvation in methanol. A frequency analysis of each TS for the model systems yielded only one imaginary frequency. For both thiirane and oxirane systems, reaction path following confirmed that the TS connected the desired reactant and product. Single point energies were calculated at the B3LYP/6-311+G(d,p) level of theory with IEF-PCM solvation and combined with the frequency data to obtain enthalpies at 298K.

- (1) Frisch, M. J.; al, el.; Revision F.02 ed.; Gaussian, Inc.: Wallingford, CT, 2007
- (2) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, 136, B864-B871.
- (3) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, 140, A1133-A1138.
- (4) Parr, R. G.; Yang, W. *Density-functional Theory of Atoms and Molecules*, 1989.
- (5) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, 46, 618-622.
- (6) Montgomery, J. J. A.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1999**, 110, 2822-2827.
- (7) Montgomery, J. J. A.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **2000**, 112, 6532-6542.
- (8) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, 37, 785-789.
- (9) Becke, A. D. *Phys. Rev. A: Gen. Phys.* **1988**, 38, 3098-3100.
- (10) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648-5652.
- (11) Tomasi, J.; Mennucci, B.; Cances, E. *THEOCHEM* **1999**, 464, 211-226.

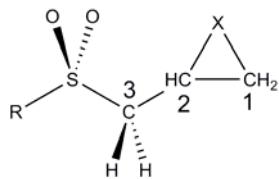
**Table S1.** Comparison of the theoretical methods for the ring-opening reaction in the gas phase

Method <sup>a</sup>	Thiirane ( <b>1</b> ) <sup>b</sup>		Oxirane ( <b>2</b> ) <sup>b</sup>	
	Barrier height	Reaction enthalpy	Barrier height	Reaction enthalpy
HF	18.3	7.0	31.6	21.7
MP2	18.4	19.5	25.9	26.2
B3LYP	11.5	11.3	20.4	19.8
CBS-QB3	12.8	14.5	24.6	20.7

(a) Enthalpies at 298K in kcal/mol. Results for calculation using HF, MP2 and B3LYP are based on the 6-311+G(d,p) basis set with optimized geometries and zero point energies obtained with the 6-31+G(d) basis set.

(b) Calculations are based on the reaction complex, and TS shown in Fig. 1.

**Table S2.** Calculated reaction barriers and reaction enthalpies for mechanism (a) and (b) in CH<sub>3</sub>OH and CH<sub>3</sub>CN solutions.<sup>a, b</sup>



Reaction	Solvent	Mechanism (a) (R = methyl)	
		Thiirane ( <b>1</b> )	Oxirane ( <b>2</b> )
SN2 at C1 attack	CH <sub>3</sub> OH	14.8 (-1.9)	18.5 (-0.6)
SN2 at C2 attack	CH <sub>3</sub> OH	17.6 (-2.3)	23.0 (2.7)
Mechanism (b) (R = methyl)			
CH abstraction at C3	CH <sub>3</sub> OH	Thiirane ( <b>1</b> )	Oxirane ( <b>2</b> )
	CH <sub>3</sub> CN	11.3 (2.9)	17.2 (10.1)
CH abstraction at C3	CH <sub>3</sub> OH	10.5 (3.0)	17.2 (10.8)
	CH <sub>3</sub> CN	8.7 (2.0)	14.9 (9.8)
Mechanism (b) (R = phenyl)			
CH abstraction at C3	CH <sub>3</sub> OH	Thiirane	Oxirane
	CH <sub>3</sub> CN	8.6 (0.6)	14.8 (8.2)

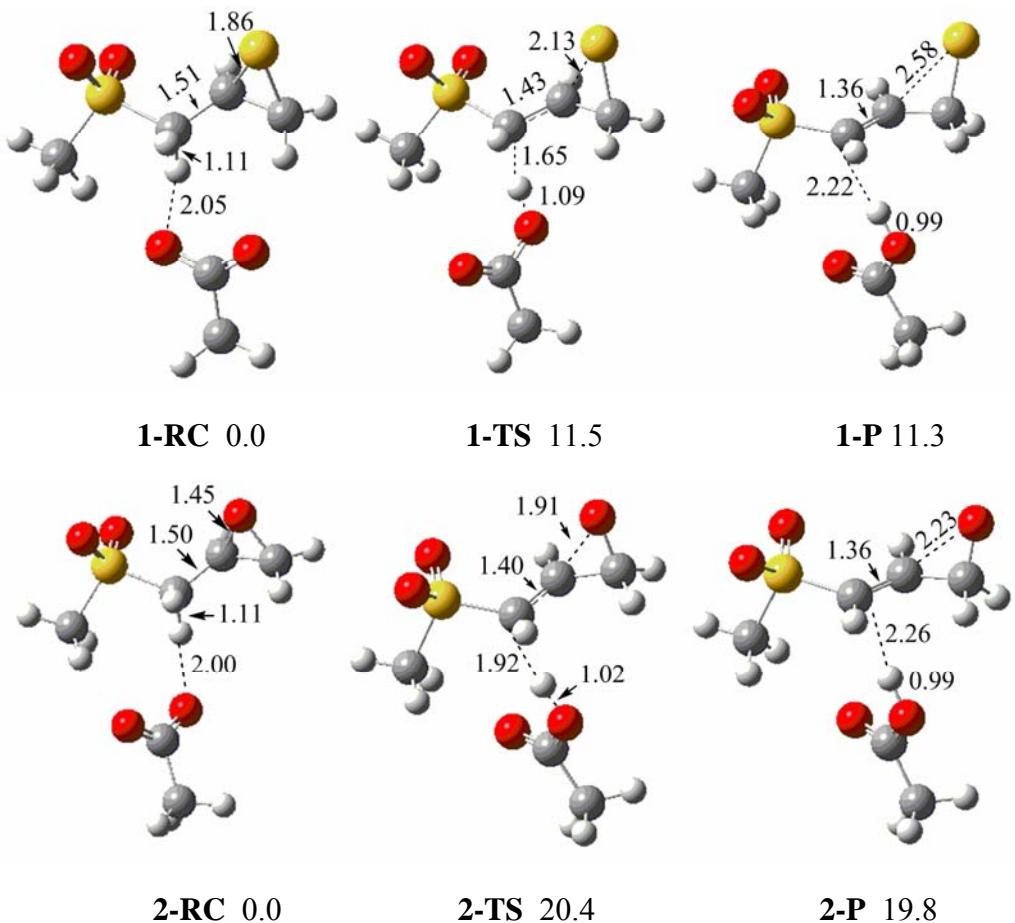
(a) IEF-PCM/B3LYP/6-311+G(d,p) energies with optimized geometries and zero point energies obtained with the 6-31+G(d) basis set (Reaction enthalpy is listed in the parenthesis.)

(b) Using the most stable conformer for the reactant complex and infinitely separated acetic acid and ring opened structures for products.

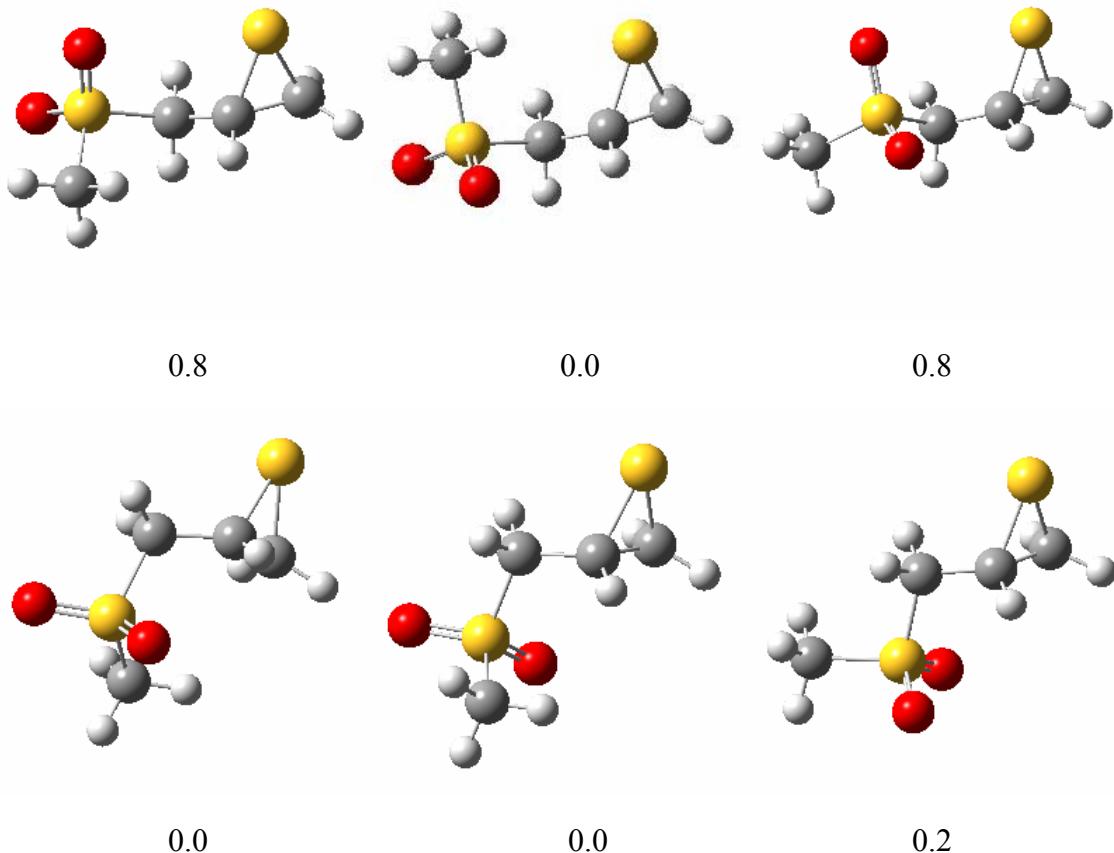
**Table S3.** Calculated relative enthalpies in methanol solution for different conformers of the model inhibitors<sup>a</sup>

	Thiirane			Oxirane		
	RC	TS	P	RC	TS	P
(a)	0.0	13.2	2.9	0.0	18.9	10.1
(b)	0.8	19.5	5.3	-1.3	24.0	13.1
(c)	1.5	11.3	4.9	-1.4	17.2	12.0
(d)	0.0	16.2	5.3	0.0	20.6	12.1
(e)	0.4	16.9	2.8	1.2	19.8	9.1
(f)	1.7	13.9	2.8	-1.1	18.3	9.1

(a) IEF-PCM/B3LYP/6-311+G(d,p) energies with optimized geometries and zero point energies obtained with the 6-31+G(d) basis set (See Table 1 in main text for TS structures).



**Figure S1.** Reactant complexes, transition states and product complexes for model sulfone thiirane and oxirane reactions optimized at the B3LYP/6-31+G(d) level of theory in the gas phase. Relative enthalpies at 298 K were calculated with the B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d) level of theory. Key bond lengths are in Ångstroms, and energies are in kcal/mol. Atoms are colored according to atom types (H, C, O, S, shown in white, grey, red, and yellow, respectively).



**Figure S2.** Six local minimum of (R)-2-[(methylsulfonyl)methyl]thiirane optimized at the (IEF-PCM)/B3LYP/6-31+G(d) level of theory in methanol. Relative enthalpies were calculated at the (IEF-PCM)/B3LYP/6-311+G(d,p)//(IEF-PCM)/B3LYP/6-31+G(d) level of theory in methanol. The three conformers on each row share the same orientation of methylene group between sulfone and thiirane ring group, but have different orientations of sulfone group.

9. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Scalmani, G.; Mennucci, B.; Barone, V.; Petersson, G. A.; Caricato, M.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Li, X.; Hratchian, H. P.; Peralta, J. E.; Izmaylov, A. F.; Kudin, K. N.; Heyd, J. J.; Brothers, E.; Staroverov, V.; Zheng, G.; Kobayashi, R.; Normand, J.; Sonnenberg, J. L.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Burant, J. C.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Chen, W.; Wong, M. W.; Pople, J. A.; Revision F.02 ed.; Gaussian, Inc.: Wallingford, CT, 2007.