Computational Study of Pharmacophores: β-Sultams

Mathew Barwick, Tareq Abu-Izneid, and Igor Novak*

Charles Sturt University, POB 883, Orange NSW 2800, Australia

Received: June 7, 2008; Revised Manuscript Received: August 29, 2008

The strain and resonance energies in β-sultam derivatives have been calculated by using a high-level ab initio method (G3/B3LYP) in order to resolve the question of the principal driving force affecting solvolysis of these new antibiotics. We found that only the combined effect of stabilizing (via amide or sulfonamide resonance interactions) and destabilizing (ring strain) influences can account for the observed rates of solvolysis in β-lactams and β-sultams.

Introduction

The molecular and electronic structure of β-lactam antibiotics has been studied extensively because they are still the most widely used type of antibiotics. β-Lactam antibiotics express their activity by inhibiting the enzyme trans-peptidase, which participates in the construction of bacterial cell walls (Scheme 1, A).[1]

However, some bacterial strains are increasingly developing antibiotic resistance by using special enzymes (e.g., serine β-lactamase) to hydrolyze the antibiotics. The mechanism of resistance involves the deprotonation of the conserved water molecule[1,2] (Scheme 1, B). Therefore, medicinal chemists are searching for compounds that can inhibit such enzymes (Scheme 1, C). One such group of compounds comprises β-sultams. It is thus not surprising that the chemical reactivity and biological activity of β-sultams have been extensively studied.

Page and co-workers[3] have investigated the possibility that β-sultams can block the activity of serine protease enzymes, which in turn inhibit the action of β-lactam antibiotics. The mechanism of β-sultam action is given in Scheme 2 and involves sulfonation of the enzyme active site.

Page and co-workers[3] have observed that some β-sultams react 10^7-10^9 times faster than their acyclic analogues, sulfonamides. On the other hand, some β-lactams react only 100 times faster than the corresponding acyclic amides. The mechanism of β-sultams solvolysis is a stepwise one and occurs via S−N bond fission.[3,4] It has been suggested[3] that one possible factor contributing to the enhanced rate of solvolysis is ring strain in the four-member ring of β-sultams and β-lactams. The role of the ring strain versus resonance in β-lactams had been discussed by Novak and Chua,[5] while Karplus and co-workers discussed strain versus solvation.[6] The former authors computed the ring strain and amide resonance effects independently for β-lactams and concluded that the four-member ring strain is of comparable magnitude to the amide resonance. This observation suggests that ring strain on its own is unlikely to influence the rates of solvolysis in β-lactams. Karplus and co-workers[6] have pointed out (on the example of sulfate esters) that solvation effects are the primary cause of enhanced rate of solvolysis of cyclic versus acyclic substrates. They argued that the gas-phase free energy profiles can not be used to account for the rate enhancement and that the cyclic transition states, being better solvated than acyclic ones, lead to faster reaction rates. These two complementary studies indicate that the question of relationship between the ring strain and the reaction rate acceleration remains controversial. One piece of information required to resolve the controversy is whether the ring strain is in fact present in these molecules and what is its magnitude. We therefore used high level computational methods to investigate the presence/absence and magnitude of ring strain in β-sultams. We have selected β-sultam pharmacophores (organic functional groups that are carriers of biological activity) listed in Scheme 3 for this study. Molecules **5**−**8** are used as references to describe various aspects of strain and resonance energies, while compound **9** is used as a check on the calculated geometries. The molecular structure of **9** has been determined experimentally.

Computational Methods

The quantum chemical calculations were performed with the Gaussian 03 program.[7] The total electron energy of each molecule in Scheme 3 was computed using the composite G3/B3LYP method,[8] which has a root-mean-square deviation of up to 8 kJ/mol. The method includes full geometry optimization at the B3LYP/6-31G* level followed by single-point QCISD-type calculations (no imaginary frequencies were detected). All the optimized structures corresponded to minima on their potential energy surfaces, as was inferred from the absence of imaginary vibrational frequencies. The estimation of ring strain energy (RSE) and sulfonamide group interaction energy (SRE) in β-sultams and their derivatives was based on the enthalpies of the isodesmic reactions given in Scheme 4.

The calculated and experimental geometries (labeled "crystal structure") for the molecules in these reactions are compared in Scheme 5 and presented as evidence that the selected method adequately describes their molecular structures.

There are no experimental data regarding the enthalpy of β-sultams or their monocyclic analogue **5** to be used for comparison with total energies of molecules in the isodesmic reactions of Scheme 4. However, we have shown previously[5] that the method employed in this work gives molecular electronic energies that are within 4 kJ/mol of the corresponding experimental reaction enthalpies.

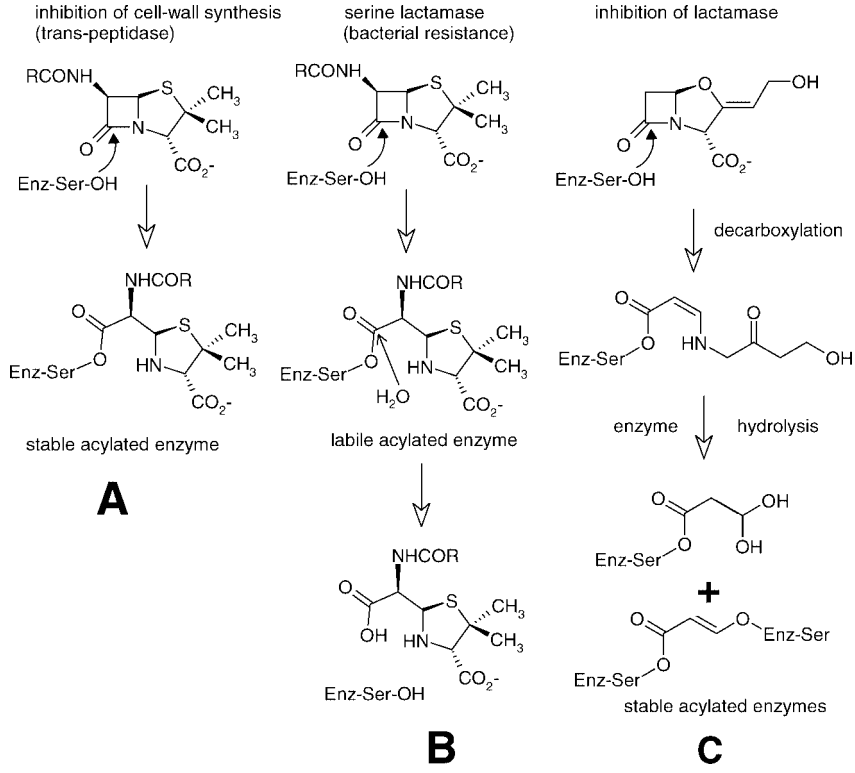
Results and Discussion

The results of our study are summarized in Tables 1 and 2. We have calculated three molecular descriptors: sulfonamide

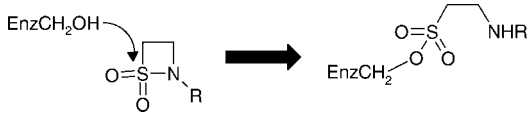
* Corresponding author. E-mail: inovak@csu.edu.au.

10.1021/jp805024y CCC: $40.75
Published on Web 10/02/2008

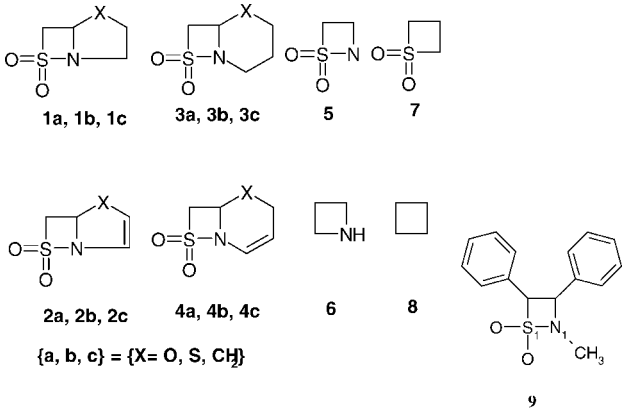
SCHEME 1: Reactions Pertaining to the Biological Importance of β-Lactams



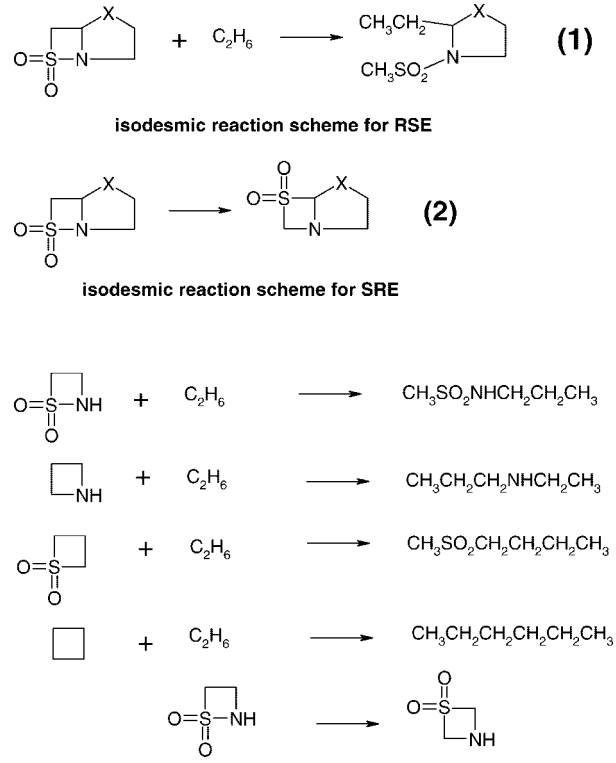
SCHEME 2: Reaction Describing the Inactivation of β-Sultams



SCHEME 3: Pharmacophores Studied in This Work



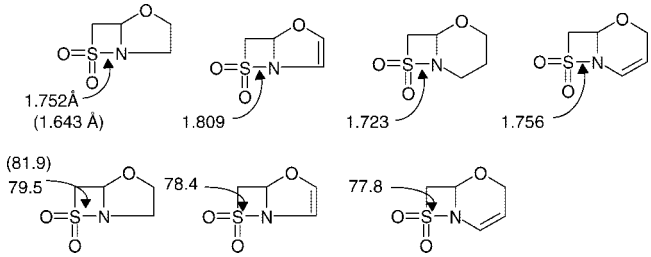
SCHEME 4: Isodesmic Reactions Used to Determine Ring Strain and Sulfonamide Interaction Energy



group interaction energy (SRE), four-member ring strain energy (RSE) and stabilization energy (Δ = RSE − SRE). Sulfonamides are weak acids,[9] with nitrogen being deprotonated in primary and secondary sulfonamides. This acidity is attributed to the intramolecular resonance stabilization of the anion by the SO_2 group. The β-sultams are tertiary sulfonamides, i.e., the nitrogen atom is devoid of hydrogen and as such can not be acidic, but the SO_2−N resonance is still operational. The term "resonance" may not be the best description of the intramolecular interaction taking place between SO_2 and nitrogen moieties, as was discussed previously for amides.[5,10] An alternative description of this interaction can be made in terms of the inductive effect of the oxo groups in SO_2, which make sulfur atoms more electron deficient and hence prone to accept electron density from the neighboring nitrogen lone pair. Nevertheless, we shall retain the term "resonance" in the subsequent discussion.

The results in Table 1 show that SRE < ARE, i.e., the resonance interactions within the amide group in β-lactams[5] are stronger than those within the sulfonamide group in β-sultams.

SCHEME 5: Comparison between Representative Density Functional Theory (DFT) and Experimental Geometries for β-Sultams[a]



[a] Numbers in brackets were taken from crystal structure in ref. 12; bond lengths in Å; angles in deg.

TABLE 1: Sulfonamide Interaction Energy (SRE/kJ mol^{-1}), Ring Strain Energy (RSE/kJ mol^{-1}), Amide Resonance Energy (ARE), Net Stabilization Δ (kJ/mol), S−N Bond Lengths (Å), and Degree of Pyramidalization of β-Sultam Nitrogen ($\Sigma\alpha_i$/deg)[a,b]

compound	SRE (ARE)	RSE (RSE)	Δ = RSE − SRE	r_{SN}	$\Sigma\alpha_i$
1a	49.5 (81.7)	76.4 (110.5)	26.9 (28.8)	1.75	317.3
1b	44.5 (75.3)	74.8 (97.5)	30.2 (22.2)	1.74	327.2
1c	40.4 (72.6)	65.7 (110.5)	25.3 (37.9)	1.74	321.6
2a	48.1 (72.5)	81.2 (129.1)	33.0 (56.6)	1.80	313.2
2b	35.7 (67.3)	68.8 (125.4)	33.1 (58.1)	1.79	323.2
2c	29.0 (57.9)	67.1 (129.4)	38.1 (71.5)	1.77	316.2
3a	71.2 (109.1)	67.6 (70.8)	−3.6 (−38.3)	1.72	337.6
3b	49.0 (102.4)	74.6 (70.7)	25.6 (−31.7)	1.71	341.4
3c	52.4 (105.4)	70.4 (60.0)	18.0 (−45.4)	1.71	341.2
4a	61.5 (93.9)	80.5 (86.8)	19.0 (−7.1)	1.76	335.7
4b	49.1–(86.1)	78.6 (71.8)	29.5 (−14.3)	1.74	344.1
4c	47.3 (85.7)	71.5 (82.1)	24.2 (−3.6)	1.74	337.9
5	42.7 (90.4)	94.9 (102.4)	52.1 (12.0)		
6		107.6			
7		86.5			
8		112.6			
9				1.643	338.1

[a] $\Sigma\alpha_i$ is the sum of SNC bond angles centered on the sultam nitrogen; the result for **9** was obtained from the crystal structure in ref 9. [b] The values in brackets correspond to β-lactam analogues from ref 5.

TABLE 2: Reaction Enthalpies (kJ mol^{-1}) for Hydrogenation (4) and Exchange Reactions (3) of β-Sultams and Their β-Lactam Analogues[a]

compound	hydrogenation	exchange
1a + 4a		11.1 (9.5)
1b + 4b		19.5 (15.0)
1c + 4c		25.8 (16.1)
2a	−128.1 (−127.8)	
2b	−118.0 (−125.9)	
2c	−123.8 (−125.1)	
4a	−117.0 (−118.2)	
4b	−98.6 (−110.9)	
4c	−98.0 (−109.0)	

[a] The values in brackets correspond to β-lactams from ref 5.

This computationally based inference is supported by the analysis of pyramidalization of the nitrogen atom. The sum of experimentally determined bond angles around nitrogen in the lactam derivative[11] is 359.5°, while in the similarly substituted β-sultam[12] it is 338.1°. The values indicate that nitrogen is more pyramidal in β-sultams than in β-lactams, which is consistent with the proposed reduced resonance within the sulfonamide group. A more pyramidal nitrogen lone pair has more sp^3 than sp^2 character, the latter being preferred for SO_2−N resonance interaction.

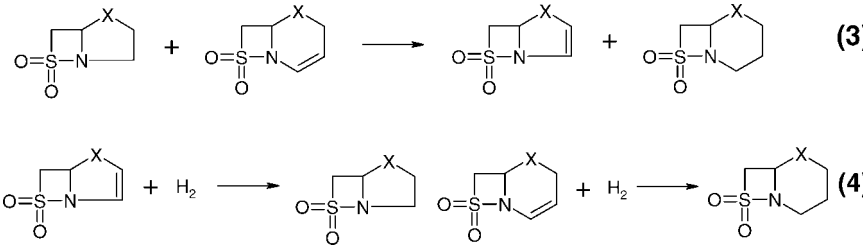
The reaction enthalpies for exchange and hydrogenation reactions (Scheme 6 and Table 2) involving β-sultams can be compared with analogous enthalpies for β-lactams. The shift of the double bond from five-member to six-member ring (Scheme 6, reaction 3) leads to slightly larger positive enthalpy in β-sultams versus β-lactams. This can be attributed to weaker nitrogen−π interactions in the former for the reasons discussed above (more pronounced nitrogen pyramidalization). Likewise, hydrogenation enthalpies (Scheme 6, reaction 4) in β-sultams are slightly less negative than in β-lactams. The qualitative rationalization of this result can be offered along the same vein. The π-bond in β-sultams is less subject to resonance delocalization with nitrogen lone pair and hence smaller energy is required to remove it (hydrogenation).

The RSE results in Table 1 show that in the series of β-sultams **1** and **2**, RSE is generally smaller than in β-lactam analogues. For the β-sultam series **3** and **4**, the RSE values are of comparable magnitude to ARE in β-lactam analogues. (One needs to bear in mind that the uncertainty in the computational method is ≤8 kJ/mol.) In general, the span of SRE values is smaller than that of the ARE values. The reason for the difference between the two series can be related to the character of the nitrogen lone pair in β-sultams versus β-lactams. Since the required nitrogen atom coordination in β-lactams is more planar (less pyramidal), the larger, fused six-member ring introduces less constraint on the coordination geometry of nitrogen and hence reduces the ring strain in the lactam ring for series **3** and **4**. The smaller fused five-member ring in β-lactams induces more constraints, which makes the ARE for β-sultam in series **1** and **2** larger.[5] In β-sultams the nitrogen coordination is always more pyramidal (less planar) and therefore less sensitive to the size of the larger, fused ring. This ensures that RSE does not vary markedly within the series **1**−**4**.

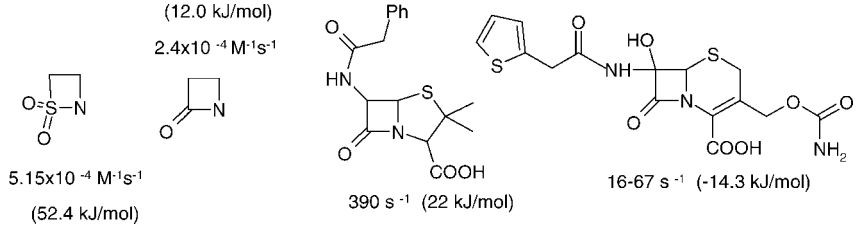
The Δ descriptor describes the net effect of stabilizing (SRE) and destabilizing (RSE) interactions. When Δ > 0 as in β-sultams, we conclude that the molecule is destabilized versus its reference molecules, and Δ < 0 indicates net stabilization. Virtually all β-sultams are destabilized to a larger or lesser extent. Among β-lactams, members of the **1**−**2** series are destabilized to a greater degree than their β-sultam analogues (Table 1). On the other hand, in the **3**−**4** series, β-sultams are destabilized while their β-lactam analogues are stabilized. A similar trend is reflected in Δ values for the parent compounds **5** (Table 1). β-Sultam has Δ = 52.14 kJ/mol, while β-lactam has Δ = 12.0 kJ/mol; the destabilization in the former is pronounced, while in the latter it is much smaller. We conclude that the enhanced reactivity of β-sultams versus β-lactams originates in the net stabilization/destabilization of the four-member ring in the two classes. The effect is not due solely to the ring strain, as was suggested previously, because the ring strain in β-sultams is smaller than or comparable to their β-lactam analogues. This argument is corroborated by the mechanistic study of the alcoholysis of β-sultam,[4] where the favored pathway includes the transition state, which is cyclic, i.e., if the ring strain was the predominant influence on reactivity, the transition state could be expected to be acyclic.

The important test of the usefulness of our calculations comprises the comparison with kinetic data for solvolytic reactions involving pharmacophores studied. We have used literature data for rates of hydrolysis of β-lactams and β-sultams

SCHEME 6: Isodesmic Reactions Used to Determine Possible Interaction between Double Bond and the β-Sultam Ring



SCHEME 7: Experimental Rate Constants for Hydroxide Ion Hydrolysis of Compounds Containing β-Sultam and β-Lactam Pharmacophores[a]



[a] The numbers in brackets correspond to Δ values, i.e., the difference between ring strain (RSE) and resonance interaction energies (SRE, ARE).

(Scheme 7) and compared such rates when they were measured under the same experimental conditions.[13−15]

The rate constants for hydrolysis of the first two compounds in Scheme 7 show that the rate of hydrolysis of parent β-sultam is approximately twice as fast as that for the β-lactam. This observation is consistent with our calculations, which show that the difference between ring strain (RSE) and amide (sulfonamide) resonance energies is positive in β-sultams (Δ > 0), but Δ < 0 in many β-lactams (Table 1). There are no published data on the rates of hydrolysis of β-sultam pharmacophores **1**−**4**, but we can compare the results for pharmacophores **5**. Δ values for the sultam and lactam pharmacophores **5** are positive and amount to 52 and 12 kJ/mol, respectively (Table 1). This is consistent with the notion that steric strain enhances the rate of hydrolysis in β-sultams more than it does in β-lactams (Scheme 7).

Positive Δ value indicates that ring strain predominates over resonance stabilization contributed by sulfonamide or lactam groups. This net destabilization of the four-member ring in β-sultams is thus consistent with and can be used to rationalize the faster hydrolysis in β-sultams compared to β-lactams.

An even more significant result concerns the experimental data for penicillins and cephalosporins (the last two compounds in Scheme 7). The hydroxide hydrolysis of these two compounds has been studied when catalyzed by cobalt-substituted β-lactamase enzyme. This is important because such conditions mimic closely the cell environment where biological degradation of antibiotics takes place, as mentioned in the Introduction.

The measured rate constants show that penicillin hydrolyzes faster that cephalosporin. The calculated differences between ring strain and amide resonance energies for these two pharmacophores amount to Δ = 22.2 kJ/mol and Δ = −14.3 kJ/mol, respectively. This concordance between experimental and computational results is significant for two reasons. First, it rationalizes on a more quantitative basis the reasons for different chemical (and biological) reactivity of antibiotic species. Second, it demonstrates that high-level computational methods can be used to predict important aspects of chemical (and by implication) biological activity in antibiotics. With respect to Scheme 7, it needs to be mentioned that the proper evaluation of kinetic data requires the consideration of strain and resonance in the transition state as well as the role of solvent effects. However, our data suggest that the kinetic behavior of lactams and sultams can be largely attributed to the intrinsic properties of reactants, which is interesting.

Summary

We discussed the influence of resonance stabilization and ring strain in a series of β-sultams on their reactivity. We have shown that β-sultams have smaller intramolecular resonance stabilization than their β-lactam analogues. The magnitude of ring strain in the two classes of compounds exhibits different behavior versus the larger fused ring: in β-sultams the size of the fused ring does not affect the four-member ring strain; in β-lactams it does.

Furthermore, we have demonstrated that the deformation of geometry is only a qualitative indicator of strain and should be substantiated by calculation of thermodynamic properties using high-level ab initio methods. Thus, for example, the suggestion that the higher solvolytic reactivity of β-sultams versus β-lactams can be attributed to large ring strain,[3] as expressed in molecular structure deformation,[3b] should be treated with caution. Calculations provide a more insightful view of stabilizing and destabilizing influences than do the molecular structure data on their own. Therefore the structural information should be complemented by thermodynamic information whenever possible when analyzing the reactivity of small, functionalized rings. The ring strain does not influence the rate of hydrolysis by itself; it is the net effect of stabilizing influences (amide or sulfonamide interaction energy) and destabilizing influences (ring strain) that determines the kinetic behavior of both β-lactams and β-sultams in solvolysis reactions.

Supporting Information Available: G3//B3LYP energies and calculated geometries for β-sultams. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Kershaw, N. J.; Kaines, M. E. C.; Sleeman, M. C.; Schofield, C. J. *Chem. Commun.* **2005**, 4251.

(2) Hermann, J. C.; Ridder, L.; Holtje, H.-D.; Mulholland, A. J. *Org. Biomol. Chem.* **2006**, *4*, 206.

(3) (a) Hinchliffe, P. S.; Wood, J. M.; Davis, A. M.; Austin, R. P.; Beckett, R. P.; Page, M. I. *Org. Biomol. Chem.* **2003**, *1*, 67. (b) Baxter, N. J.; Rigoreau, L. J. M.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2000**, *122*, 3375. (c) Page, M. I. *Acc. Chem. Res.* **2004**, *37*, 297. (d) Tsang, W. Y.; Ahmed, N.; Harding, L. P.; Hemming, K.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2005**, *127*, 8946. (e) Tsang, W. Y.; Ahmed, N.; Hinchliffe, P. S.; Wood, J. M.; Harding, L. P.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2005**, *127*, 17556. (f) Page, M. I.; Tsang, W. Y.; Ahmed, N. *J. Phys. Org. Chem.* **2006**, *19*, 446.

(4) He, M.; Feng, D.; Zhu, F.; Cai, Z. *J. Phys. Chem. A* **2004**, *108*, 7702.

(5) Novak, I.; Chua, P. J. *J. Phys. Chem. A* **2006**, *110*, 10521.

(6) Lopez, X.; Dejaegere, A.; Karplus, M. *J. Am. Chem. Soc.* **1999**, *121*, 5548.

(7) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 03*, Revision D1, Gaussian, Inc.: Pittsburgh, PA, 2003.

(8) Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghvachari, K. *J. Chem. Phys.* **1999**, *110*, 7650.

(9) Gomes, J. R. B.; Gomes, P. *Tetrahedron* **2005**, *61*, 2705.

(10) Böhm, S.; Exner, O. *Org. Biomol. Chem.* **2003**, *1*, 1176.

(11) Kabak, M.; Guner, V.; Elerman, Y.; Durlu, T. N. *Anal. Sci.* **2003**, *19*, 969.

(12) Chiaroni, P. A.; Riche, C.; Loiseau, P.; Bonnafous, M.; Adam, Y. *Acta Crystallogr.* **1985**, *C41*, 1265.

(13) Rao, S. N.; O'Ferrall, R. A. M. *J. Am. Chem. Soc.* **1990**, *112*, 2729.

(14) Badarau, A.; Damblon, C.; Page, M. I. *Biochem. J.* **2007**, *401*, 197.

(15) Wood, J. M.; Hinchliffe, P. S.; Laws, A. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **2002**, 938.

JP805024Y