

A Theoretical Study of the Exceptional Thermal Reactivity of 2-Phenyloxazolo-3-sulfolene: Roles Played by Aromaticity and Strain

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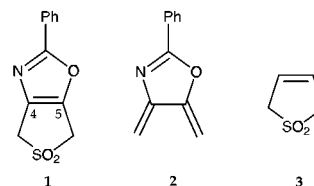
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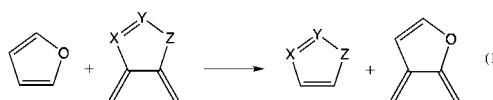
The continuous isolation and characterization of a wide range of oxazole-containing natural products in recent years have drawn increasing interests of organic chemists in the synthesis and reactions of this class of heteroaromatic compounds.¹ Nesi and Turchi et al. used 4-nitro-2-phenyloxazole to react with 4π electron systems at the C₄ and C₅ positions of oxazole to afford carbo- and heteroannulated oxazolo products.² Another potentially useful methodology to prepare derivatives of oxazole-containing compounds at the same positions is to begin with the extremely reactive oxazolo-*o*-quinodimethanes. In the past few years we and others have successfully demonstrated that heteroaromatic-fused 3-sulfolenes are ideal precursors for the corresponding *o*-quinodimethanes.^{3–5} Although not characterized in great detail, most of the heteroaromatic-fused 3-sulfolenes require temperatures at about 160–180 °C or even higher to undergo SO₂ extrusion reactions,^{3,4} but 2-phenyloxazolo-3-sulfolene (**1**) loses SO₂ at room temperature in 6 h.⁵ In fact, it is advantageous that oxazolo-*o*-quinodimethanes (**2**) can be generated so easily because it means that derivatization reactions such as 1,4-addition or [4 + 2] cycloaddition can take place at very mild conditions.⁵

Previously, we ascribed the fact that heteroaromatic-fused 3-sulfolenes require higher temperature (above 160 °C) than simple 3-sulfolenes (100–120 °C) to undergo SO₂ extrusion to the following reasons: (1) aromaticity of the heteroaromatic moiety is destroyed during SO₂ extrusion; (2) there is less double bond character between C₄–C₅ (see **1**) of heteroaromatic-fused 3-sulfolenes than that of 3-sulfolenes.⁶ We are intrigued by the ease of SO₂ extrusion of 2-phenyloxazolo-3-sulfolene because the above reasoning fails to explain its exceptional thermal reactivity. For example, no fused aromatic ring is

affected in SO₂ extrusion of 3-sulfolenes (**3**), and yet the reaction temperature range is significantly higher than that of 2-phenyloxazolo-3-sulfolene.



Oxazole is known to be less aromatic than many five-membered aromatic heterocycles^{7,8} and to undergo Diels–Alder reaction readily.⁹ How this weak aromaticity affects the reactivity of oxazole-containing sulfolene is one of our main concerns. One way to estimate the stabilization energy originated from electron delocalization is to calculate the reaction energy of a homodesmotic reaction,¹⁰ in which reactants and products have the same number of each bond type (such as C_{sp²}–C_{sp²}, C_{sp³}–C_{sp²}) and the same number of non-hydrogen atoms with zero, one, two, or three attached hydrogen atoms (e.g., CH₂). To evaluate how the change of electron delocalization during the reaction contributes to the reactivity of oxazolo-3-sulfolene, we carried out calculations¹¹ of homodesmotic reactions (eq 1) which involve the π units



of reactants and products. If the reaction energy of homodesmotic reaction eq 1 (ΔE) is positive, the change of π electron delocalization favors the heterocycle under investigation over furan for dearomatization to give *o*-quinodimethane; if the energy is negative, the heterocycle is less favored. Results calculated at the HF/6-31G**/HF/6-31G* and MP2(FC)/6-31G**/HF/6-31G* levels are shown in Table 1. As can be seen in Table 1, that oxazole (X = N, Z = O) indeed affords positive reaction energy of reaction (eq 1) and is the compound that undergoes dearomatization more readily than furan, isoxazole, pyrazole, and thiazole. The reaction energy of homodesmotic reaction for 2-phenyloxazole at the level of HF/6-31G* is ca. 1.3 kcal/mol more positive than that of oxazole; therefore, the effect of the phenyl ring attached to C₂ of oxazole is to further facilitate the ease of dearomatization. Since more extended conjugation reduces the HOMO–LUMO gap, it is not surprising that the aromaticity of the oxazole moiety in 2-phenyloxazole is weaker than that in the parent oxazole.

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(6) 3-Sulfolene, with a full double bond character between C₃–C₄, undergo SO₂ extrusion at 100–120 °C, whereas sulfolene, with a single bond character between C₃–C₄, undergoes SO₂ extrusion and fragments at temperature higher than 500 °C. See ref 4 for more discussion.

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(11) All calculations are carried out with Gaussian 94, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Latham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Pittsburgh, PA, 1995.

Table 1. Reaction Energies of Homodesmotic Reactions in kcal/mol. ΔE is the Reaction Energy of Homodesmotic Reaction in Equation 1 and $\Delta\Delta E$ is the Difference of Reaction Energies of Homodesmotic Reactions Equations 2 and 3 ($\Delta E(\text{eq } 2) - \Delta E(\text{eq } 3)$)

	ΔE		$\Delta\Delta E$		sum MP2 ^b
	HF(ZPVE) ^a	MP2 ^b	HF(ZPVE) ^a	MP2 ^b	
Z = O	0.0(0.0)	0.0	8.44(8.58)	7.15	7.15
X = N, Z = O	3.28(3.25)	2.96	13.57(13.64)	11.77	14.73
X = N, Y = CPh, Z = O	4.62				
Y = N, Z = O	-5.22(-5.04)	-5.51	12.74(12.79)	10.65	5.14
Y = N, Z = N	-12.00(-11.70)	-12.91	7.76(8.05)	5.84	-7.07
X = N, Z = S	-2.42(-2.57)	-1.36	6.51(6.55)	4.74	3.38

^a Results obtained at the HF/6-31G**//HF/6-31G* level. Energies corrected for zero point vibrational energy (ZPVE) are presented in parentheses. ^b Results obtained at the MP2/6-31G**//HF/6-31G* level.

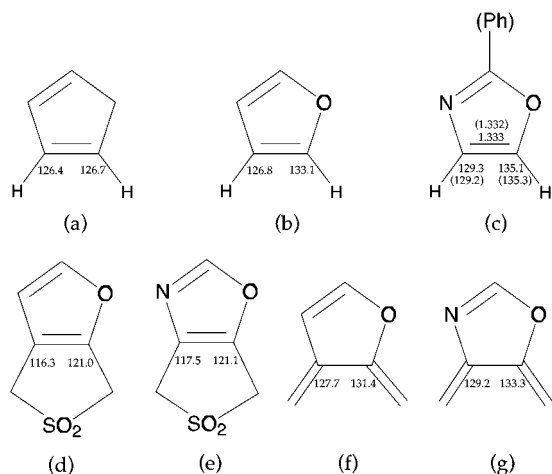


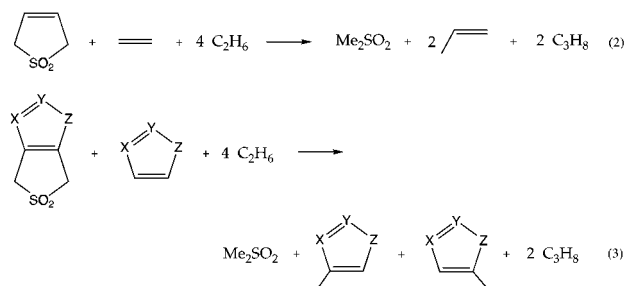
Figure 1. Exocyclic bond angles calculated at the HF/6-31G* level for (a) cyclopentadiene, (b) furan, (c) oxazole, (d) furano-3-sulfolene, (e) oxazolo-3-sulfolene, (f) furano-2,3-quinodimethane, and (g) oxazolo-4,5-quinodimethane. To show the structural resemblance of the oxazolo moiety in oxazole and 2-phenyloxazole, the exocyclic bond angles and C₄-C₅ bond length of 2-phenyloxazole are shown in parentheses.

An examination of AM1¹²-optimized structures of cyclopentadiene, furan, and oxazole shows that the replacement of a carbon atom with an oxygen atom in cyclopentadiene opens the exocyclic angles $\angle\text{HCC}$; additional replacement with nitrogen opens the angles further. This angle-opening trend is confirmed by structures calculated at the RHF/6-31G* level for cyclopentadiene, furan, and oxazole, for furano-3-sulfolene and oxazolo-3-sulfolene, and for furano-2,3-quinodimethane and oxazolo-4,5-quinodimethane. Angles of interest are labeled in Figure 1; it is found that the angles of the oxazolo compound are always larger than that of the furano compound in the same family. It is also found that in 3-sulfolenes (Figure 1d,e) the angles (ca. 120°) are 10° smaller than that of simple heteroaromatic compounds (Figure 1a-c) or that of *o*-quinodimethanes (Figure 1f,g) (ca. 130°). Therefore, it seems plausible that SO₂ extrusion is accompanied by relieving strain of the sulfolenyl ring. In other words, the strain in the SO₂-containing ring may play a role in the relative reactivity of 3-sulfolenes. It should be noted that geometry parameters of 2-phenyloxazole are very similar to those of oxazole (Figure 1c). Therefore, oxazolo-3-sulfolene was used as a model to evaluate the importance of ring strain in 2-phenyloxazolo-3-sulfolene in the following discussion.

Homodesmotic reactions have also been effective in evaluating the strain energy in cyclic compounds;¹³

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therefore, we carried out calculations of homodesmotic reactions (eqs 2 and 3) to estimate the sulfolenyl ring strain of heteroaromatic-fused 3-sulfolenes relative to the parent 3-sulfolene. In eq 2, the energy of the sulfolenyl ring is compared to its acyclic counterparts. In eq 3, only the sulfolene ring is opened; the heteroaromatic ring



remains intact on both sides of the reaction. Therefore, the energy difference between eqs 2 and 3 ($\Delta\Delta E = \Delta E(\text{eq } 2) - \Delta E(\text{eq } 3)$) is an indicator of the importance of sulfolenyl ring strain in heteroaromatic-fused 3-sulfolenes; a large positive value for $\Delta\Delta E$ means the parent sulfolene needs more energy to open the sulfolenyl ring and thus implies a good amount of strain in the heteroaromatic-fused sulfolenyl ring relative to the parent 3-sulfolene. As shown in Table 1, it is found that results from theory levels HF/6-31G**//HF/6-31G* and MP2/6-31G**//HF/6-31G* both show that oxazole causes more strain in the sulfolenyl ring than other five-membered aromatic heterocycles. Furthermore, significantly larger sulfolenyl ring strain in oxazolo-3-sulfolene relative to 3-sulfolene is in line with the observation that 3-sulfolene undergoes SO₂ extrusion reaction at temperatures above 100 °C,¹⁴ whereas 2-phenyloxazolo-3-sulfolene decomposes at room temperature.¹⁵

If one only considers the effect of change of electron delocalization during SO₂ extrusion, based on the value of ΔE in Table 1, the reactivity of oxazolo-, furano-, and thiazolo-3-sulfolenes should not differ to a great extent. On the other hand, if one only considers the effect of sulfolenyl ring strain, oxazolo- and isoxazolo-3-sulfolenes should be both very reactive based on their close strain energy $\Delta\Delta E$ (Table 1). However, if the sums of ΔE and $\Delta\Delta E$ are used to roughly score the cumulative effect of both factors, the reactivity of oxazolo-3-sulfolene

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(15) As discussed in the previous paragraph, the strain in the sulfolenyl ring of 2-phenyloxazolo-3-sulfolene is assumed to be similar to that of oxazolo-3-sulfolene.

stands out (the sums at MP2/6-31G**//HF/6-31G* level are shown in Table 1). At the HF/6-31G*//HF/6-31G* and MP2(FC)/6-31G**//HF/6-31G* levels, oxazolo-3-sulfolene indeed afforded the lowest activation energies, as well as the lowest reaction energies, among the five simple sulfolenes described in Table 1. The excellent linear correlation (correlation coefficient $R = 0.998$) between the reaction energies and the energy sums of homodesmotic reactions (Table 1, sum) implied that we have succeeded in finding and separating the reaction controlling factors with designed homodesmotic reactions. Nevertheless, the homodesmotic reactions involved only reactants and products of the SO₂ extrusion reactions, not the transition states. If the controlling factors found above were important in the transition states, the energy sums should also correlate with the activation energies. This was indeed the case; the correlation coefficient for the activation energy – sum of homodesmotic reactions correlation was 0.976. If a weighted sum was considered (i.e., ΔE is multiplied by 0.7 and $\Delta\Delta E$ is multiplied by 0.3), the R value of the activation energy-weighted sum of homodesmotic reactions correlation was 0.997. Therefore, in the transition state, aromaticity is the leading controlling factor and strain is of secondary importance. The correlation plots and the computational results discussed in this paragraph have been included in the Supporting Information.

Finally, it should be pointed out that the above rationalization based on aromaticity and strain not only provides an explanation for the reactivity of 2-phenyloxazolo-3-sulfolene, but is also in line with the high reaction temperature requirement (210–240 °C) for SO₂ extrusion of six-membered aromatic-fused 3-sulfolenes.⁴ For these compounds, their aromaticity is higher than the five-membered aromatic compounds,¹⁶ and the strain in the sulfolenyl ring should be small since the exocyclic angle

of the six-membered aromatic compound is around 120°,¹⁷ close to the corresponding angles in the sulfolenyl ring.

In summary, with the help of homodesmotic reactions, we have investigated the roles of electron delocalization and strain in determining the thermal reactivity of five-membered heteroaromatic-fused 3-sulfolenes. We found that the weak aromaticity of the 2-phenyloxazole unit and the strain, caused by the oxazole moiety, in the sulfolenyl ring contribute to the exceptional thermal reactivity of 2-phenyloxazolo-3-sulfolene. By studying this interesting experimental observation, we have shown that five-membered heteroaromatic groups may cause quite different strain to the fused neighboring rings and thus modify their reactivities.

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Supporting Information Available: Correlations of reaction energies versus sums of homodesmotic reaction energies and of activation energies versus sums of homodesmotic reaction energies (Figure S1), correlation of activation energies versus weighted sums of homodesmotic reaction energies (Figure S2), and coordinates and energies of computed structures (including the transition states mentioned in text) (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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