esters stops short of completion. Since methyl cyclohexanecarboxylate (entry 11) and methyl 2-phenylbutyrate (entry 12) react smoothly under the given conditions, this effect cannot be adequately explained by steric factors. However, for these substrates, complete conversion is achieved by the addition of $PhSiH_3$, presumably due to its smaller size and more reactive Si–H bonds.[7] Several other limitations of this method have been discovered to date. For instance, α,β-unsaturated esters react to give mixtures of 1,2 reduction and fully saturated products. In addition, α-bromo esters and ω-cyano esters have not been successfully converted to the desired products.

We are at present unsure as to the nature of the active catalyst in this system. One possibility is that this is a simple Lewis acid-catalyzed hydrosilylation.[3a] However, we have determined that the conversion of ethyl decanoate to decanol is unaffected, in terms of either rate of formation or yield of product, by the addition of 20 equiv (relative to catalyst) of Lewis bases such as pyridine, THF, or PMe_3. A radical mechanism is unlikely since no rearrangement products are found in the reduction of a vinylcyclopropyl ester (Table I, entry 15).[8] An alternate scenario is that the active species in this system is an anionic pentavalent silicon hydride.[9] These species are also known to be electron donors toward organic halides, forming reductive coupling products. However, under our described conditions, ethyl 6-bromohexanoate is converted cleanly to the alcohol with no traces of reductive dimerization (Table I, entry 4). Also, in a control experiment where 1 equiv each of $Ti(O\text{-}i\text{-}Pr)_4$, $(EtO)_3SiH$, and benzyl bromide were combined, and the mixture was heated at 45 °C, no bibenzyl was detected after 2 days. Finally, our working hypothesis involves the initial formation of a titanium hydride species, as we believe occurs in the $Cp_2TiCl_2/2$ *n*-BuLi system. Yet we have found that carrying out the reduction procedure in the presence of 20 equiv of MeI has no effect on the rate or yield of the reaction.[10] A detailed mechanistic study of this intriguing new process is clearly necessary.

In summary, we have developed a new, air-stable catalyst system for the conversion of esters into primary alcohols. The experimental simplicity and mild reaction conditions of this procedure should make it useful to synthetic chemists. We are currently investigating the mechanism of this novel catalyst system and its action on other carbonyl groups and related functionality.

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Supplementary Material Available: Detailed experimental procedures for the preparation of and spectroscopic characterization of the products given in Table I (5 pages). This material is contained in many 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.

(7) Ojima, I.; Kogure, T.; Nihonyanagi, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3506.
(8) Kochi, J.; Krusic, P. J.; Eaton, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 1877.
(9) Corriu, J. P.; Guérin, C.; Henner, B.; Wang, Q. *Organometallics* **1991**, *10*, 2297, 3200, and 3574.
(10) Manriquez, J. M.; McAlister, D. R.; Sanner, R. D.; Bercaw, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 2716.

Why Are Isoxazoles Unreactive in Diels–Alder Reactions? An ab Initio Computational Study

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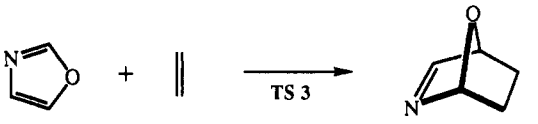
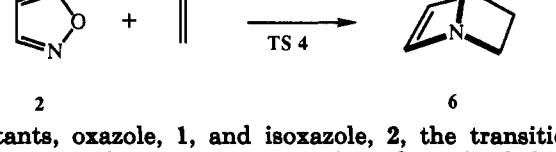
Summary: Ab initio calculations show why isoxazole Diels–Alder reactions have high activation energies and are generally not observed.

One of the most intriguing unsolved problems in heterocyclic chemistry is the different ability of oxazole and isoxazole rings to participate in Diels–Alder reactions. Diels–Alder reactions of oxazoles, **1**, have been widely exploited because of their synthetic versatility. Reactions with alkenes lead to pyridines, including Vitamin B_6, pyridoxine analogs, and condensed pyridines such as ellipticine,[1] while acetylenic dienophiles give furans.[1,2] Oxazoles also react readily with a variety of heterodienophiles.[3] Amazingly, however, there are no reports on Diels–Alder reactions of simple isoxazoles, **2**.[4]

We report here the results of a theoretical study of the Diels–Alder reactions of both oxazole and isoxazole, using ab initio molecular orbital theory. The geometries of the



1 **5**



2 **6**

reactants, oxazole, **1**, and isoxazole, **2**, the transition structures for the parent reactions of **1** and **2** with ethylene,

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(1) For a recent review, see: Maryanoff, B. E. In Oxazoles; Turchi, I. J., Ed.; The Chemistry of Heterocyclic Compounds series; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1986; Vol. 45, p 963.
(2) (a) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *Tetrahedron Lett.* **1989**, *30*, 7173 and references cited therein. (b) Whitney, S. C.; Rickborn, B. *J. Org. Chem.* **1988**, *53*, 5595.

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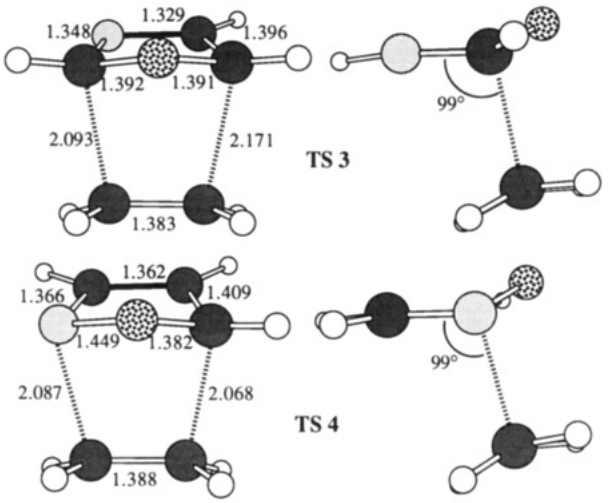


Figure 1. 3-21G optimized transition structures for the Diels–Alder reaction of oxazole (**3**) and isoxazole (**4**) with ethylene. (Bond lengths in Å; bond angles in deg.)

3 and **4**, and the corresponding Diels–Alder adducts, **5** and **6**, were optimized at the RHF/3-21G theory level;[5] the energies were also calculated at RHF/6-31G* and RMP2/6-31G* levels on the 3-21G geometries.[6] The energies of these stationary points are indicated in Table I, and the transition structures, **TS 3** and **TS 4**, are shown in Figure 1.

The geometries of the transition structures are very similar to those found for the Diels–Alder reaction of butadiene and ethylene and of 1-azabutadiene and 2-azabutadiene with ethylene.[7,8] Both transition structures are slightly asynchronous, with forming bond lengths of 2.093 and 2.171 Å in **TS 3** and 2.087 and 2.068 Å in **TS 4** (see Figure 1); these values are slightly shorter than in the reactions of azabutadienes.[8] These forming bond lengths are also shorter than the ones reported for the transition structure for the Diels–Alder reaction of cyclopentadiene with ethylene.[7c] As in the case of the transition structures for the Diels–Alder reaction of azabutadienes with ethylene,[8] there is a very small charge transfer from ethylene to oxazole (0.01 electrons) or to isoxazole (0.06 electrons). Calculations at higher levels on simpler Diels–Alder reactions indicate that these conclusions will be only slightly altered by better calculations.[7]

Consistent with the lack of reactivity of isoxazoles in Diels–Alder reactions, this process has a high activation energy. The activation energy for the isoxazole reaction is higher than for the oxazole reaction by 13 kcal/mol at the highest level of theory. Not only is the activation energy high, but the Diels–Alder reaction of isoxazole is endothermic by 4.0 kcal/mol at the MP2/6-31G*//3-21G level. At room temperature or above, the equilibrium constant for this reaction will be far on the isoxazole plus ethylene side. The reaction of oxazole, however, is quite exothermic, with a heat of reaction of −19.7 kcal/mol. For comparison, the cyclopentadiene–ethylene reaction is exothermic by 32.0 kcal/mol.[7c] Even considering the unfavorable entropy of these bimolecular reactions, the highly exothermic reactions will have favorable free energies, while that of the isoxazole reaction will be quite unfavorable.

Table I. Calculated Energetics of the Diels–Alder Reactions of Oxazole and Isoxazole with Ethylene[a]

	RHF/3-21G		RHF/6-31G*//3-21G		RMP2/6-31G*//3-21G	
reaction	E_a	ΔE (rxn)	E_a	ΔE (rxn)	E_a	ΔE (rxn)
oxazole (**1**)	33.7	−18.6	41.9	−18.2	16.0	−19.7
isoxazole (**2**)	41.5	−0.1	54.9	0.9	28.9	4.0

[a] Energies are in kcal/mol. The total energies (au) of the reactants are as follows: oxazole (**1**) −243.251 05 (RHF/3-21G), −244.628 66 (THF/6-31G*//3-21G), −245.345 67 (RMP2/6-31G*//3-21G); isoxazole (**2**) −243.210 69 (RHF/3-21G), −244.582 86 (RHF/6-31G*//3-21G), −245.309 57 (RMP2/6-31G*//3-21G); ethylene, see ref 6.

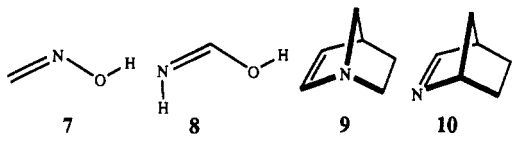
From these data, we conclude that the inability of isoxazole to participate in Diels–Alder reactions stems from the high activation barrier and the reaction endothermicity. This will also be true for a variety of substituted derivatives, since most substituents will interact in a more stabilizing fashion with isoxazole than with the adduct.

What causes the Diels–Alder adduct of isoxazole and ethylene **6** to be so unfavorable? As shown in Table I, **6** is less stable than **5** by 45.9 kcal/mol at the MP2/6-31G*//3-21G level. The reactants show the same order of stability; isoxazole is less stable than the oxazole by 22.6 kcal/mol (MP2/6-31G*//3-21G). Surprisingly, the *less* stable isoxazole is the *less* reactive diene! The calculated difference in energy agrees very well with the thermochemical measurements: the heats of formation of oxazole and isoxazole have been measured,[9] and the values for the gas phase are −3.71 ± 0.13 and 18.78 ± 0.13 kcal/mol, respectively. This gives a $\Delta\Delta H_f^\circ$ = 22.49 ± 0.13 kcal/mol, in excellent agreement with the MP2/6-31G* result of 22.6 kcal/mol. The 3-21G and 6-31G* values are 25.3 and 28.7 kcal/mol, respectively.

In order to understand better these energy differences, calculations on model systems **7**–**9** were performed. The difference between the stabilities of oxazole and isoxazole appears to result from the weakness of the N–O bond as well as the possibility of resonance involving an oxygen lone pair and the CN π bond in structures like **8**, but not **7**. Thus, in the case of the model systems formaldehyde oxime, **7**, and formamidic acid, **8**, ab initio calculations[10] indicate that **7** is less stable than **8** by 34.7 kcal/mol.

The presence of a nitrogen at the bridgehead in the Diels–Alder adduct **6** appears to be an additional factor leading to instability. To test this possibility, the structures of 1-aza- and 2-azanorbornene, **9** and **10**, were optimized.[11] Compound **9** is less stable than **10** by 21.3

(3) Hassner, A.; Fischer, B. *J. Org. Chem.* **1991**, *56*, 3419.
(4) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987.
(5) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(6) The calculations described here were performed with the GAUSSIAN 88 program: GAUSSIAN 88. Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. Gaussian Inc., Pittsburg, PA, 1988.
(7) (a) Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554. (b) Bernardi, F.; Bottini, A.; Field, M. J.; Guest, M. F.; Hillier, I. H.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1988**, *110*, 3050. (c) Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172. (d) Townshend, R. E.; Ramunni, G.; Segal, G.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1976**, *98*, 2190. (e) Ortega, M.; Oliva, A.; Lluch, J. M.; Bertran, J. *Chem. Phys. Lett.* **1983**, *102*, 317.
(8) González, J.; McCarrick, M. E.; Houk, K. N. Unpublished results.
(9) McCormick, D. G.; Hamilton, W. S. *J. Chem. Thermodynam.* **1978**, *10*, 275.
(10) The RHF/3-21G geometries and energies for **7** and **8** were taken from *The Carnegie-Mellon Quantum Chemistry Archive*, 3rd ed., 1983. The RHF/6-31G* and RMP2/6-31G* single point calculations were performed on the RHF/3-21G geometry. Total energies (au) are as follows: formaldoxime (**7**) −167.897 52 (RHF/3-21G), −168.899 06 (RHF/6-31G*//3-21G), −169.363 34 (RMP2/6-31G*//3-21G); formamidic acid (**8**) −167.950 41 (RHF/3-21G), −168.836 95 (RHF/6-31G*//3-21G), −169.307 98 (RMP2/6-31G*//3-21G).



7 8 9 10

3-21G	33.2	0.0	16.7	0.0
6-31G*	39.0	0.0	22.1	0.0
MP2/6-31G*	34.7	0.0	21.3	0.0

kcal/mol at the highest level. The bridge constrains the C-N-C angle to be 104° (the value in a typical amine is around 110°) and prevents enamine conjugation. These two factors contribute to make the Diels-Alder adduct 6 more unstable than 5 and are manifested as well in the higher energy of the TS 4.

In summary, the long-standing problem of the different reactivity of oxazole and isoxazole in Diels-Alder cycloadditions has been addressed by ab initio calculations, and the higher activation barrier and endothermicity of the isoxazole reaction can be seen as the reason for that difference. This conclusion is generally applicable to hetero-Diels-Alder reactions. There are many five-membered heterocycles with two heteroatoms. No Diels-Alder reactions are known where two heteroatoms are directly bonded so that one heteroatom appears at a bridgehead in the cycloadduct.[12] The reason is the same as that identified here for isoxazoles.

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(11) The total energies (au) are the following: 1-azanorbornene (9) -285.242 59 (RHF/3-21G), -286.830 01 (RHF/6-31G*//3-21G), -287.768 58 (RMP2/6-31G*//3-21G); 2-azanorbornene (10) -285.269 26 (RHF/3-21G), 286.865 22 (RHF/6-31G*//3-21G), -287.802 50 (RMP2/6-31G*//3-21G).

(12) An exception to this assertion is the Diels-Alder reaction of benzisoxazoles with *N*-phenylmaleimide; see: Taylor, E. C.; Eckroth, D. R.; Bartulin, J. *J. Org. Chem.* **1966**, *32*, 1899. In this case, aromatization of the cycloadduct appears to be the driving force of the reaction.

Electrolytic Partial Fluorination of Organic Compounds. 4.[1] Regioselective Anodic Monofluorination of 4-Thiazolidinones and Its Application to the Synthesis of Monofluoro β-Lactams

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Summary: Anodic partial fluorination of sulfur-containing heterocycles has been performed for the first time: 2-aryl-4-thiazolidinones 1 were monofluorinated highly regioselectively. In addition, thermolysis of the sulfones derived from fluorinated 1 provided monofluoro β-lactams in excellent yields.

Fluoro organic compounds have special chemical and physical properties. Particularly, partially fluorinated compounds are useful in the fields of material science and medicinal chemistry.[2] Therefore, selective direct fluorination is becoming increasingly important. Among selective oxidative fluorination,[3] anodic partial fluorination is attractive because fluorine atoms can be introduced into organic molecules in one step under safe conditions. However, in contrast to well-established anodic perfluorination, anodic partial fluorination has been unexplored owing to low selectivity for the fluorination and low nucleophilicity of fluoride ions.[4-6] Therefore, the development of methods for efficient selective anodic partial fluorination is an important goal of modern organofluorine research.

Recently, we achieved regioselective anodic monofluorination of sulfides bearing various electron-withdrawing groups using $Et_3N{\cdot}3HF$ as a supporting electrolyte.[7] Furthermore, we reported the first example of the successful anodic monofluorination of simple alkyl phenyl sulfides.[8]

Partially fluorinated heterocycles are the focus of much biological interest.[2,9] However, very few examples of successful anodic partial fluorination of heterocycles have been reported up to date.[10] They are limited to only nitrogen- and oxygen-containing heterocycles, and the yields are generally quite low. To the best of our knowledge, no successful electrochemical fluorination of sulfur-containing heterocycles has been reported so far.

(1) Part 3: Fuchigami, T.; Hayashi, T.; Konno, A. *Tetrahedron Lett.*, in press.

(2) (a) *Carbon-Fluorine Compounds; A CIBA Foundation Symposium*; Elsevier: Amsterdam, 1972. (b) Schlosser, M. *Tetrahedron* **1978**, *34*, 3. (c) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha & Elsevier Biomedical: Tokyo, 1982. (d) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (e) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Books: Washington, D.C., 1991.

(3) Yoneda, N. *Tetrahedron* **1991**, *29*, 5358.

(4) (a) Childs, W. V.; Christensen, L.; Klink, F. W.; Kolpin, C. F. In *Organic Electrochemistry*, 3rd ed.; Lund, H., Baizer, M. M., Ed.; Marcel Dekker: New York, 1991; Chapter 24. (b) Laurent, E.; Marquet, B.; Tardivel, R. *Tetrahedron* **1991**, *47*, 3969.

(5) Landini, D.; Angelmaria, M.; Rampoldi, A. *J. Org. Chem.* **1989**, *54*, 328.

(6) Meurs, J. H. H.; Eilenberg, W. *Tetrahedron* **1991**, *47*, 705.

(7) Fuchigami, T.; Shimojo, M.; Konno, A.; Nakagawa, K. *J. Org. Chem.* **1990**, *55*, 6074.

(8) Konno, A.; Nakagawa, K.; Fuchigami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1027.

(9) (a) *Fluorocarbon and Related Chemistry*; Banks, R. E., Barlow, M. G., Eds.; Chemical Society: London, 1971, 1974, 1976; Vols. 1-3. (b) Tanaka, K. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 16. (c) Silvester, M. J. *Aldrichim. Acta* **1991**, *24*, 31.

(10) (a) Gambaretto, G. P.; Napoli, M.; Franccaro, C.; Conte, L. *J. Fluorine Chem.* **1982**, *19*, 427. (b) Ballinger, J. R.; Teare, F. W. *Electrochim. Acta* **1985**, *30*, 1075. (c) Makino, K.; Yoshioka, H. *J. Fluorine Chem.* **1988**, *39*, 435. (d) Meurs, J. H. H.; Eilenberg, W. *Tetrahedron* **1991**, *47*, 705.

0022-3263/92/1957-3755$03.00/0 © 1992 American Chemical Society