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# Novel Concerted Fragmentation upon Alcoholysis of a Urazole

**Yanjun Wei* and David M. Lemal***

*Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755*

*david.m.lemal@dartmouth.edu*

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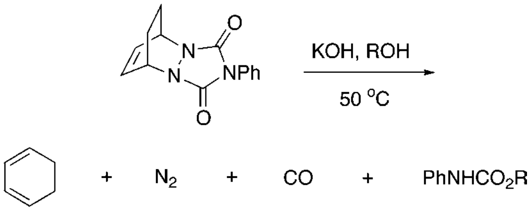
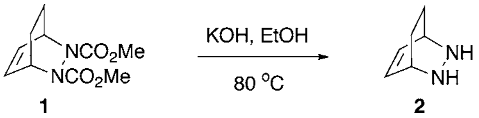
## ABSTRACT

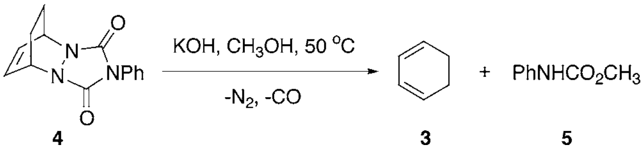


**Instead of yielding the expected hydrazine, alcoholysis of the above heterocycle results in fragmentation via a highly unusual pathway.**

Askani showed that alkaline cleavage of **1**, the Diels−Alder adduct of 1,3-cyclohexadiene (**3**) with azoester, gives 2,3-diazabicyclo[2.2.2]oct-5-ene (**2**), as anticipated.[1]

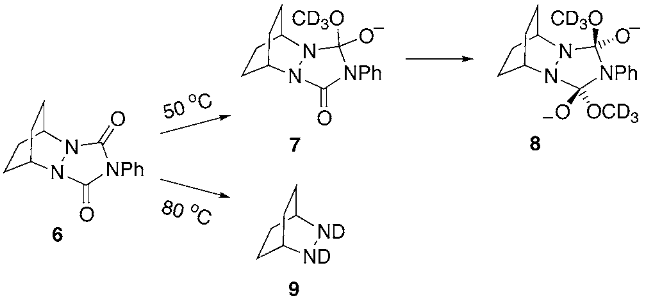


Hydrolysis (or alcoholysis) of Diels−Alder adducts of triazolinediones generally requires vigorous conditions,[2] but we have found that the adduct **4**[3] of diene **3** with 4-phenyl-1,2,4-triazolinedione is quite easily cleaved by methoxide. Surprisingly, the products are **3**, nitrogen, carbon monoxide, and methyl *N*-phenylcarbamate (**5**). Formation of carbon monoxide was confirmed both by its infrared absorption at 2171 and 2117 cm$^{-1}$ [4] and by its reaction with PdCl$_2$/CuCl$_2$ to give a black precipitate.[5,6]



For comparison, hydrogenated adduct **6**[7] was subjected to methanolysis under identical conditions (Scheme 1). No scission of the heterocyclic ring was detected. Adduct **6** was slowly transformed into methoxide-$d_3$ adduct **7**, which in turn added a second equivalent of methoxide-$d_3$ to give **8**.[8] Formation of the unsymmetrical **7** was revealed by the development of two new $^1$H NMR signals at $\delta$ 4.22 and 4.06

**Scheme 1**



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(1) Askani, R. *Chem. Ber.* **1965**, *98*, 2551.

(2) See, for example: Altundas, A.; Akbulut, N.; Balci, M. *Helv. Chim. Acta* **1998**, *81*, 828. Adam, W.; Hill, K. *J. Am. Chem. Soc.* **1985**, *107*, 3686.

(3) Gillis, B. T.; Hagarty, J. D. *J. Org. Chem.* **1967**, *32*, 330.

(4) Williams, G. D.; Whittle, R. R.; Geoffrey, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1987**, *109*, 3936.

(5) Oranskaya, O. M.; Shmulyakovskii, Y. E.; Semenskaya, I. V. *Neftepererab. Neftekhim.* **1976**, *6*, 47.

(6) Eguchi, H.; Hamada, H.; Nishitani, S. Japanese Patent 76-152731 19761217, 1978.

(7) Snyder, J. P.; Bandurco, V. T.; Darack, F.; Olsen, H. *J. Am. Chem. Soc.* **1974**, *96*, 5158.

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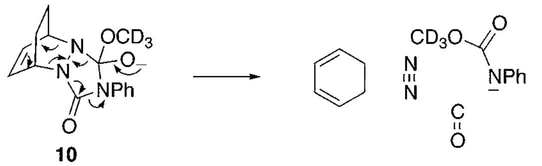
for the bridgehead hydrogens, which slowly diminished at the expense of one newer signal at $\delta$ 4.14 as $C_2$-symmetric dianion **8** appeared. The configuration of **8** is tentatively assigned as trans simply on electrostatic grounds. That ring opening had not occurred was clear from the fact that acidification caused immediate disappearance of the bridgehead peak for **8** and more slowly the pair of peaks for **7**, returning the starting material. The negative charges in adducts **7** and **8** must enjoy considerable stabilization by the geminal heteroatoms, through both inductive electron withdrawal and negative hyperconjugation. Thus, generation of **7** and **8** is driven by the fact that they are weaker bases than methoxide, and after acidification that driving force is gone.[9] Cleavage of **6** to diazabicyclo[2.2.2]octane **9** occurred only after long heating at higher temperatures.

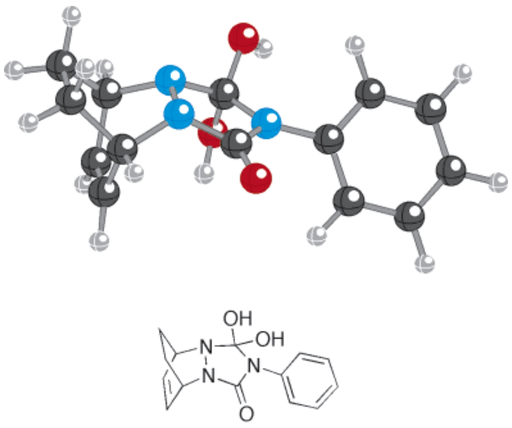
The unsaturated adduct **4** disappears with pseudo-first-order rate constant $k = 2 \times 10^{-3}\ s^{-1}$ at 50 °C in 3:1 $CD_3OD/CD_3SOCD_3$, 2 M in KOH.[10] It reacts about 10 times faster than **6** under these conditions. A pair of bridgehead signals at $\delta$ 4.94 and 4.89 corresponding to $CD_3O^-$ adduct **10** are detectable in the $^1H$ NMR spectrum during the reaction. In contrast to the behavior of **7**, **10** fragments readily via what we believe to be the fully concerted process depicted in Scheme 2.

**Scheme 2**



**10**

This transformation actually comprises two linked concerted events, fragmentation of the heterocyclic ring and *retro*-Diels−Alder reaction. They are made energetically feasible by the simultaneous formation of both $\pi$ bonds of the very stable molecular nitrogen. Whereas the newly forming carbonyl bond is poorly aligned to stabilize the negative charge developing on nitrogen, the phenyl ring may play that role. Alternatively, covalent bonding to a hydrogen-bonded deuteron may occur as the charge develops at nitrogen. Formation of the mutually perpendicular N−N $\pi$ bonds is facilitated by the fact that the nitrogen atoms are already pyramidalized in the ground state, as shown in the B3LYP/6-31G* structure of the hydrate **11** of urazole **4** (Figure 1).[11] The crystal structure of urazole **6** reveals a similar degree of pyramidalization.[12]

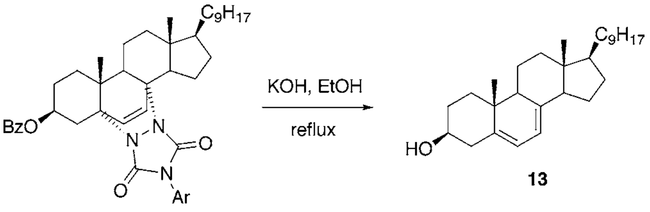


**11**

**Figure 1.**

Normal hydrolysis or alcoholysis of a urazole ring, producing a hydrazine, leaves the carbonyl carbons in the +IV oxidation state. In this case, oxidation occurs at nitrogen with the result that a carbonyl carbon is reduced to the +II oxidation state. The fact that alcoholysis of **4** is far easier than that of its saturated counterpart **6** indicates that the concerted fragmentation enjoys significant driving force.

Barton et al. recovered ergosterol (**13**) from its adducts with triazolinediones (**12**) upon treatment with KOH in ethanol.[13] They suggested that the reaction proceeds with formation of a diimide, as shown in Scheme 3. This pathway



**12**

**13**

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(8) For examples of stable "hemiketals" and hydrates formed from structurally related carbonyl groups, see: Addink, R.; Berends, W. *Tetrahedron* **1981**, *37*, 833. Yakushijin, K.; Suzuki, R.; Kawaguchi, N.; Tsuboi, Y.; Furukawa, H. *Chem. Pharm. Bull.* **1986**, *34*, 2049. Goerlitzer, K.; Buss, D. *Arch. Pharm.* **1985**, *318*, 97. Capuano, L.; Lazik, W.; Zander, R. *Chem. Ber.* **1974**, *107*, 3237. Tanaka, F. S.; Hoffer, B. L.; Wien, R. G. *J. Agric. Food Chem.* **1988**, *36*, 180. Barr, D. A.; Grigg, R.; Gunaratne, H. Q. N.; Kemp, J.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1988**, *44*, 557.

(9) Consistent with this finding are calculations of the free energy of addition of water across, and of hydroxide ion to, the carbonyl group of a simple amide. In this case, both processes are thermodynamically unfavorable, but hydroxide addition to give the "hemiketal" anion is considerably less so. Guthrie, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 3608.

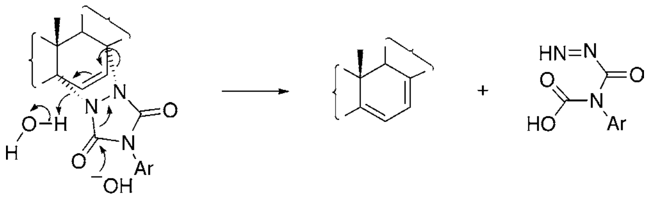
(10) The *p*-nitro analogue of **4** reacts somewhat faster. In the same medium but at 30 °C, its pseudo-first-order rate constant $k$ is $1 \times 10^{-3}\ s^{-1}$.

(11) *Gaussian 98*, Revision A.5; 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.; Stratman, 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.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc.; Pittsburgh, PA, 1998.

(12) van der Ende, C.; Offereins, B.; Romers, C. *Acta Crystallogr.* **1974**, *B30*, 1947.

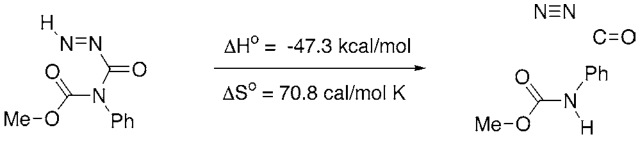
(13) Barton, D. H. R.; Lusinchi, X.; Ramirez, J. S. *Bull. Soc. Chim. Fr.* **1985**, 849. Barton, D. H. R.; Shioiri, T.; Widdowson, D. A. *J. Chem. Soc. C* **1971**, 1968.

**Scheme 3**

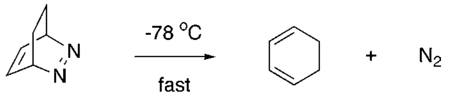


lacks the driving force of forming molecular nitrogen, and it is not clear why the bonds to the ergosterol moiety should be broken. We have compared the thermodynamics of Barton's mechanism and ours for the alcoholysis of **4** with calculations at the B3LYP/6-31G* level of theory.[14] Because 1,3-cyclohexadiene (**3**) is common to both, it sufficed to compare the other fragments from the two pathways, as shown in Scheme 4. The great difference in both enthalpy and entropy, corresponding to $\Delta G° = -68.4$ kcal/mol at 25 °C, provides strong support for the interpretation offered in Scheme 2.

**Scheme 4**



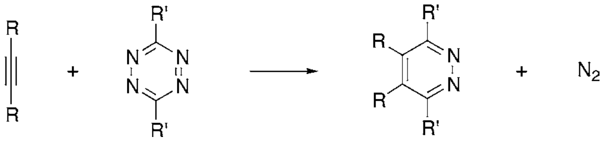
Regarding just the *retro*-Diels–Alder component of the coupled concerted process, fragmentation of 2,3-diazabicyclo-[2.2.2]octa-2,5-diene (**14**) occurs quickly at −78 °C.[15] From B3LYP/6-31G* calculations, $\Delta H° = -39.5$ kcal/mol and $\Delta S° = 42.4$ cal/mol K for this process, corresponding to $\Delta G° = -52.2$ kcal/mol at 25 °C.



**14** **3**

The transformation shown in Scheme 2 belongs to the class of concerted reactions termed *coarctate*, because at each of the two linked nitrogens two bonds are broken and two new ones are formed.[16] Not all reactions in which concerted processes are coupled necessarily fit the definition of coarctate reactions, however. A case in point would be an acetylene-tetrazine reaction in which Diels–Alder addition is concerted with nitrogen loss to give a pyridazine, a *retro*-Diels–Alder reaction (Scheme 5). According to a detailed theoretical analysis of one such transformation, it is "conceivable that reaction . . . actually involves the addition of acetylene and elimination of nitrogen occurring in a one-step, yet asynchronous, process."[17]

**Scheme 5**



Finally, the question remains why the azoester adduct (**1**) of 1,3-cyclohexadiene gives the hydrazine **2** upon treatment with alcoholic base instead of fragmentation products. A likely reason is that in the favored conformations of **1** the bicyclic system is twisted, and the free energy barrier for "bridge flipping" is 16.4 ± 0.3 kcal/mol.[18] Thus, considerable energy would be required to bring the methoxycarbonyl groups into proper alignment for the concerted process depicted in Scheme 2.

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**Supporting Information Available:** Experimental details, including characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The calculations take account of zeropoint energy differences and thermal corrections to 289.15 K.

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(16) Herges, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 255.

(17) Cioslowski, J.; Sauer, J.; Hetzenegger, J.; Karcher, T.; Hierstetter, T. *J. Am. Chem. Soc.* **1993**, *115*, 1353. See also: Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885.

(18) Anderson, J. E.; Lehn, J. M. *Tetrahedron* **1968**, *24*, 123.