substrate (40%), intermediate (40%), and product (20%). The phosphoryl intermediate appeared to be moderately base stable at pH 13, with no significant decomposition after 4 h at 4 °C. However, after overnight scanning there were detectable changes in the ^{31}P NMR spectrum. The integral area for the peak at 16.1 ppm (phosphocysteine intermediate) was reduced while the peak at 5.5 ppm (inorganic phosphate) was increased, indicating decomposition. In addition, a small resonance appeared at −1.0 ppm. This resonance could be an Enz-N-PO_3^{2-} resulting from intramolecular transfer of the phosphate from the active site cysteine to the adjacent histidine (transfer from Cys 1522 to His 1521). The spectral characterization coupled with our rapid quench kinetics along with previous data provides definitive identification of the covalent phosphorylcysteine intermediate in the LAR PTPase reaction pathway. We can now conclude with confidence that the reaction proceeds by forming a covalent phosphocysteine intermediate which is subsequently hydrolyzed to product.

Although there are numerous examples of covalent phosphoryl intermediates utilizing oxygen as the nucleophilic species,[18,19] there are relatively few examples which employ cysteine.[10,15] It is likely that the utilization of the cysteine active site nucleophile is a common mechanistic feature of both low molecular weight and high molecular weight PTPases. The implications of this reaction mechanism are not fully understood; however, they may have a major impact on designing inhibitors and modulating the activity of the PTPase enzymes.

Acknowledgment. This work was supported by the NIH (RR03475), NSF (DMB8610557), and ACS (RD259). We thank Dr. Ian Armitage, Eric Miller, and Pierre Casagrande for help with NMR experiments.

(18) Schwartz, J. H.; Lipmann, F. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 1996–2005.
(19) VanEtten, R. L. *Ann. N.Y. Acad. Sci.* **1982**, *390*, 27–51 and references cited therein.
(20) Anderson, K. S.; Sikorski, J. A.; Johnson, K. A. *Biochemistry* **1988**, *27*, 7395–7406.
(21) The rapid quench apparatus was obtained from KinTek Instruments, 106 Althouse Lab, University Park, PA 16802.

Regioselectivity in Intramolecular Cycloaddition of Double Bonds to Triplet Benzenes

Peter J. Wagner,* Masami Sakamoto, and Ahmad E. Madkour

Chemistry Department, Michigan State University East Lansing, Michigan 48824

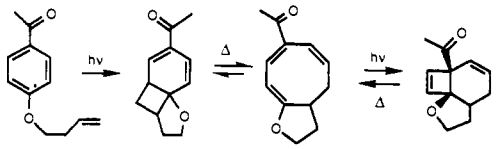
Received November 18, 1991

A few years ago we reported that double bonds undergo intramolecular 2 + 2 ortho cycloaddition to the π,π^* triplet states of acylbenzenes, when tethered ortho or para to the acyl group.[1-3] In the cases first studied, the initial bicyclo[4.2.0]octa-2,4-dienes undergo rapid thermal opening to cyclooctatrienes, which undergo further photochemistry as shown in Scheme I.[2] We now report that ring substituents promote high regioselectivity in the formation of stable cycloadducts. The selectivity appears to reflect inductive effects both on the initial triplet-state cycloaddition and on the competing thermal and photochemical electrocyclization reactions of the photoproducts.

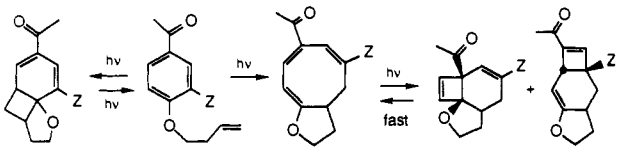
We have prepared[4] and studied several meta-substituted *p*-butenoxyacetophenones **1a–e**. Scheme II summarizes the results in terms of stable, isolable products. Irradiation[5] of the amide

(1) Wagner, P. J.; Nahm, K. *J. Am. Chem. Soc.* **1987**, *109*, 4404.
(2) Wagner, P. J.; Nahm, K. *J. Am. Chem. Soc.* **1987**, *109*, 6528.
(3) Wagner, P. J.; Sakamoto, M. *J. Am. Chem. Soc.* **1989**, *111*, 9254.
(4) Fries rearrangement of the acetates of ortho-substituted phenols provide the phenol precursors to **1** in good yields. All materials were fully characterized as to structure and purity before use.

Scheme I



Scheme II



2a **1a-d** **3b,c,d** **4b,c,d** **5c**

a : Z = OMe **b** : Z = $CONH_2$ **c** : Z = CN **d** : Z = CH_3 **e** : SCH_3

1b produces a >90% yield of a single photoproduct, **4b**.[6] Whereas the cyclobutenes reported earlier take days to open to cyclooctatrienes,[7] **4b** opens to **3b**[8] in a few hours. Near-UV irradiation of isolated **3b** converts it quantitatively to **4b**, which begins to revert to **3b** as its NMR spectrum is being recorded.

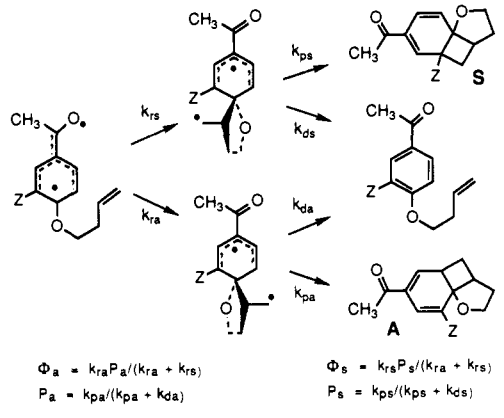
Similar irradiation of the nitrile **1c** produces, in >90% total yield, the two isomeric cyclobutenes **4c** and **5c**[9] produced by disrotatory electrocyclization of each diene unit in cyclooctatriene **3c**. Cyclobutene **4c** is formed by closure of the same diene unit that closes in **3b**, while **5c** represents the first example that we have seen of the other diene unit closing so that the acetyl group ends up on the cyclobutene double bond. (Gilbert reported an analogous structure as the only product from *p*-butenoxybenzonitrile.[10]) Upon standing, the mixture of **4c** and **5c** converts to **3c** and **4c** within 1 day, while **5c** requires 2 weeks. The linear cyano group at the bridgehead position apparently produces less steric driving force for opening than do the acetyl and carboamido groups, although the photoinduced closure does not show the converse effect. Irradiation of isolated **3c**[11] again produces a mixture of **4c** and **5c**.

Irradiation of methyl-substituted **1d** at 313 nm produces mainly **4d** plus a minor amount of a di-π-methane rearrangement product

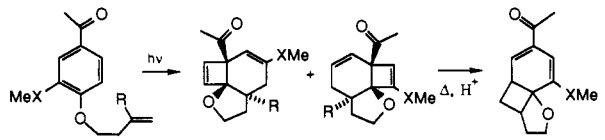
(5) Benzene solutions 0.02 M in ketone were prepared in argon-flushed, sealed NMR tubes that were attached to the outside of a quartz immersion well containing a medium-pressure mercury arc filtered only by Pyrex (λ > 290 nm). They were irradiated until no starting material remained (3 h for **1a,e**, 1 h for **1b–d**). (These times represent quantum yields in the 0.03–0.10 range.) Reaction progress was monitored by NMR spectroscopy. In preparative runs, 100 mg in 200 mL of argon-flushed solvent was irradiated in a Pyrex-filtered immersion well. After solvent was removed, the crude product was examined by NMR and then chromatographed on silica gel. Decoupling experiments on the products were consistent with the proposed structures.
(6) **4b**: ^1H NMR (CD_3OD) δ 1.77 (m, 1 H), 1.89 (m, 1 H), 2.21 (s, 3 H), 2.24 (ddd, J = 17.0, 5.7, 3.0 Hz, 1 H), 2.45 (m, 1 H), 2.71 (dd, J = 17.0, 3.0 Hz, 1 H), 3.71 (ddd, J = 8.6, 8.2, 3.7 Hz, 1 H), 3.78 (ddd, J = 9.9, 8.2, 6.9 Hz, 1 H), 6.31 (d, J = 2.8 Hz, 1 H), 6.48 (dd, J = 2.8, 0.6 Hz, 1 H), 6.58 (d, J = 3.0 Hz, 1 H); ^{13}C NMR δ 24.14, 28.02, 30.12, 31.40, 40.76, 68.03, 132.51, 132.89, 139.35, 140.99, 173.31, 212.84.
(7) Cheng, K.-L. Unpublished results.
(8) **3b**: ^1H NMR (CD_3OD) δ 1.89 (m, 1 H), 2.25 (m, 1 H), 2.37 (s, 3 H), 2.44 (dd, J = 13.8, 7.9 Hz, 1 H), 2.89 (dd, J = 13.8, 2.8 Hz, 1 H), 3.05 (m, 1 H), 4.16 (ddd, J = 10.1, 8.3, 5.7 Hz, 1 H), 4.25 (ddd, J = 8.3, 8.3, 2.5 Hz, 1 H), 5.49 (dd, J = 8.5, 2.0 Hz, 1 H), 7.16 (s, 1 H), 7.30 (d, J = 8.5 Hz, 1 H).
(9) **5c**: ^1H NMR (C_6D_6) δ 0.87 (tdd, J = 11.7, 11.1, 8.6 Hz, 1 H), 0.99 (dd, J = 13.0, 11.9 Hz, 1 H), 1.23 (m, 1 H), 1.55 (m, 1 H), 1.61 (s, 3 H), 1.7 (dd, J = 13.0, 5.2 Hz, 1 H), 3.29 (ddd, J = 11.7, 8.6, 5.7 Hz, 1 H), 3.59 (d, J = 6.5 Hz, 1 H), 3.62 (ddd, J = 8.6, 8.6, 0.8 Hz, 1 H), 4.99 (dd, J = 6.5, 2.5 Hz, 1 H), 5.54 (s, 1 H). **4c**: δ 6.34 (br d, J = 2.8 Hz, 1 H), 5.80 (dd, J = 2.8, 0.5 Hz, 1 H), 5.37 (d, J = 2.8 Hz, 1 H), 3.44 (m, 1 H), 1.85 (s, 3 H). **5c** was isolated; the partial spectrum of **4c** is from the initial ~3:1 mixture of the two formed by irradiation. The peaks attributed to **4c** disappear upon standing and are replaced by those for **3c**.
(10) Cosstick, K. B.; Drew, M. G. B.; Gilbert, A. *J. Chem. Soc., Chem. Commun.* **1987**, 1867.
(11) **3c**: ^1H NMR (C_6D_6) δ 1.00 (m, 1 H), 1.13 (m, 1 H), 1.82 (ddd, J = 15.0, 8.7, 1.1 Hz, 1 H), 1.84 (s, 3 H), 1.95 (dd, J = 15.0, 3.0 Hz, 1 H), 2.28 (m, 1 H), 3.39 (ddd, J = 8.7, 8.6, 6.5 Hz, 1 H), 3.46 (ddd, J = 8.7, 7.6, 4.3 Hz, 1 H), 5.28 (dd, J = 8.2, 1.75 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 7.20 (br s, 1 H).

0002-7863/92/1514-7298$03.00/0

Scheme III



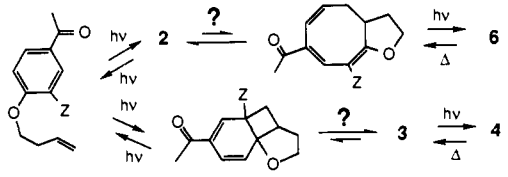
of **4d**. Irradiation at >334 nm produces **4d** quantitatively.[12] Heating or treatment with acid converts **4d** to **3d**. In contrast, irradiation to 20% conversion of the methoxy-substituted **1a** provides **2a** in >80% yield.[13] Irradiation to complete conversion is very slow but results in a 1:4 mixture of cyclobutenes **4a** and **6a**, the workup of which provided only **2a**. Similar irradiation of **1e** produces only **6e**. Methoxy-substituted **2a**, unlike all of the bicyclo[4.2.0]octa-2,4-dienes studied earlier,[2] is strongly favored in equilibrium with cyclooctatriene, none of which is detectable by NMR spectroscopy. Irradiation of **2a** produces mainly **1a**. The same behavior has been observed for an analog of **2a** in which the anchoring oxygen is replaced with a methylene group.[14] The regioselectivity afforded by the methoxy group in **1a** is completely reversed by a methyl group on the double bond, as in **1f**.



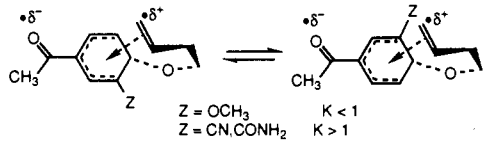
Strong electron-donating and -withdrawing substituents clearly foster opposite regioselectivities. The specificity induced by the electron-withdrawing groups is not surprising, since we also observed complete specificity for *o*-butenoxyacetophenones[2] and acetonaphthones,[3] as did Gilbert for the ortho-substituted benzonitrile.[11] The opposite effect for methoxy suggests that there is an inductive effect on the orientation in which the double bond approaches and reacts with the excited benzene ring. However, the fact that alkyl groups produce the same absolute selectivity as electron-withdrawing groups indicates that there is a second major factor that determines regioselectivity.

We are inclined to believe that one regioselectivity factor operates on the initial triplet-state cycloaddition and a second on the subsequent competing electrocyclic reactions. Our initial kinetic studies showed that the double bond acts as an electron donor[1] and the benzene ring an acceptor[15] but that the rate-determining step likely is biradical formation.[1,3] This step produces a spiro structure that fixes the regiochemistry of the cycloadduct. The ratio of the two modes of addition is determined by the product of the two rate ratios shown in Scheme III, just as in the well-known cycloaddition of triplet enones to double bonds.[16,17]

Scheme IV



The efficient cis–trans isomerization of the double bond observed earlier[1,3] indicates that the probability of cyclization, P, is only 20–30%. There is no obvious reason why P_a and P_s would differ enough to produce the near 100% regioselectivity observed, unless Z causes huge differences in spin densities at the two ends of the pentadienyl radical moiety. We conclude that initial adduct regioselectivity is controlled primarily by the k_{ra}/k_{rs} ratio. The values of k_{ra} and k_{rs} cannot reflect differences in biradical energies, since the pentadienyl radical moiety is conjugated to Z in each mode of addition and steric effects would always favor k_{ra} (except when there is a substituent on the double bond as in **1f**). The simplest explanation is based on the CT character expected for an exciplex intermediate, so that the donor double bond shuns electron-rich sites on the benzene ring (such as near methoxy) and is attracted to the more electron deficient sites near electron-withdrawing groups. This picture is analogous to the one first proposed to explain regioselectivity in the photocycloaddition of enones to alkenes.[18] Recently, however, the importance of such exciplexes and CT effects in enone cycloadditions has been seriously questioned.[16,19] However, unlike the situation for enones,[19] we *we do observe the postulated donor–acceptor behavior in the triplet decay kinetics of compounds* ***1a–e***.[3] Exciplex orientational preferences also provide the best explanation for the regiochemistry observed in the meta cycloadditions that excited singlet states of similar benzene derivatives undergo.[20]



Finally, the substituent effects that we see on the thermal stability of photoproducts **2** and **5** reinforce our earlier suggestion that these electrocyclic reactions are accelerated by significant charge transfer from oxygen to the acyl group.[2] A methoxy group on the acceptor π system slows down opening of the cyclohexadiene unit dramatically, while an extra electron-withdrawing group on the acceptor π system speeds up opening of the cyclobutenes significantly. The efficient photoreversion of the stable **2a** to phenyl ketone **1a** explains the low quantum efficiency for conversion of **1a** to **4a** and **6a**. It also suggests the possibility that different thermal chemistry of the two possible regioisomeric bicycloocta-2,7-dienes may be a major factor determining overall regioselectivity. Perhaps only the bicycloocta-2,7-diene that opens faster to cyclooctatriene produces observable bicycloocta-2,4-diene, as Scheme IV suggests.

Acknowledgment. This work was supported initially by NSF Grant CHE88-05520 and later by NIH Grant GM-39821. The NMR spectra used for structural identifications were obtained with partial support from NSF Grant CHE88-00770 and NIH Grant RR047550.

(12) **4d**: ^{1}H NMR (C_6D_6) δ 1.33 (dddd, J = 11.8, 6.7, 6.7, 2.9 Hz, 1 H), 1.57 (br s, 3 H), 1.68–1.75 (m, 2 H), 1.85–1.91 (m, 2 H), 2.13 (s, 3 H), 3.52 (ddd, J = 9.3, 8.0, 7.0 Hz, 1 H), 3.67 (ddd, J = 8.8, 8.3, 2.9 Hz), 5.50 (br s, 1 H), 5.91 (d, J = 2.88 Hz, 1 H), 6.07 (dd, J = 2.8, 0.5 Hz, 1 H).

(13) **2a**: ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.75 (dddd, J = 12.6, 6.1, 3.7, 2.65 Hz, 1 H), 1.91 (ddd, J = 12.1, 10.5, 3.8 Hz, 1 H), 2.05 (dt, J = 12.1, 8.6 Hz, 1 H), 2.13 (dddd, J = 12.6, 9.0, 8.7, 7.8 Hz, 1 H), 2.30 (s, 3 H, $COCH_3$), 3.25 (m, 1 H), 3.30 (dddd, J = 10.5, 8.6, 5.8, 1.8 Hz, 1 H), 3.66 (s, 3 H, OCH_3), 4.20 (ddd, J = 9.0, 9.0, 6.1, Hz, 1 H), 4.24 (ddd, J = 9.0, 7.8, 3.7 Hz, 1 H), 5.75 (d, J = 0.8 Hz, 1 H), 6.44 (dd, J = 5.8, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.22, 29.96, 33.71, 40.79, 48.49, 55.40, 69.24, 81.41, 92.34, 131.77, 134.52, 155.78, 196.95.

(14) H. Alehashem, unpublished work.

(15) Wagner, P. J.; Sakamoto, M. *J. Am. Chem. Soc.* **1989**, *111*, 8723.

(16) Wagner, P. J. *Top. Curr. Chem.* **1976**, *66*, 1.

(17) Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8525.

(18) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570. de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41.

(19) Schuster, D. I.; Heibel, G. E.; Brown, P. B.; Turro, N. J.; Kumar, C. V. *J. Am. Chem. Soc.* **1988**, *110*, 8261.

(20) Wender, P. A.; Siggel, L.; Nuss, J. M. *Org. Photochem.* **1989**, *10*, 358. Gilbert, A. *Pure Appl. Chem.* **1980**, *52*, 2669. (b) Mattay, J. *Tetrahedron.* **1985**, *41*, 2405.