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Intramolecular [4 + 4] Photocycloadditions: Substituent-Mediated Product Control

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Summary: Photolysis of three-carbon tethered 2-pyridones with an alcohol at C-3 yields [4 + 4] products that are exclusively trans and either syn or anti isomers depending on the nitrogen substitution.

The dominant photoreaction for concentrated solutions of 2-pyridones is a head-to-tail [4 + 4] dimerization that yields a richly functionalized 1,5-cyclooctadiene (Scheme I).[1,2] Our laboratory is exploring the intramolecular version of this photoreaction as a synthetic entry into complex cyclooctane-containing natural products.[3] One component of this investigation is to define parameters for control of the four incipient stereogenic centers by a center of chirality on the tether. For the three-carbon tether, we have reported[3] that an alcohol at C-1 (**6**, Scheme II) can substantially influence the ratio of products, a result that was shown to be solvent dependent. Anticipating that a substituent at C-3 with its proximity to the substitutable pyridone nitrogen might lead to an even greater degree of control, we have prepared bis-2-pyridone **8** and studied its photochemistry.

Initial reports of the photodimerization of 2-pyridones such as **1** concluded that only a single trans, head-to-tail isomer **2** was formed.[4-6] A detailed study by Nakamura, however, demonstrated that under some circumstances all four of the possible [4 + 4] photodimers were produced (Scheme I).[7] Significantly, he also reported the complete absence of [4 + 2] and [2 + 2] products.

Our initial photochemical results with a three-carbon tether,[3,8] with and without an alcohol at C-1 (**5**, Scheme II), were fully compatible with Nakamura's study. These reactions gave a very clean photocycloaddition to produce a mixture of four products, *trans*-**7** and *cis*-**7**, with the former dominating by a factor of 2-4. Only traces of other components could be discerned by TLC or NMR of the crude photolysis mixture. The overall ratio of trans/cis isomers was fairly constant, whether protic (methanol) or aprotic (methylene chloride) solvents were used.

It was therefore surprising that photolysis of **8** in methanol produced only the trans isomers **9** and **10**. More puzzling was the very slow photoreactivity for this compound in methylene chloride: irradiation for nearly 60 h resulted in a 30% recovery of **8** and isolation of *trans-syn*-**9** and cyclobutane **11** (major). Cyclobutane **11**, the apparent product of a [2 + 2] cycloaddition, is the first observation of this reactivity mode in the direct photolysis of 2-pyridones.[7,9]

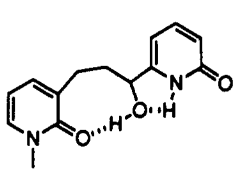
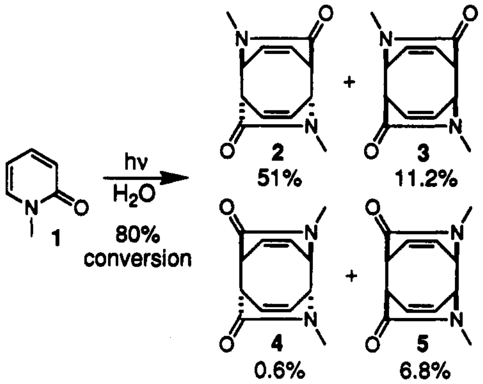
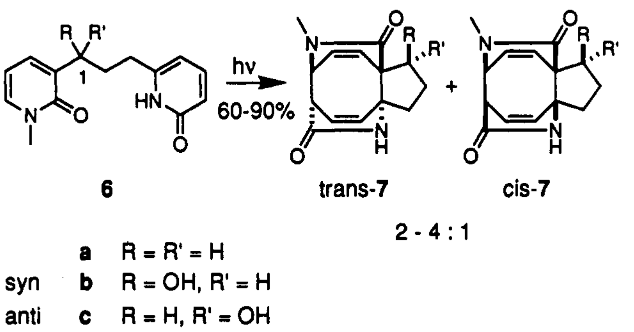


Figure 1. Possible hydrogen bonding regime for **8** in an aprotic solvent.

Scheme I. Photodimerization of 2-Pyridones Yields Predominantly the Trans, Head-to-Tail Isomer[1]



Scheme II. Photolysis of 1-Hydroxy or Tether-Unsubstituted Bis-2-pyridone 5 Yields a Trans/Cis Mixture of [4 + 4] Products



The well-known proclivity for hydrogen bonding in pyridones,[10] and the importance of hydrogen bonding in our other pyridones photochemistry studies, suggested its role in mediating the results shown in Scheme III. A possible hydrogen bonding motif is shown in Figure 1. X-ray structures[11] of **9** and **11** (Figure 2) reinforced this idea, clearly showing the NH-alcohol interaction. Interestingly, an X-ray structure of **8** only reveals *inter*molecular hydrogen bonding.

Preliminary studies support hydrogen bond donor and acceptor roles for the alcohol; disruption of these hydrogen

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[1] Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Chem. Commun.* **1978**, 620-621.

[2] Matsushima, R.; Terada, K. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1445-1448.

[3] Sieburth, S. McN.; Chen, J.-l. *J. Am. Chem. Soc.* **1991**, *113*, 8163-8164. Minor photochemical products isolated during the course of the work described in this publication have subsequently been identified as cis [4 + 4] isomers. The details will be covered in a full paper.

[4] Taylor, E. C.; Paudler, W. W. *Tetrahedron Lett.* **1960**, *25*, 1-3.

[5] Slomp, G.; MacKellar, F. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 4472-4473.

[6] Taylor, E. C.; Kan, R. O.; Paudler, W. W. *J. Am. Chem. Soc.* **1961**, *83*, 4484-4485.

[7] Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187-1191.

[8] Sieburth, S. McN.; Lin, C.-H. Unpublished results.

[9] Sharp, L. J., IV; Hammond, G. S. *Mol. Photochem.* **1970**, *2*, 225-250.

[10] For examples and lead references see: Gallant, M.; Phan Viet, M. T.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 721-723. Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696-4698.

0022-3263/93/1958-1661$04.00/0

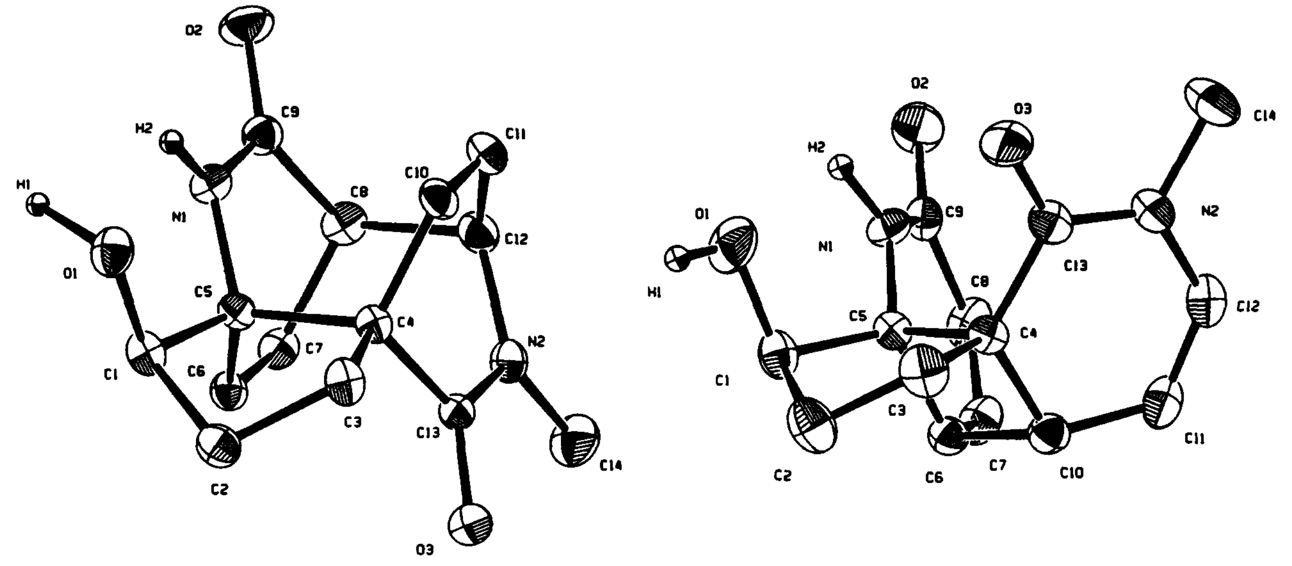
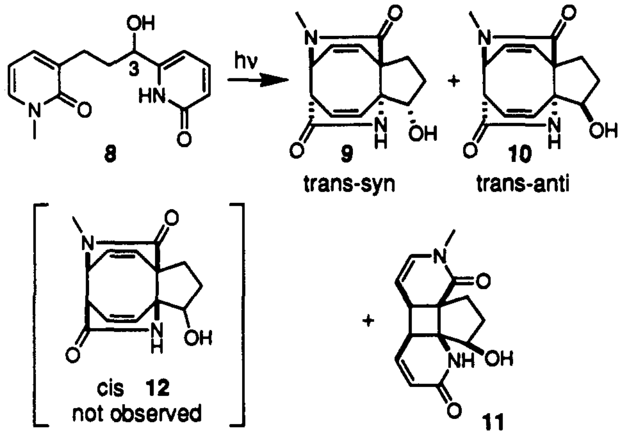


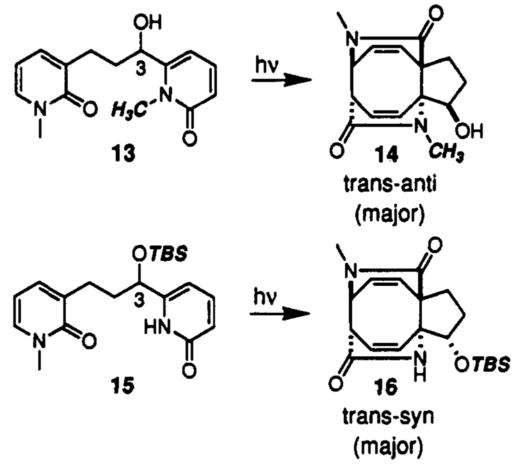
Figure 2. X-ray structures of 9 and 11.

Scheme III. Photolysis of 3-Hydroxy 8 Yields Only Trans [4 + 4] Products, and in Methylene Chloride the Major Product Is the [2 + 2] Isomer 11



solvent	reaction time	conversion	9 : 10 : 11
CH_3OH	10 h	88%	54 : 16 : 0%
CH_2Cl_2	54 h	70%	5 : 0 : 12%

Scheme IV. N-Alkylation of 8, To Give 13, Changes the Major Product from *trans-syn*-9 to *trans-anti*-14. Replacing the Alcohol Proton with a Silicon To Give 15 Retains the Syn Preference and Removes the Solvent Dependence of the Reaction



bonds was effected with derivatives *N,N'*-dimethyl 13 and (*tert*-butyldimethylsilyl)oxy 15 (Scheme IV). Irradiation of a methanol solution of 13, which cannot have a nitrogen–oxygen hydrogen bond, yields the trans-anti isomer 14 as the major photoproduct. Photolysis of 13 in methylene chloride gave, once again, a very slow conversion of 13 and a [2 + 2] isomer as the dominant product.

In contrast, photolysis of silyl ether 15, where the ether oxygen can only be a hydrogen bond acceptor,[12,13] yields at least three [4 + 4] adducts, with [2 + 2] isomers comprising no more than 5% of the product mixture. The trans-syn isomer remains the major product, and the photolysis reaction rates and product ratios are similar in both methanol and methylene chloride.

The syn selectivity for 8 and 15, and the anti selectivity for 13, are consistent with a pyridone nitrogen–alcohol hydrogen bond directing syn product formation.[14] Hydrogen bonding by the alcohol to the distal pyridone carbonyl in aprotic solvents,[15] as in Figure 1, could slow

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[11] Compound 9 crystallizes in the triclinic space group $P\bar{1}$ with a = 6.346(1) Å, b = 8.395(2) Å, c = 12.023(2) Å, α = 78.80(1)°, β = 75.25(1)°, γ = 76.74(1)°, V = 596.5(4) Å^3, and Z = 2. Final least-squares refinement using 1228 unique reflections with $I > 3s(I)$ gave $R(R_w)$ = 0.071 (0.084). Compound 11 crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 6.521(2) Å, b = 10.022(2) Å, c = 19.132(10) Å, V = 1250(1) Å^3, and Z = 4. Final least-squares refinement using 1261 unique reflections with $I > 3s(I)$ gave R (R_w) = 0.041 (0.054). The authors have deposited atomic coordinates for these compounds with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

[12] Shepherd, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5581–5583.

[13] Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697–703.

[14] Although a protic solvent might be expected to compete with intramolecular hydrogen bonding, the syn-directing effect in 8 in methanol may be an example of hydrogen bond cooperativity. For examples and references see: Steiner, T.; Saenger, W. *J. Am. Chem. Soc.* **1992**, *114*, 7123–7126. Jeffrey, G. A.; Gress, M. E.; Takagi, S. *J. Am. Chem. Soc.* **1977**, *99*, 609–611. Tse, Y.-C.; Newton, M. D. *J. Am. Chem. Soc.* **1977**, *99*, 611–613. Lemieux, R. U.; Pavia, A. A. *Can. J. Chem.* **1969**, *47*, 4441–4446. For a discussion of silyl ether basicity and hydrogen bonding, see ref 12.

[15] For a crystal structure of a similar hydrogen bond see: Gallant, M.; Phan Viet, M. T.; Wuest, J. D. *J. Org. Chem.* **1991**, *56*, 2284–2286.

photoreaction by enforcing a photounreactive conformation.[16] It is unclear, however, why this would favor the formation of [2 + 2] product over [4 + 4] product. Further studies are in progress.

A tether substituent at C-3 exerts a significant influence on the photochemistry of this bis-2-pyridone system. These results should prove useful in synthetic applications of this intramolecular [4 + 4] photocycloaddition.

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Supplementary Material Available: Physical data and spectra for 8–11 and experimental procedures for their preparation (17 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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(16) An alternative explanation for the low reactivity of 8 in methylene chloride would be the dominance of a pyridinol tautomer, rather than the pyridone depicted. This explanation is inconsistent, however, with the UV spectrum of 8 in this solvent (λ_{max} = 312, 234) and the similar photochemical behavior of 13. For a discussion of pyridone–pyridinol tautomerization, see ref 10.