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Solvent-Dependent Stereoselectivity of Bis-2-pyridone [4 + 4] Photocycloaddition Is Due to H-Bonded Dimers

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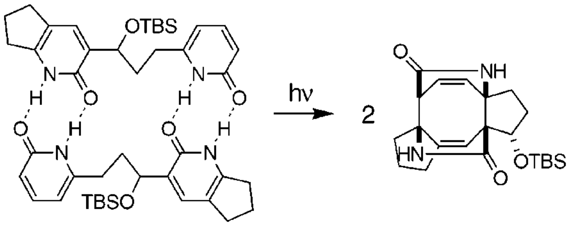
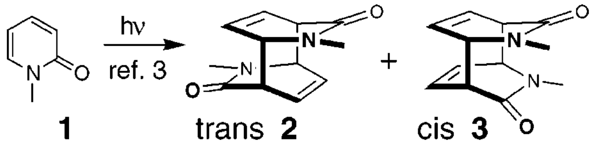
ABSTRACT



A solvent-dependent stereoselectivity found for intramolecular [4 + 4] photocycloaddition of tethered 2-pyridones is concentration dependent, indicating that a dimeric structure with four hydrogen bonds plays a critical role in the observed cis selectivity found for nonpolar solvents.

Photodimerization of 2-pyridones **1**,[1] first described in 1960, is an efficient [4 + 4] cycloaddition that is highly regiospecific and often stereoselective.[2] For example, many reports describe the formation of trans, head-to-tail isomers such as **2**. Other reports describe the formation of head-to-tail trans/cis mixtures **2** and **3**. Interestingly, changes in solvent have had little effect on the trans/cis ratio. Nakamura found that dimerization of **1** and similar pyridones led to a trans/cis ratio of approximately 60:40 in both benzene and ethanol (Scheme 1).[3] For photocycloaddition of pyridones joined by a three-carbon tether, stereoselectivity is likewise unaffected by changes in solvent.[4]

Scheme 1. Stereoselectivity in 2-Pyridone Photodimerization Is Solvent Insensitive



1 trans **2** cis **3**

solvent	C_6H_6	EtOH
2 : 3	60 : 40	56 : 44

We recently reported the first example of solvent-dependent stereoselectivity in the photocycloaddition of tethered pyridones **4** (Scheme 2).[5] Notably, the solvent-dependent stereoselectivity was only observed with **4a**, in which both pyridone nitrogens were unsubstituted. Introduction of a single methyl group (**4b**, or two *N*-methyl groups, data not shown here) results in complete selectivity for the trans isomer **5b**.[5,6] A study of this photocycloaddition in 11 solvents, spanning a solvent polarity (E_t) from 34 (benzene) to 55 (methanol), found that increases in the proportion of

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[1] Sieburth, S. McN. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI: Greenwich, CT, 1999; Vol. 5, pp 85−118.
[2] Taylor, E. C.; Paudler, W. W. *Tetrahedron Lett.* **1960**, *No. 25*, 1−3.
[3] Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187−1191.
[4] Sieburth, S. McN.; Hiel, G.; Lin, C.-H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80−87.
[5] Sieburth, S. McN.; McGee, K. F., Jr.; Al-Tel, T. H. *J. Am. Chem. Soc.* **1998**, *120*, 587−588.

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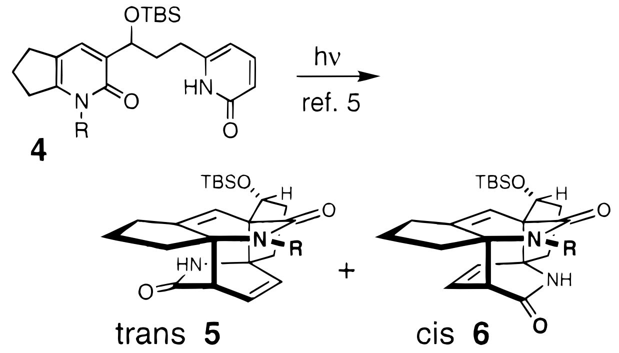
Scheme 2. Stereoselectivity for Intramolecular Pyridone Cycloaddtition Is Solvent Insensitive, Except for Nitrogen-Unsubstituted **4a**



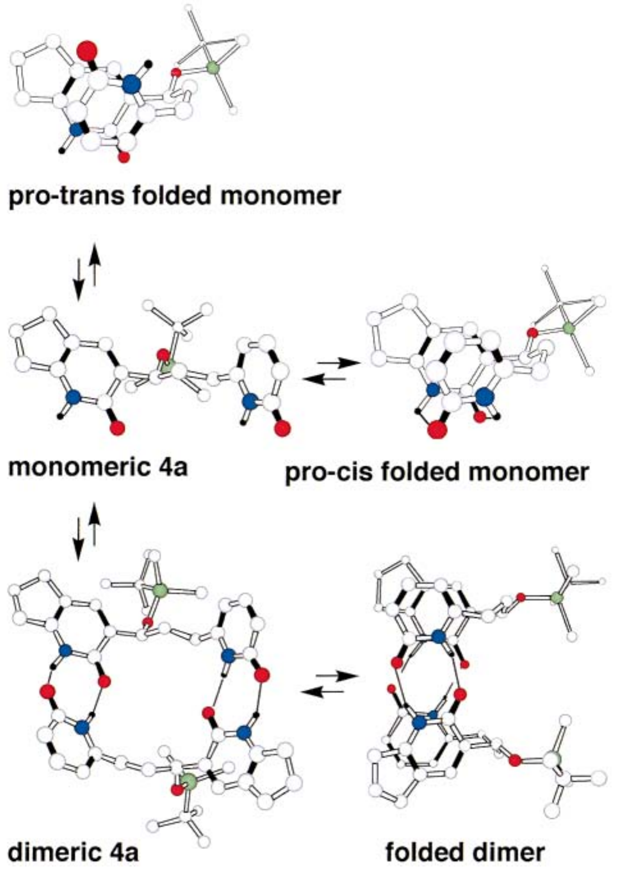
5 : 6	solvent C_6H_6	 MeOH
4a R = H	<1 : >99	90 : 10
4b R = Me	>99 : <1	>99 : <1

the cis product **6a** formed correlated with decreases in solvent polarity.[5] It is well known that *N*-unsubstituted 2-pyridones strongly associate through two hydrogen bonds.[7] It was assumed that the cis-selectivity of this cycloaddition in nonpolar solvents was due to a hydrogen-bonding effect.

Two hydrogen-bonded intermediates can explain the cis-selectivity of **4a** photocycloaddition: an intramolecularly hydrogen-bonded monomer having two hydrogen bonds and a dimeric structure having four hydrogen bonds (Scheme 3). Bis-2-pyridone **4a** has the potential for forming intramolecular hydrogen bonds.[8] Under the constraints of the three-carbon tether, the two hydrogen bonds fold **4a** into a pro-cis conformation (see pro-cis folded monomer). The hydrogen bonds in this structure are far from the ideal, however.[9]

Alternatively, the head-to-tail tethering of the pyridones allows for the association of two molecules of **4a**, engaging two complementary pairs of hydrogen bond donors and acceptors. Folding of this dimer leads to a pro-cis conformation for both molecules (see folded dimer). Note that the stereogenic center in **4a** must be identical to permit both molecules in this dimer to maintain the silyloxy groups in equivalent pseudoequatorial conformations.

Scheme 3. Dimerization of **4a** Forms Four Hydrogen Bonds. Folding of This Dimer Results in a Pro-cis Conformation for Both Molecules (Chem3D Models Shown)



Whereas either hydrogen-bonded intermediate could explain the observed effect of solvent polarity on the stereochemical outcome of the photocycloaddition of **4a**, only the dimeric intermediate would be sensitive to changes in substrate concentration. Evidence for the dimerization of **4a** can be observed in the proton NMR in benzene-d_6, a solvent in which photocycloaddition yields exclusively the cis isomer **6a**. In this solvent, both NH pyridone protons for **4a** are well-defined signals near 14 ppm.[10] The hydrogen-bonding arrangement of the dimer shown in Scheme 3 is similar to the self-assembling head-to-tail bis-2-pyridones reported by Wuest,[11] wherein the hydrogen-bonded pyridone protons had similar chemical shifts.

To differentiate the possible roles of monomeric and dimeric hydrogen-bonded intermediates, photocycloadditions were conducted with solutions of **4a** over a range of concentrations in three solvents: MTBE ($E_{\mathrm{t}} = 35.5$), THF ($E_{\mathrm{t}} = 37.4$), and ethyl acetate ($E_{\mathrm{t}} = 38.1$). The concentration of the substrate was varied over more than 3 orders of magnitude, from 50 to 0.25 mM. Our original study was conducted with a standard concentration of 25 mM. Use of chlorobenzene ($E_{\mathrm{t}} = 36.8$) failed to yield photoproducts **5a** or **6a** at the critical lower concentrations, where the absorbance of the solvent presumably overwhelmed that of the substrate.

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(6) The trans selectivity of 2-pyridone photodimerization has been rationalized in terms of dipole interactions (Matsushima, R.; Terada, K. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1445−1448) and the steric effects of pyridone solvation (ref 4). Hydrogen bonding of **4a** to solvent would enhance both of these effects.

(7) Beak, P.; Covington, J. B.; Smith, S. G.; White, J. M.; Zeigler, J. M. *J. Org. Chem.* **1980**, *45*, 1354−1362.

(8) Dado, G. P.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 8630−86321.

(9) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761−5766.

(10) The chemical shift of the protons is somewhat concentration dependent, gradually moving upfield as the concentration is lowered, eventually disappearing from the spectrum. This effect has been seen in benzene-d_6, THF-d_8, and chloroform-*d*.

(11) Gallant, M.; Phan Viet, M. T.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 721−723.

Irradiation of these solutions confirmed that the stereoselectivity of **4a** cycloaddition is dependent on both the concentration of the substrate and the polarity/hydrogen-bonding properties of the solvent. The percentage of cis isomer **6a** formed for each solvent and concentration is shown graphically in Figure 1.

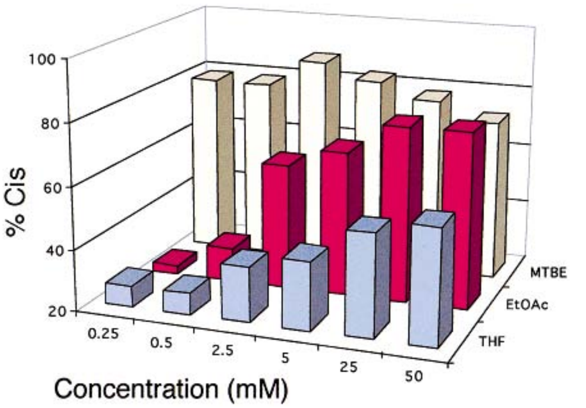


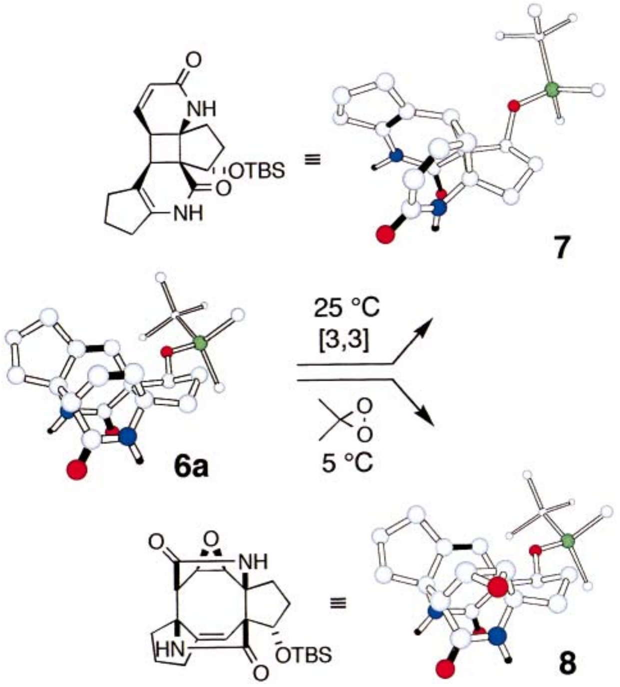
Figure 1. Percent of cis **6a** varies with concentration in solvents of intermediate polarity.

In THF and ethyl acetate, both of which are polar solvents and good hydrogen bond acceptors, formation of cis product **6a** increased with increasing **4a** concentration. The differences in stereoselectivity were most dramatic in ethyl acetate, where at the lowest concentration (0.25 mM) the product was nearly 80% trans and at the highest concentration (50 mM) the product was nearly 80% cis. These results are consistent with the presence of an equilibrium mixture of monomeric and dimeric **4a**. The hydrogen-bonded dimer of **4a**, favored at higher concentrations, leads to the cis isomer **6a**. The monomeric **4a**, dominating at lower concentrations, yields primarily, or perhaps exclusively, the trans isomer **5a** (see pro-trans folded monomer, Scheme 3).[6] *N*-Methylated **4b**, which cannot form cis-productive hydrogen-bonded dimers, yields only trans **5b** (Scheme 2).

Photocycloaddition in *tert*-butyl methyl ether (MTBE) provided predominantly cis product, with only a minor variation in the trans:cis ratio with concentration changes. This hindered ether cannot hydrogen bond effectively with **4a**, which apparently remains largely in dimeric form at the concentrations tested.

In each case, the photocycloadditions were conducted for 3 h using a Pyrex-filtered medium-pressure mercury lamp, with ice cooling of the reaction (ca. 5 °C). The **5a**:**6a** product ratio was determined by ^{1}H NMR, following thermal rearrangement of **6a** at 60 °C. Cis **6a** undergoes a facile and quantitative Cope rearrangement at ambient temperature to cyclobutane **7** (see Scheme 4), whereas trans **5** is thermally stable under these conditions.[12] Despite its instability, photoproduct **6a** can be readily intercepted as the monoepoxide **8** by treatment of the photoproduct (formed using benzene or toluene as solvent) with dimethyldioxirane.[13] Epoxide **8** can be isolated as a single isomer in 90% yield from **4a**. The stereochemistry of this product has been confirmed by X-ray crystallography of a derivative. This will be described elsewhere.

Scheme 4. Cis Isomer **6a** Undergoes a Facile Cope Rearrangment but Can Be Readily Intercepted by Epoxidation with DMDO



Solvent- and concentration-dependent stereoselective photocycloaddition of tethered pyridones has not been described previously and provides a level of stereochemical control that will prove useful in synthetic applications. The solvent and concentration dependence of this example is likely to be general for other tethered, hydrogen-bonding heterocycles.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (GM45214).

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[12] Sieburth, S. McN.; Lin, C.-H. *J. Org. Chem.* **1994**, *59*, 3597−3599.

[13] Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811−822.