Tether-Mediated Stereocontrol in Intramolecular Azomethine Ylide Cycloadditions

Philip P. Garner,* Philip B. Cox, and Stephen J. Klippenstein

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078

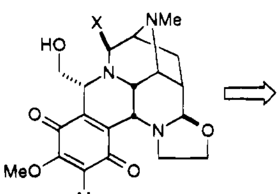
Wiley J. Youngs† and David B. McConville

Department of Chemistry, University of Akron, Akron, Ohio 44325

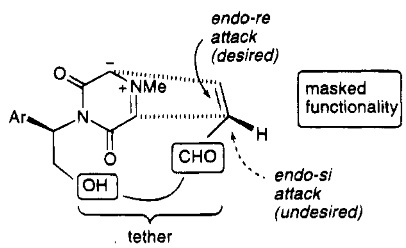
Received August 16, 1994®

Summary: The computationally guided design of a silicon-based tether system for stereoselective intramolecular azomethine ylide cycloadditions is described.

In 1989 we reported an approach to the 3,8-diazabicyclo[3.2.1]octane substructure of the DNA-reactive alkaloid naphthyridinomycin (**1**) and cyanocycline A (**2**) based on an *intramolecular* 1,3-dipolar cycloaddition reaction.[1] At issue was whether this key cycloaddition would proceed via *endo-re* attack on the prochiral alkene versus the *endo-si* alternative. Qualitative TS conformation analysis suggested that the correct "endo-re" diastereomer should form preferentially—a prediction that was borne out experimentally with an acetal-based tether (see Table 1, entry 1). Destructive siphoning-off of one of the acetal diastereomers as well as tether-imposed steric strain appeared to be responsible for the modest yield associated with this reaction and suggested that alternative (i.e., longer) tethers might lead to a better result. We now describe the results of a study which utilized computational TS modeling to help guide the design of an optimal silicon-based tether[2] for this intramolecular dipolar cycloaddition reaction.



1 (X = OH)
2 (X = CN)



Building on the intramolecular Diels–Alder work of Shea,[2a] we initially considered the use of a disposable silicone-based tether since it would lead to the formation of an unstrained 13-membered ring. However, in stark contrast to substrate **3**, photolysis of the silicone-tethered aziridine acrylate **15**[3] resulted in the preferential formation of the (undesired) *endo-si* diastereomer **17** (Table 1, entry 5).[4] Since we were unable to predict or rationalize this result using our simple intramolecular TS model,[1] we decided to evaluate the effect of this and other flexible silicon based tethers on the two competing diastereomeric transition states computationally.[5] In order to isolate the effect of tether length (if any) on the diastereoselectivity, we initially modeled "generic" tethers made up of unsubstituted sp^3 carbon atoms. The main insight provided by these crude modeling studies was that the diastereoselectivity of this intramolecular cycloaddition appeared to undergo a crossover from *endo-re* to *endo-si* as a function of tether length.[6]

Indeed, while the allylsilicone[2b,c,e,f]-tethered aziridine **9** and disiloxane[7] tethered aziridine **12** also exhibited endo-si selectivity (Table 1, entries 3 and 4), the allylsilyl ether[2g] tethered aziridine **6** resulted in preferential formation of the desired *endo-re* product (Table 1, entry 2). Stereochemical assignments for cycloadducts **7/8**, **10/11** (Figure 1), and **13/14** are based on chemical correlation experiments[8] tied in with an X-ray crystal structure of **11** (Figure 2).[9] As shown in Table 1, the experimental trends were reproduced *a posteriori* by more refined TS modeling of systems incorporating "real" tether atoms.[10]

† Author to whom inquiries concerning the X-ray structure determination should be addressed.

® Abstract published in *Advance ACS Abstracts,* October 1, 1994.

(1) Garner, P.; Sunitha, K.; Ho, W.-B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041.

(2) (a) Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885. (b) Craig, D.; Reader, J. C. *Ibid.* **1990**, *31*, 6585. (c) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Ibid.* **1991**, *32*, 1145. (d) Shea, K. J.; Staab, A. J.; Zandi, K. S. *Ibid.* **1991**, *32*, 2715. (e) Fleming, S. A.; Ward, S. C. *Ibid.* **1992**, *33*, 1013. (f) Craig, D.; Reader, J. C. *Ibid.* **1992**, *33*, 4073. (g) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578.

(3) Synthesis of the unsymmetrical silicones **9** and **15** was conveniently accomplished in one pot (60–70% yield) by the slow addition of either allyl alcohol or 2-hydroxyethyl acrylate + Et_3N to an equimolar quantity of Ph_2SiCl_2 followed by the sequential addition of another equivalent of Et_3N and then the starting aziridine alcohol. The unsymmetrical siloxane **12** was prepared in a similar manner using $(i\text{-}Pr_2SiCl)_2O$. Standard silylation of the aziridine alcohol using $ClSiPh_2CH_2CH{=}CH_2$ afforded the silyl ether **9** in 78% yield. Details will be reported in the full account of this work.

(4) The structure of **17** was assigned via the following correlation experiment: Exposure of **17** to acidic methanol to remove the silicone tether (concomitant transesterification) followed by protection of the alcohol produced a compound, whose ^1H NMR data *did not* match that of an isomeric compound derived from **4**. (Ho, W. B. The Asymmetric Synthesis of (−)-Quinocarcin. Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH 1992).

(5) (a) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439. (b) Lipkowitz, K. B.; Peterson, M. A. *Ibid.* **1993**, *93*, 2463.

(6) Analogous *intermolecular* azomethine ylide cycloadditions to acrylate esters show no diastereofacial discrimination. See: Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893.

(7) Cf. Markiewicz, W. T.; Padyukova, N. Sh.; Samek, S.; Smrt, J. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1860.

(8) Stereochemical assignments for cycloadducts **7/8**, **10/11**, and **13/14** were based on their correlation with the diastereomeric lactones **18** and **19**, obtained as follows:

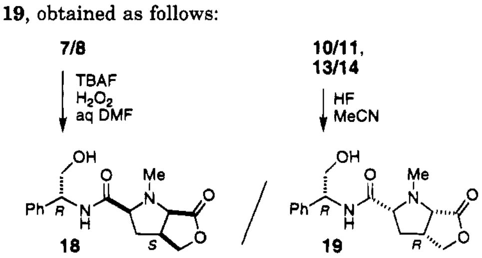
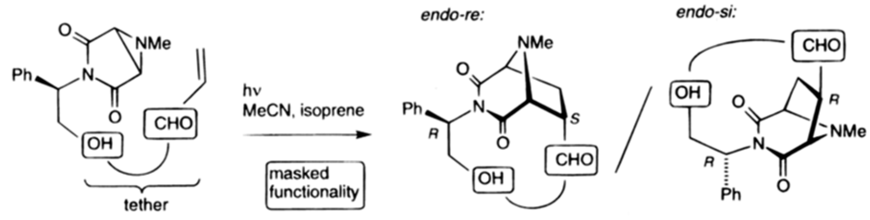


Table 1. Tether Controlled Dipolar Cycloadditions[a]



entry	aziridine	tether structure	ring size	experimental *re/si* ratio[b]	% yield of major adduct[c]	calcd ΔE_{re-si}, kcal/mol
1	**3**	$-OCH(OMe)-$	8	**4/5** = 1.0	35	−6.245
2	**6**	$-OSiPh_2CH_2-$	9	**7/8** = 16/1	64 (71)	−8.303
3	**9**	$-OSiPh_2OCH_2-$	10	**10/11** = 1/5	72 (79)	5.242
4	**12**	$-OSi(i\text{-}Pr)_2OSi(iPr)_2OCH_2-$	12	**13/14** = 1/4	53 (67)	0.028
5	**15**	$-OSiPh_2OCH_2CH_2OCO-$	13	**16/17** = 1/12	46 (72)	1.415

[a] Procedure: A degassed 0.01 M solution of the indicated aziridine in MeCN was placed in a quartz vessel under Ar and irradiated at 2537 Å (3000 Å for **15**) in a Rayonet photochemical reactor until the reaction was judged to be complete by TLC. Photolyses were conducted in the presence of isoprene to help retard product decomposition. Upon reaction termination, the volatiles were removed *in vacuo* and the residue purified by flash chromatography on SiO_2 eluting with hexanes−EtOAc. [b] Diastereomer ratios determined from ^1H NMR spectra of unresolved mixtures. [c] Yield in parantheses is based on unreacted starting material.

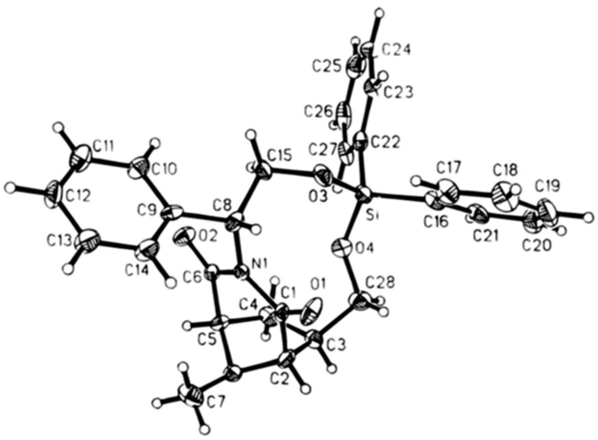


Figure 1. ORTEP of compound **11**. Thermal ellipsoids are drawn at the 50% probability level with the H atoms in their calculated positions.

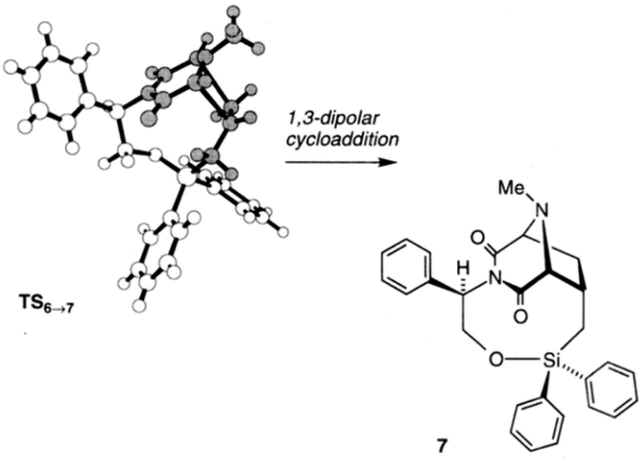


Figure 2. Composite TS model leading to *endo-re* cycloadduct **7**. In this model, the QM-derived atoms are shaded whereas the MM-derived atoms are not. (See ref 10 for modeling details.)

These modeling studies clearly revealed the importance of employing geometrically accurate (i.e., asynchronous) transition structures in such calculations. Even so, the calculated magnitude of ΔE_{re-si} did not correlate quantitatively with the observed *re/si* ratio, possibly due to inadequacies associated with the rigid TS model, the generic force field, and/or the conformational sampling protocol.

In any event, we note that the ability to control diastereoselectivity by simply changing the tether structure represents a new approach to this sort of problem (compare ref 2d). The synthesis of cycloadduct **7** in upwards of 70% yield augurs well for our proposed asymmetric synthesis of naphthyridinomycin. More importantly, this study extends the application of silicon-based tethers to dipolar cycloadditions and further encourages the application of semiquantitative molecular modeling to problems that do not lend themselves to simple transition state analysis.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences. We wish to thank Professor Ken Houk and Dr. Kenske Nakamura (UCLA) for providing us with TS data for $[CH_2NHCH_2 + CH_2{=}CH_2]$ as well as valuable insight into the TS modeling problem.

Supplementary Material Available: Experimental procedures and characterization data for compounds **6-19** (6 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.

(9) Racemic **11** (mp 223−224 °C from hexs−EtOAc) crystallized in the space group $Pna2_1$ with 4 formula units per unit cell. The orthorhombic cell dimensions were a = 25.073(5) Å, b = 11.770(2) Å, c = 8.267(2) Å, V = 2439.8(9) Å^3. The data set was collected using an ω-scan over the range 3.5° ≤ 2θ ≤ 50° at 130 K. All hydrogen atoms were located from difference Fourier maps and subsequently refined using a riding model. Refinement of 316 parameters on 1803 observed reflections with $|F_o| > 4.0\sigma(|F_o|)$ gave R = 5.58%, wR = 4.88%, and GOF = 1.34. Refinement using all 2617 unique reflections produced R = 9.05% and R_w = 5.43%.

(10) Cycloaddition transition structures were calculated using quantum mechanics (Hartree−Fock self-consistent field calculations with a STO-3G basis set). Substituents that could possibly influence the TS geometry were included. The remaining molecular structures were then built in by substituting for relevant hydrogens using the Biograf 3.22 software package. Conformational space was explored by inputing likely starting ring conformations manually and then performing 20 ps of quenched molecular dynamics at 3000 K followed by energy minimization (Dreiding II Force Field, R_{Si-C} set to X-ray derived value of 1.86 Å) to an rms < 0.1 (kcal/mol)/Å. Atomic charges were calculated for each atom using Biograf's Q-equilibrate function. A "rigid TS" model was employed in which the positions of the QM-derived atoms were kept "fixed" relative to the rest of the molecule. In each case, the lowest energy structure was taken to be the saddle point.