On the Reactivity of 1-Amino-3-siloxy-1,3-dienes: Kinetics Investigation and Theoretical Interpretation

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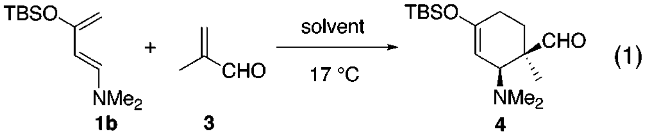
Introduction

Dienes possessing heteroatoms capable of donating their electron density into the conjugated π-system are known to display high reactivity in various [4 + 2] cycloaddition reactions.[1] The accepted rationale for this phenomenon, in accord with frontier molecular orbital (FMO) theory, is that the electron-rich heteroatoms increase the diene's HOMO energy. This perturbation decreases the energy difference between the diene HOMO and the dienophile LUMO, consonant with greater stabilization of the transition state and reflected in a higher reaction rate.[2] Activation of the diene increases as electron-donating substituents are incorporated into the diene structure, ideally at 1- and 3-positions, which causes a cooperative increase in reactivity.[3−5]

According to this general trend, 1-amino-3-siloxy-1,3-butadienes (e.g., **1**), which have the enamine and enol ether fragments in synergistic arrangement, were expected to display high reactivity in the Diels−Alder reaction. Indeed, we have recently demonstrated that such dienes can be prepared efficiently and that they undergo [4 + 2] cycloadditions with a wide range of dienophiles under very mild reaction conditions, with complete regiocontrol.[6] Amino siloxy diene **1** also appeared to display significantly higher reactivity than analogous dialkoxy dienes, such as Danishefsky's diene (**2a**).[6a] As a part of a program directed toward the investigation of the utility of 1-amino-3-siloxy-1,3-butadienes in organic synthesis,[7] we initiated a study aimed at providing fundamental quantitative information regarding the Diels−Alder kinetics of amino siloxy dienes and 1-methoxy-3-siloxy-1,3-butadienes. We were particularly interested in determining if these highly polarized dienes underwent cycloadditions by a concerted or stepwise mechanism. We present here the results of this investigation, which combines kinetic measurements and a theoretical treatment of the results using the FMO theory.

Results and Discussion

Kinetics. The difference in reactivity between amino siloxy diene **1** and Danishefsky's diene (**2a**) quickly became apparent in the course of the first few Diels−Alder reactions of diene **1**, which took place at much lower temperatures (by 30−90 °C) for **1** than that reported in the literature for diene **2a**.[6a,8] This observed difference in reactivity was borne out in a competition experiment wherein dienes **1** and **2a** were allowed to compete directly for the same dienophile, methacrolein.[6a] To obtain quantitative information, the kinetics of the reaction of amino siloxy diene **1** with methacrolein (**3**) were investigated (eq 1). The reaction rate was monitored by following the formation of the product (**4**) by 500 MHz ^{1}H NMR spectroscopy. Three different solvents were examined: chloroform-*d*, acetonitrile-*d*$_3$, and benzene-*d*$_6$.



(1)

The calculated second-order rate constants, as well as the relative rates, are collected in Table 1.[9] The reaction clearly displayed a measurable solvent dependence. The cycloaddition conducted in benzene was found to be the slowest ($k_2 = 2.0 \times 10^{-3}$ M^{-1} s^{-1}). The change to the more polar solvent acetonitrile led to a 1.5-fold increase in the reaction rate. Interestingly, the cycloaddition was six times faster in chloroform than in benzene.[10] The moderate solvent dependence of Diels−Alder reaction rates is consistent with that previously observed.[11]

With the kinetics data on the Diels−Alder reactivity of amino siloxy diene **1** in hand, it was of interest to compare its reactivity in quantitative terms with that for

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(4) For 1,3-bis(dimethylamino) dienes, see: (a) Gomper, R.; Sobotta, R. *Tetrahedron Lett.* **1979**, 921. (b) Gomper, R.; Heinemann, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 216.

(5) For 1-amino-3-siloxy dienes, see: (a) Smith, A. B., III; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1308. (b) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098. (c) Schlessinger, R. H.; Pettus, T. R. R. *J. Org. Chem.* **1994**, *59*, 3246.

(6) (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252. (b) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039. (c) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165. (d) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562.

(7) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523.

(8) (a) Baldwin, S. W.; Greenspan, P.; Alaimo, C.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 5877. (b) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996. (c) Vorndam, P. E. *J. Org. Chem.* **1990**, *55*, 3693.

(9) See the Supporting Information for a second-order rate plot.

(10) This increased rate does not appear to arise from traces of acid present in the chloroform, since the higher rate is also seen when K$_2$CO$_3$-treated chloroform is used.

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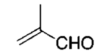
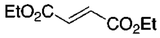
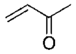
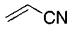
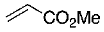
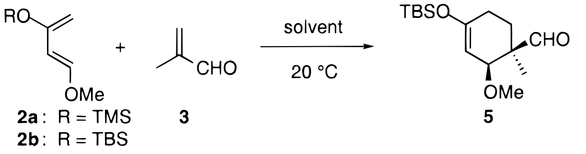
Table 1. Second-Order Rate Constants for Cycloadditions of Diene 1 with Methacrolein in $CDCl_3$, CD_3CN, and C_6D_6

entry	solvent	k_2 (M^{-1} s^{-1})	relative rates
1	C_6D_6	2.0×10^{-3}	1
2	CD_3CN	2.9×10^{-3}	1.5
3	$CDCl_3$	1.2×10^{-2}	6

Table 2. Rate Constants for Cycloadditions of Diene 1 with Various Dienophiles at 17 °C in C_6D_6

Entry	Dienophile	*endo:exo*	k_2 ($M^{-1}s^{-1}$)	Relative Rates
1		>99:1	2.0×10^{-3}	28.6
2		1.4 : 1	1.5×10^{-3}	21
3		1.1 : 1	6.5×10^{-4}	9.3
4		1 : 4	1.7×10^{-4}	2.4
5		1 : 1.5	7.0×10^{-5}	1

Danishefsky's diene (**2a**). Such direct comparison of dienes **1** and **2a** is of fundamental importance from both mechanistic and practical viewpoints. It is noteworthy that despite its popularity and widespread use in organic synthesis, the Diels−Alder kinetics of diene **2a** appear never to have been reported. We measured the rate of reaction of methacrolein with the TBS-protected diene **2b**[12] rather than the TMS-protected diene **2a**, since the former is more closely related to amino siloxy diene **1** (eq 2).



(2)

The kinetic measurements were carried out at 20 °C in $CDCl_3$. Six data points were collected, ca. 12 h apart from each other. Although the reaction was quite slow, an acceptable linear second-order rate plot was obtained.[9] The calculated rate constant obtained from this experiment is $k_2 = 3.6 \times 10^{-6}$ M^{-1} s^{-1}. From the kinetics data, it is clear that the difference in reactivity between dienes **1** and **2b** is considerably greater than originally estimated.[6a] Since both measurements were conducted in the same solvent ($CDCl_3$) under similar conditions (17 and 20 °C, respectively), the two rates can be directly compared: *1-(dimethylamino)-3-siloxy-1,3-butadiene* **1** *was found to be 3300 times more reactive than 1-methoxy-3-siloxybutadiene* ***2b***.

To assess the relative reactivity of different dienophiles with diene **1**, we determined the Diels−Alder kinetics for four additional dienophiles: diethyl fumarate, methyl vinyl ketone, acrylonitrile, and methyl acrylate (Table 2). The relative rates observed in these cycloadditions are consistent with the reactivity of similar dienophiles in previously reported Diels−Alder reactions with dienes such as 9,10-dimethylanthracene and cyclopentadiene.[13]

Table 3. Activation Parameters for Reaction of Diene 1 with Methacrolein in Toluene-d_8

ln *A*	E_a[a]	$\Delta H^{\ddagger a}$	$\Delta S^{\ddagger b}$	$\Delta G^{\ddagger a}$
11.3	10	9.6	−38	21

[a] Measured in kcal mol^{-1}. [b] Measured in cal mol^{-1} K^{-1}.

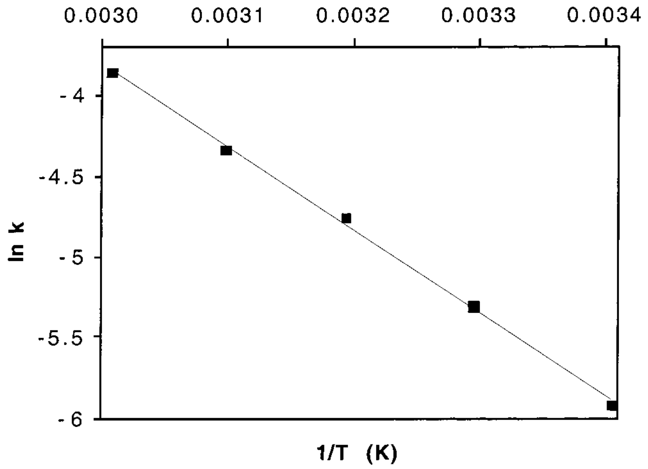


Figure 1. Arrhenius plot. The rate constants were measured at 25, 35, 45, 55, and 65 °C. ($[\text{diene}]_0 = 4.3-9.0 \times 10^{-2}$ M, $[\text{dienophile}]_0 = 1.2-2.5 \times 10^{-1}$ M).

Given the very highly polarized nature of amino-siloxy diene **1**, it was possible that the Diels−Alder adducts were formed by a stepwise process rather than through a concerted mechanism. To address this issue, we determined the activation parameters for the reaction in eq 1 by measuring the temperature dependence of the rate constants (Figure 1). These measurements were carried out using toluene-d_8 as a solvent over the temperature range of 25−65 °C. The Arrhenius activation parameters, log *A* and E_a, as well as the entropy and enthalpy of activation are shown in Table 3. The entropy of activation of −38 eu is characteristic of a highly ordered transition state, which is expected for the Diels−Alder reaction.[14] Combined with the relatively small value of 10 kcal mol^{-1} for the activation energy, these results are consistent with the cycloaddition of amino siloxy diene **1** with methacrolein proceeding via a concerted [4 + 2] mechanism.[15,16] The moderate solvent dependence observed for this reaction is also consistent with this conclusion.

Calculations. The difference in reactivity between amino siloxy dienes (e.g., **1**) and alkoxy siloxy dienes (e.g., **2a**) was investigated using FMO theory, which is known to provide accurate, semiquantitative predictions of the behavior of dienes and dienophiles in [4 + 2] cycloadditions.[17] The ground-state geometries of 1-(dimethylamino)-3-trimethylsiloxy-1,3-butadiene (**1a**) and 1-methoxy-3-

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[12] The TBS-protected Danishefsky's diene (**2b**) was conveniently prepared using the KHMDS/TBSCl protocol used for the synthesis of 1-amino-3-siloxy-1,3-dienes (see ref 6c).

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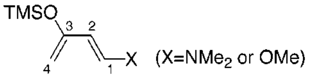
Table 4. HOMO Eigenvalues and $2p_z$ Eigenvectors of the Dienes 1a and 2a



entry	diene	eigenvalue (eV)	$2p_z$ eigenvectors				
			C4	C3	C2	C1	X (N or O)
1	*s-cis*-**1a** (X = NMe_2)	−7.18	0.28	0.14	−0.29	−0.19	0.28
2	*s-cis*-**2a** (X = OMe)	−8.08	0.33	0.20	−0.23	−0.22	0.17
3	*s-trans*-**1a** (X = NMe2)	−6.94	0.30	0.13	−0.30	−0.20	0.29
4	*s-trans*-**2a** (X = OMe)	−7.79	0.33	0.20	−0.26	−0.26	0.22

trimethylsiloxy-1,3-butadiene (**2a**) were optimized at the B3LYP/6-31G[18] level using GAUSSIAN 94.[19] Trimethylsilyl groups were used instead of the *tert*-butyldimethylsilyl group in order to simplify the calculations. We have found experimentally that this change does not significantly alter the behavior of the two dienes. The energy minima corresponding to the s-trans and s-cis conformations of each diene were located.[20] The s-trans conformation was lower in energy for both diene **1a** and **2a**,[21] to approximately the same extent (3.2 vs 3.7 kcal mol^{-1}, respectively), and the s-cis forms were twisted out of planarity by 25−28°. The HOMO energies of both dienes were obtained through single-point RHF calculations using the 6-31G basis at the B3LYP/6-31G geometries, a procedure known to provide more accurate orbital energies than the B3LYP method. The eigenvalues and the $2p_z$ eigenvectors of the HOMOs of dienes **1a** and **2a** are collected in Table 4.

The results of the calculations lend support to the notion that 1-(dimethylamino)-3-siloxy-1,3-butadiene **1a** should be more electron rich and more polarized than methoxy diene **2a**. The calculated HOMO of amino siloxy diene **1a** is 0.85−0.90 eV higher in energy than that of the alkoxy siloxy diene **2a**.[20] The smaller diene−dienophile HOMO−LUMO gap for the former is in accord with the observed faster reaction rate. The greater donation of the nitrogen lone pair into the diene π-system is reflected in the higher $2p_z$ coefficient (0.28 and 0.29) on the nitrogen atom, compared to the 1-oxygen (0.17 and 0.22) on diene **2a**. It is noteworthy that the HOMOs of both dienes are strongly polarized, which is expected to lead to highly asynchronous transition states and, as a result, to high regioselectivity in the Diels−Alder reaction. Indeed, essentially complete regioselectivity has been observed experimentally in the cycloadditions involving Danishefsky's diene[3b−d] and 1-amino-3-siloxy-1,3-dienes.[6]

In summary, the kinetics data presented above provide strong evidence that cycloadditions of amino siloxy dienes proceed via a concerted [4 + 2] mechanism, with a relatively low activation barrier. It was also found that the reactivity of amino siloxy diene **1** significantly exceeds (>3000 times) that of Danishefsky's diene (**2a**). This difference in reactivity was rationalized on the basis of FMO theory, which found the HOMO energy of 1-amino-3-siloxy-1,3-diene **1a** to be 0.85−0.90 eV higher than of 1-methoxy-3-siloxy-1,3-diene **2a**, consistent with the higher reaction rates observed experimentally.

Experimental Section

Representative Procedure for Kinetic Measurements. A stock solution containing diene **1** (47 mg, 0.20 mmol) and naphthalene (14.4 mg, 0.11 mmol), which was used as an internal standard, in toluene-d_8 (2.007 g) was prepared. To an aliquot of this solution (400 mg) was added in one portion methacrolein (10 μL, 0.12 mmol). The resulting solution was immediately transferred into an NMR tube, and progress of the reaction was monitored by 500 MHz ^{1}H NMR spectroscopy at the temperature specified. The observed second-order rate constants were calculated according to the rate expression $k_2 = [1/t(a - b)]\ln[b(a - x)/a(b - x)]$.

Diene 1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.98 (s, 9H), 2.70 (s, 6H), 3.84 (s, 1H), 3.92 (s, 1H), 4.78 (d, $J = 13.2$ Hz, 1H), 6.57 (d, $J = 13.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, 18.3, 25.9, 40.5, 85.8, 95.9, 140.9, 156.4; IR (neat) 2930, 1647 cm^{-1}.

Diene 2b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.98 (s, 9H), 3.60 (s, 6H), 4.07 (s, 1H), 4.11 (s, 1H), 5.36 (d, $J = 112.3$ Hz, 1H), 6.90 (d, $J = 12.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, 18.2, 25.8, 56.3, 90.8, 103.2, 150.2, 154.1; IR (neat) 2930, 2858, 1652 cm^{-1}.

Cycloadduct 4: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.93 (s, 9H), 1.06 (s, 3H), 1.50 (m, 1H), 2.0−2.2 (m, 3H), 2.20 (s, 6H), 3.28 (d, $J = 5.0$ Hz, 1H), 4.84 (d, $J = 5.0$ Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, 18.0, 20.4, 24.7, 25.6, 25.9, 43.1, 47.5, 65.4, 97.3, 153.6, 204.0; IR (neat) 2930, 1725, 1661 cm^{-1}; HRMS m/z [M^+] calcd for $C_{16}H_{31}NO_2Si$ 297.2124, found 297.2110.

Cycloadduct 5: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.93 (s, 9H), 1.02 (s, 3H), 1.60 (m, 1H), 2.0−2.2 (m, 3H), 3.30 (s, 3H), 3.75 (d, $J = 5.0$ Hz, 1H), 5.10 (d, $J = 5.0$ Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.4, 17.1, 18.0,, 24.7, 24.1, 25.6, 26.5, 48.1, 56.1, 79.3, 100.7, 155.4, 205.1; IR (neat) 2930, 1734, 1658 cm^{-1}.

The spectral data for the endo and exo [4 + 2] cycloadducts of diene **1** with diethyl fumarate, methyl vinyl ketone, acrylonitrile, and methyl acrylate have been described.[6b]

Acknowledgment. This work was supported in part by the National Institutes of Health (R01-GM-55998). We also thank Pfizer Inc. for generous financial assistance.

Supporting Information Available: The second-order rate constant plots for reactions of dienes **1** and **2b** with methacrolein, optimized molecular geometries of dienes **1a** and **2a**, as well as an FMO energy diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

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