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Origin of Stereoselectivity in the (4 + 3) Cycloadditions of Chiral Alkoxy Siloxyallyl Cations with Furan

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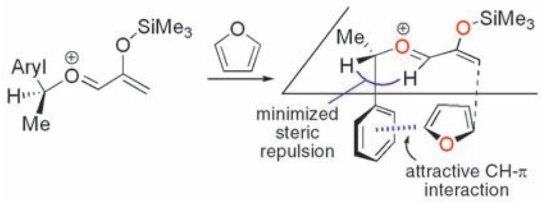
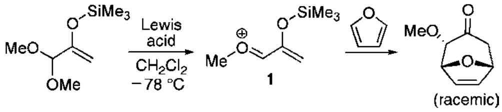
ABSTRACT



The mechanisms and stereoselectivities of (4 + 3) cycloadditions between chiral alkoxy siloxyallyl cations and furan are examined using density functional theory calculations. These cycloadditions are predicted to take place via stepwise mechanisms. The stereoselectivities of cycloadditions involving siloxyallyl cations derived from chiral α-methyl benzylic alcohols are controlled by two effects: minimization of steric repulsion between the α-Me group and the allyl group and attractive CH−π interactions between the furan and the aryl group.

The (4 + 3) cycloadditions of allyl cations with dienes constitute a widely used approach to seven-membered carbocycles.[1] Albizati reported the cycloaddition of an alkoxy-substituted siloxyallyl cation, **1**, with furan (Scheme 1); the cation was generated by treatment of the corresponding allylic acetal with a Lewis acid.[2] Hoffmann subsequently developed an asymmetric variant of this procedure, using mixed acetals derived from chiral α-methyl benzylic alcohols (Scheme 2).[3] Cycloaddition of the chiral oxyallyl cations **2** with furan led to the *endo* (also termed “compact”)[4] cycloadducts **3a** and **3b**, in diastereomer ratios varying from 10 to 100%. Stereoselectivity depended on the solvent, temperature, and the choice of aryl group at the stereogenic center. A 2-naphthyl group provided **3a** as a single diastereomer in CH_2Cl_2 at −95 °C.[5]

Scheme 1. Albizati’s (4 + 3) Cycloaddition of an Alkoxy-Substituted Siloxyallyl Cation with Furan



Hoffmann proposed[3] that in noncoordinating solvents the cation **2** adopted the structure shown in the box in Scheme

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(1) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1–19. (b) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371–2395.

(2) Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109–4112.

(3) (a) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1266–1268. (b) Stark, C. B. W.; Pierau, S.; Wartchow, R.; Hoffmann, H. M. R. *Chem.—Eur. J.* **2000**, *6*, 684–691.

(4) Hoffmann introduced the terms “compact” and “extended” to describe the geometries of (4 + 3) cycloadditions. See: Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1973**, *12*, 819–835.

(5) In ref 3b, the *S* enantiomer was used for the Ph-containing oxyallyl cation, but the *R* enantiomer was used for the 2-naphthyl-containing cation. The cycloadduct for the 2-naphthyl case was therefore enantiomeric to **3a**.

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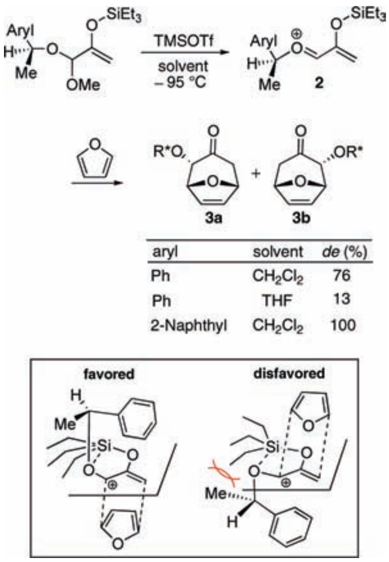
Scheme 2. Hoffmann's Asymmetric (4 + 3) Cycloadditions of Alkoxy-Substituted Siloxyallyl Cations with Furan



aryl	solvent	*de* (%)
Ph	CH_2Cl_2	76
Ph	THF	13
2-Naphthyl	CH_2Cl_2	100

2, with an intramolecular Si−O interaction and an attractive cation−aryl interaction. Furan could add to either diastereomer via the less-hindered diastereoface, and the preferred stereoisomer would be the one in which steric interference between the alkoxy Me group and the $SiEt_3$ group is minimized. This proposal seemed unlikely to us, requiring coordination of a relatively non-nucleophilic oxygen with oxonium character to Si.

We have recently studied[6] (4 + 3) cycloadditions of oxyallyls bearing a chiral oxazolidinone substituent, which were developed by Hsung.[7] Density functional theory calculations indicate a novel explanation for the stereoselectivity of these oxyallyls toward furans, which prompted us to investigate Hoffmann's chiral alkoxy-substituted oxyallyl cations. Here we report the results of B3LYP/6-31G(d) calculations in Gaussian 03[8] on the mechanisms and selectivities of the cycloadditions of alkoxy siloxyallyl cations with furans.

The structure of the simple alkoxy-substituted siloxyallyl cation **1** is shown in Figure 1. At the B3LYP/6-31G(d) level, four isomers of **1** were located. The most stable isomer (**1a**) has a "W"-type structure, with the OMe and $OSiMe_3$ groups *syn* to each other. "Sickle"-type structures, where the OMe and $OSiMe_3$ groups are *anti* to one another, were also found (**1c**,**d**), but these are 2.6 kcal/mol or more higher in energy.

Although Hoffmann had postulated that a cyclic O−Si interaction takes place in alkoxy siloxyallyl cations (Scheme 2), we were unable to locate any cyclic isomers of **1** at the B3LYP/6-31G(d) level. The Lewis basicity of the OMe group is low, due to conjugation of the OMe lone pair with the allyl cation. The OMe group is coplanar with the allyl group, and the MeO−C bond length (1.27 Å) is only 0.06 Å longer than the C=O bond length of formaldehyde.

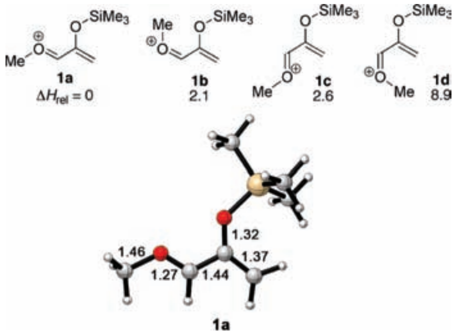


Figure 1. Conformers and most stable geometry of **1**. Enthalpies are in kcal/mol at 0 K; bond lengths are in Å.

B3LYP calculations indicate that the *endo* (or "compact")[4] (4 + 3) cycloaddition of **1** with furan is a stepwise process. A free energy diagram for the reaction is shown in Figure 2. Furan adds to **1** via the unsubstituted allylic terminus (**TS-1**), leading to the intermediate **Int-1**. Ring closure via $\mathbf{TS\text{-}1_{rc}}$ furnishes the cationic cycloadduct, which would subsequently lose R_3Si^+ (as R_3SiOTf) to yield the bicyclic ketone. We expect this last step (not shown) to be exergonic in solution. In **TS-1**, the methoxy group remains in the plane of the allyl group, maximizing overlap between the oxygen lone pair and the allyl π^* orbital. Although only one C−C bond is forming in **TS-1** (indicated by the green line), the interaction of another allyl terminus with furan (dotted line) is stabilizing. A TS where this interaction is absent is 3.4 kcal/mol higher in energy ($\Delta\Delta H^{\ddagger}_{0K}$). Other modes of addition, including the initial attack at the oxygen-substituted carbon of **1a** and reactions of the sickle conformer **1c**, were also considered but lie at least 1.5 kcal/mol higher in energy.

In the gas phase, ring closure of the intermediate ($\mathbf{TS\text{-}1_{rc}}$) is 0.8 kcal/mol more difficult than the initial reaction of **1a** with furan (**TS-1**). This situation is reversed in solution, however. Free energies of solvation were computed using the Conductorlike Polarizable Continuum Model (CPCM),[9] and when the solvation energies in CH_2Cl_2 are added to the gas-phase free energies, **TS-1** lies 0.8 kcal/mol higher than $\mathbf{TS\text{-}1_{rc}}$. The blue line in Figure 2 shows the free energy surface in CH_2Cl_2. The surface in THF is almost identical to that in CH_2Cl_2.

For the (4 + 3) cycloaddition of the chiral siloxyallyl cation **2** (Aryl = Ph) with furan, three low-energy transition states were found. These are shown in Figure 3. The lowest-energy TS (**TS-2a**) leads to the experimental major product **3a**. The other two transition states (**TS-2b** and **TS-2c**) lead to the minor diastereomer **3b** and lie 1.2 and 1.7 kcal/mol ($\Delta\Delta H^{\ddagger}_{0K}$) above **TS-2a**. In **TS-2a**, the alkoxy substituent is oriented so that the Ph group is aligned face-to-edge with

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[6] Krenske, E. H.; Houk, K. N.; Lohse, A. G.; Antoline, J. E.; Hsung, R. P., submitted.

[7] Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174–7175.

[8] Frisch, M. J. *Gaussian 03*, Revision C.02; Gaussian, Inc.; Wallingford, CT, 2004.

[9] (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001. (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404–417.

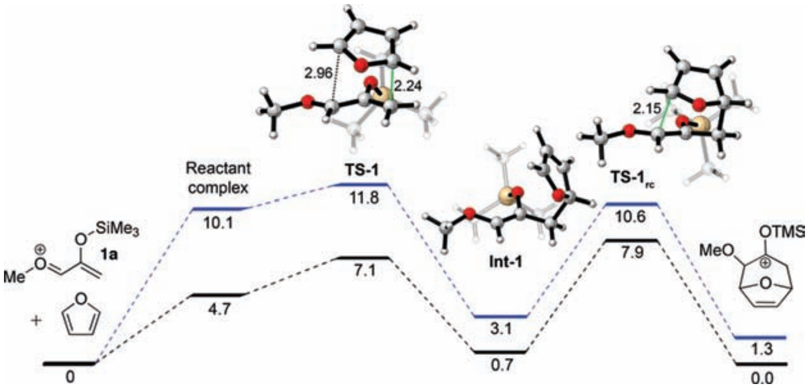

Figure 2. Free energy diagram for the cycloaddition of **1a** with furan. Black line denotes gas-phase reaction profile; blue line denotes reaction profile in CH_2Cl_2. Free energies in kcal/mol at 1 M and 298.15 K; bond lengths in Å.

the incoming furan. The furan−Ph distance is approximately 3 Å, suitable for an attractive edge-to-face CH−π interaction.[10] This type of stabilizing interaction is absent in **TS-2b**. In **TS-2c**, an attractive CH−π interaction is present, but there is also a destabilizing steric interaction between the Me group and the nearby hydrogen on the allyl group (red line).

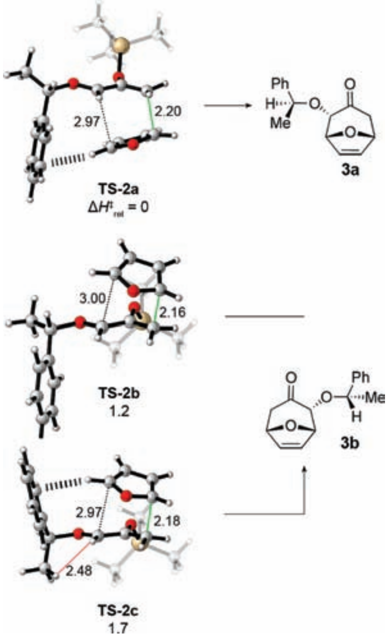

Figure 3. Transition states for cycloaddition of **2** (Aryl = Ph) with furan. Enthalpies in kcal/mol at 0 K; bond lengths in Å.

The predicted diastereomer ratios (**3a**:**3b**) at −95 °C were calculated based on a Boltzmann distribution of **TS-2a**, **TS-2b**, and **TS-2c**. Values of the relative activation free energies and the corresponding de's are shown in Table 1. For the gas phase reaction, B3LYP predicts a de of 84%, but the diastereoselectivity is lower in solution. The predicted de in CH_2Cl_2 is 44%, while in THF it is 12%. The latter value agrees well with the experimental de of 13% in THF, but the CH_2Cl_2 prediction falls somewhat short of the experimental de of 76%.[3]

Table 1. Activation Energies and Predicted de's for Cycloaddition of **2** with Furan at −95 °C[a]

	$\Delta G^{\ddagger}_{\mathrm{rel}}$, **TS-2b**	$\Delta G^{\ddagger}_{\mathrm{rel}}$, **TS-2c**	calcd de (%)	exptl de (%)
B3LYP				
gas phase	0.9	1.6	84	
CH_2Cl_2	0.2	1.3	44	76
THF	0.1	1.2	12	13
M06-2X//B3LYP				
gas phase	2.1	1.3	95	
CH_2Cl_2	1.5	1.0	86	76
THF	1.4	0.9	82	13

[a] Free energies in kcal/mol at 1 mol/L. B3LYP geometries and the 6-31G(d) basis set were used throughout. The M06-2X data were calculated from the M06-2X electronic energies in conjunction with B3LYP thermochemical corrections and free energies of solvation.

We also carried out single-point calculations on **TS-2a−c** at the M06-2X/6-31G(d) level.[11] The M06-2X functional contains attractive interactions that mimic dispersion[12] and is likely to capture more strongly the stabilizing CH−π interactions in **TS-2a** and **TS-2c**. When M06-2X electronic energies are used in place of the B3LYP values to calculate free energies, **TS-2b** rises by 1.2 kcal/mol (relative to **TS-2a**), while **TS-2c** drops by 0.3 kcal/mol. The de in the gas phase is 95%. The calculated de in CH_2Cl_2 (86%) is in better agreement with experiment, but the stereoselectivity in THF is overestimated. Both sets of solvent calculations for **TS-2a−c** deviate from the experimental selectivities due to the combined errors associated with the gas-phase free energies and the solvent corrections. Nevertheless, within the expected bounds of these limitations, the calculations do predict the correct trends in each case.

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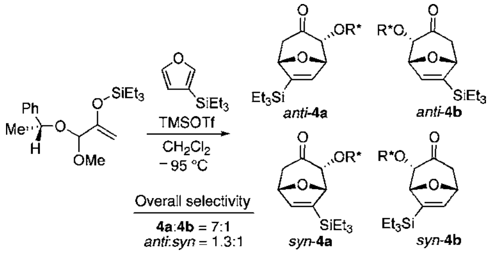
(10) Wheeler, S. E.; Houk, K. N. *Mol. Phys.* **2009**, *107*, 749–760.

Hoffmann reported that the cycloaddition of **2** (Aryl = 2-naphthyl) with furan was completely stereoselective (CH_2Cl_2, −95 °C).[3] We also calculated transition states for this derivative. Again, three low-energy TSs are found, which are analogous to **TS-2a−c** (Supporting Information). The predicted de in the gas phase is 90% according to B3LYP calculations and 98% with M06-2X. Although the stereoselectivity is underestimated slightly by both methods, the better stereoinduction by the 2-naphthyl group is reproduced.

Consistent with the idea that CH−π interactions are important for stereocontrol, Hoffmann observed that the cycloaddition of **2** (Aryl = Ph) with 2,5-dimethylfuran gave poor diastereoselectivity.[13] For 2,5-dimethylfuran, steric repulsion in the transition state corresponding to **TS-2a** results in a longer forming bond (2.34 Å) and a weakened secondary C···C interaction (3.24 Å), and the calculated stereoselectivity is only $\Delta\Delta H^{\ddagger}_{0K} = 0.1$ kcal/mol (Supporting Information). Eliminating the CH−π interaction by replacing the aryl group of **2** with a cyclohexyl group is also predicted to give lower stereoselectivity; $\Delta\Delta H^{\ddagger}_{0K}$ for furan is 0.5 kcal/mol.

Scheme 3. Hoffmann's Regioselective (4 + 3) Cycloaddition



Hoffmann also studied the regioselectivity of cycloadditions involving **2**, including the example shown in Scheme 3.[13] Using 3-Me_3Si-furan as a model for 3-Et_3Si-furan, we find that the two lowest-energy transition states are analogous to **TS-2a**; the regioisomer having the Me_3Si group *anti* to the alkoxy group is 0.6 kcal/mol lower in energy than that with Me_3Si *syn* (Supporting Information).[14] A third TS, corresponding to **TS-2b** with Me_3Si *syn*, is also accessible, at 0.6 kcal/mol. These results are in good qualitative agreement with the experimental stereo- and regioselectivities.

In summary, density functional theory calculations indicate that two effects control the stereoselectivities of alkoxy-substituted siloxyallyl cations toward furan: (1) minimization of repulsive interactions between the allyl cation and the Me group of the chiral auxiliary and (2) TS stabilization by attractive CH−π interactions. The preferred direction of attack is, unexpectedly, contra-steric.

Acknowledgment. We thank the NSF for generous financial support and the NCSA and UCLA ATS for computer resources.

Supporting Information Available: B3LYP geometries and energies, additional figures, and complete citations for refs 8 and 11. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] M06-2X/6-31G(d) calculations were carried out in NWChem 5.1.1 using the xfine grid: Bylaska, E. J. et al. *NWChem, A Computational Chemistry Package for Parallel Computers*, version 5.1.1; Pacific Northwest National Laboratory: Richland, WA, 2009.

[12] Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157–167.

[13] Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883–886.

[14] The benzylic carbon in **TS2a–c** has the *S* configuration, while the experimental study in reference 13 employed the *R* enantiomer. Taking this into account, **TSs** analogous to **TS-2a** correspond to the experimental cycloadduct **4a**, and **TSs** analogous to **TS-2b/c** correspond to cycloadduct **4b**.