Origin of Diastereoselectivity in the Nitrile Oxide Cycloadditions with Oppolzer's Chiral Sultams: Coulombic Interaction as the Key Role in Diastereofacial Differentiation

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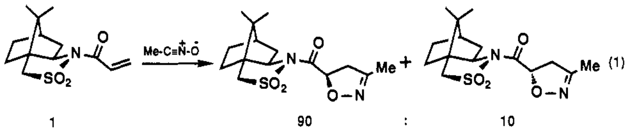
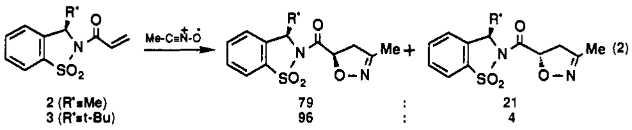
Abstract: Diastereofacial selectivity in the nitrile oxide cycloadditions with Oppolzer's chiral sultams cannot be explained with the conventional face shielding by sterically bulky groups. To find the origin of the diastereoselectivity, the transition states for the cycloadditions have been studied with semiempirical quantum mechanical calculations using the PM3 method. The calculated product ratios are in good agreement with experiment. We find that the activation barriers for the favored and disfavored transition states are strongly correlated with the Coulombic repulsions between the dipolar oxygen and the sultam oxygens. Such correlation is also found from *ab initio* calculations using the PM3 optimized geometries. In addition, when two oxygen atoms of the sulfone group in the sultam systems are removed, these isothiazolidine systems have very small energy differences between the top-facial and bottom-facial transition states, showing no diastereoselectivity. Therefore, we suggest that the electrostatic effect is a main factor governing the diastereofacial selectivity for the sultam systems. These systems can be considered as one of the most typical case of Hehre's claim that the electrostatic effect is a very general determinant of π-facial selectivity.

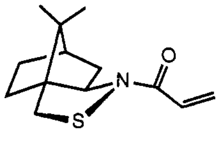
I. Introduction

Asymmetric 1,3-dipolar cycloadditions to chiral dipolarophiles provide versatile heterocyclic intermediates in optically active form. The vital diastereoselectivities depend largely on asymmetric environments of chiral auxiliary systems of chiral dipolarophiles. Oppolzer's chiral camphorsultam[1] was used as a chiral auxiliary in asymmetric nitrile oxide cycloadditions,[2] silyl nitronate cycloadditions,[3] azomethine ylide cycloadditions,[4] and cyclopropanation with diazomethane.[5] *N*-Acryloylbornane-10,2-sultam (**1**) derived from Oppolzer's chiral camphorsultam gave good π-face diastereoselectivities (ca. 90:10) in the nitrile oxide cycloadditions (eq 1). Recently, Oppolzer introduced chiral toluenesultams[6] and demonstrated their use as chiral auxiliaries in the asymmetric nitrile oxide cycloadditions[7] (eq 2). In particular, various nitrile oxide cycloadditions with the chiral *tert*-butylsultam dipolarophile **3** provided the major cycloadducts with excellent diasteroselectivities (>95:5).

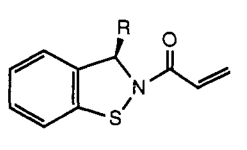




The origin of π-face differentiation of **1** was suggested tentatively by the effect of the pyramidal nitrogen atom[8] and a steric or electronic encumbrance of one of the sulfone oxygens.[2a] *N*-Acryloylsultams **2** and **3** derived from Oppolzer's toluenesultams gave the major cycloadducts by the attack of nitrile oxides from the sterically more hindered faces which have alkyl substituents, like the bulky *tert*-butyl group. This puzzling stereoelectronic bias for Oppolzer's chiral sultams **1–3** deserves a more precise understanding. Therefore, we have studied the transition states of the nitrile oxide cycloadditions with the chiral sultams, using molecular orbital calculations. From our calculation results, we find that the activation barriers of the favored and disfavored transition states are directly correlated with the Coulombic interactions between the dipolar oxygen and the sultam oxygens of the chiral dipolarophile systems. Thus, for comparison we also investigated if diastereoselectivities are possible for isothiazolidine systems **1′–3′** in which the two oxygens in the sulfone group in the sultam systems are removed.



1′



2′(R=Me) 3′(R=t-Bu)

II. Calculation Method

The transition states for the cycloadditions of Oppolzer's chiral sultams **1–3** with fulminic acid (formonitrile oxide) and acetonitrile oxide are too big to be amenable to Hartree–Fock (HF) *ab initio* molecular orbital treatments. Thus, semiempirical quantum mechanical calculations using

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[1] (a) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035. (b) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

[2] (a) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555. (b) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.

[3] (a) Kim, B. H.; Lee, J. Y.; Kim, K.; Whang, D. *Tetrahedron: Asymmetry* **1991**, *2*, 27. (b) Kim, B. H.; Lee, J. Y. *Tetrahedron: Asymmetry* **1991**, *2*, 1359.

[4] (a) Garner, P.; Ho, W. B. *J. Org. Chem.* **1990**, *55*, 3973. (b) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893.

[5] Vallgarda, J.; Hacksell, U. *Tetrahedron Lett.* **1991**, *32*, 5625.

[6] (a) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117. (b) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015. (c) Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019.

[7] Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett.* **1991**, *32*, 4893.

[8] (a) Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.

0002-7863/93/1515-7472$04.00/0

Table I. PM3 and HF/4-31G Structures of the Transition States for the Cycloadditions of Nitrile Oxides (RC≡NO) with Ethene[a]

	PM3		HF/4-31G		MC-SCF/4-31G[b]	MC-SCF/STO-3G[b]
	R = H	R = Me	R = H	R = Me	R = H	R = H
distances (Å)						
"C···C"	2.06	2.10	2.20	2.21	2.08	2.42
"C···O$_d$"	2.15	2.12	2.24	2.17	2.32	2.30
C–N	1.23	1.23	1.17	1.18	1.22	1.24
N–O$_d$	1.23	1.23	1.28	1.29	1.25	1.32
C–C	1.37	1.37	1.36	1.36	1.38	1.36
angles (deg)						
∠CNO$_d$	136.7	136.2	137.7	137.0	135.4	133.1
∠C···C–C	103.8	103.6	100.6	100.7	103.5	99.9
∠C–C–O$_d$	101.2	101.4	103.6	103.9	100.0	104.2
∠NC···C	100.4	99.3	102.0	100.2	105.7	100.6
∠NO$_d$···C	97.9	99.6	96.2	98.2	95.4	102.2

[a] "C···C" and "C···O$_d$" represent the partial bonds formed in the transition states. [b] Reference 13.

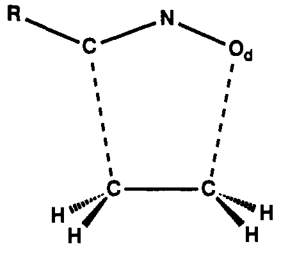
the PM3 method[9] were carried out to locate the transition states. Since these systems have up to 126 internal coordinates, it was extremely difficult to find the transition states. Nevertheless, with frequency analysis we confirmed that each predicted transition state indeed gave only one imaginary vibrational frequency mode. The same calculation methods were applied to the isothiazolidine systems 1′–3′.

At the PM3-predicted transition-state geometries, we performed Hartree–Fock (HF) *ab initio* calculations using Gaussian 90.[10] The 4-31G basis sets were used except for the sulfur atom, for which the 4-31G plus a polarized basis set (with the exponent of 0.6) was used. Then, the HF-predicted structure for dimethyl sulfoxide was in good agreement with experiment. For example, the predicted bond length of S═O was 1.44 Å, in agreement with the experimental length of 1.44 ± 0.01 Å.[11]

The parameters used in the PM3 calculations were originally optimized to fit experimental standard enthalpies of molecules at 298 K,[9] but the energies reported with *ab initio* calculations represent internal energies at 0 K. The Coulombic interaction energies were obtained from the intermolecular electrostatic energies between two reactants (i.e., nitrile oxides and sultams or isothiazolidines) by using the atomic charges. The atomic charges were obtained by the Mulliken population analysis in PM3 calculations and by the natural orbital population analysis[12] in *ab initio* calculations.

III. Results and Discussion

As a simple model study of the cycloadditions of nitrile oxides (RCNO) with the sultam systems, we investigated the transition states **4** for the cycloadditions with ethene (where R = H or CH$_3$) by using the PM3 and *ab initio* calculations. McDouall et al.[13] reported the synchronous transition state for R = H with multiconfiguration self-consistent field (MC-SCF) calculations. As shown in Table I, the distance of partial bonds "C···C" is almost the same as (or not too significantly different from) that of partial bonds "C···O$_d$" regardless of the level of theory. This signifies that the transition states **4** are (almost) synchronous. The structural differences between the PM3 and HF/4-31G transition states are not significant compared with those between the MC-SCF/4-31G and MC-SCF/STO-3G transition states. In terms of synchronous/asynchronous transition states, the PM3 results are between the HF/4-31G and MC-SCF/4-31G results, and between the MC-SCF/4-31G and MC-SCF/STO-3G results. In addition, we find that the structural differences between the transition states for R = H and R = CH$_3$ are very small for both PM3 and *ab initio* calculations.



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The PM3-predicted results of the transition states for the cycloadditions of formonitrile and acetonitrile oxides with the chiral sultams (**1**, **2**, and **3**) are listed in Table II. From this table, we note that there is no significant difference between the results for formonitrile and acetonitrile oxides. The structures of the transition states for the acetonitrile oxides with the sultams **1**, **2**, and **3** are shown in Figures 1, 2, and 3, respectively. As shown in the figures, O$_d$ denotes the dipolar oxygen in the nitrile oxide, and O$_c$, O$_x$, and O$_n$ denote the carbonyl oxygen, exo-like sultam oxygen, and endo-like sultam oxygen, respectively. The structures of the transition states for the formonitrile oxide are not shown here because of their structural similarity to those for the acetonitrile oxide.

The distances of the partial bonds "C···C" and "C···O$_d$" formed in the transition states are almost the same for all the systems studied regardless of the favored and disfavored transition states. This indicates that the pentagonal shapes formed in the transition states are little affected by bulky substituents.

The six transition states for R = H have almost the same imaginary vibrational frequencies of ~785*i* cm^{-1}. This frequency is similar to the imaginary frequency of the transition state for the cycloaddition of ethene with HCNO (~788*i* cm^{-1}). Similarly, the six transition states for R = CH$_3$ have almost the same imaginary frequencies of ~750*i* cm^{-1}. This frequency is also similar to the imaginary frequency of the transition state for the cycloaddition of ethene with CH$_3$CNO (~754*i* cm^{-1}).

The atomic charges in the transition states change little with substituents. For example, for the PM3 calculations, the charges of O$_c$ and O$_d$ are −0.36 ± 0.01 and −0.37 ± 0.01 au, respectively, and the charges of both O$_x$ and O$_n$ are −0.82 ± 0.01 au. The charges of S and N are 2.26 ± 0.05 and −0.52 ± 0.01 au, respectively. For the *ab initio* calculations, the charges were obtained using the natural orbital population analysis. Then, the natural charges of O$_c$ and O$_d$ are −0.64 ± 0.01 and −0.41 ± 0.01 au, respectively, and the natural charges of both O$_x$ and O$_n$ are −0.98 ± 0.01 au. The natural charges of S and N are 2.35 ± 0.03 and −0.81 ± 0.01 au, respectively. The charges of O$_c$ and N are rather strongly enhanced in the *ab initio* results. Consequently,

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[9] Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

[10] Frish, M. J.; Head-Gordon, M.; Trucks, J. B.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Segger, C. F.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. *Gaussian 90*; Gaussian Inc.: Pittsburgh, PA, 1990.

[11] (a) Jacob, E. J.; Lide, D. R. *J. Chem. Phys.* **1971**, *54*, 4591. (b) Saito, S.; Makino, F. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 92. (c) Hargittai, I.; Hargittai, M. *Acta Chim.* (*Hung.*) **1973**, *75*, 129. (d) Hargittai, I.; Hargittai, M. *J. Mol. Struct.* **1973**, *15*, 399. (e) Sands, D. E. *Acta Crystallogr.* **1963**, *B28*, 2463. (f) Langs, D. A.; Silverton, J. V.; Bright, W. M. *J. Chem. Soc., Chem. Commun.* **1970**, 1653.

[12] Reed, E. A.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.

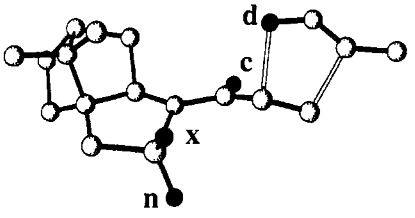
[13] McDouall, J. J. W.; Robb, M. A.; Niazi, U.; Bernardi, F.; Schlegel, H. B. *J. Am. Chem. Soc.* **1987**, *109*, 4642.

Table II. PM3 Results of the Disfavored Transition States Relative to the Favored Ones for the Cycloadditions of Nitrile Oxides (RC≡NO) with Sultam Systems **1**, **2**, and **3**[a]

R = H	**2**(Me)	**1**(Cam)	**3**(*t*-Bu)
relative energies (kcal/mol)			
$\Delta\Delta H^{\ddagger}$	0.70	1.13	1.46
ΔV_q	0.32	0.69	1.06
product ratios	77:23	87:13	92:8
distances (Å)			
"C- -C"	2.00:2.00	2.00:2.01	2.00:2.01
"C- -O_d"	2.18:2.17	2.18:2.17	2.18:2.17
O_d–O_c	3.15:3.10	3.17:3.13	3.13:3.02
O_d–O_x	4.51:5.37	4.59:4.77	5.00:5.31
O_d–O_n	5.28:4.01	5.55:3.86	5.29:3.82
O_d–S	4.69:4.52	4.79:4.29	4.92:4.48
O_d–N	3.64:3.73	3.62:3.75	3.73:3.89
imaginary freq (*i* cm^{-1})	783:786	784:784	784:787

R = Me	**2**(Me)	**1**(Cam)	**3**(*t*-Bu)
relative energies (kcal/mol)			
$\Delta\Delta H^{\ddagger}$	0.72	1.12	1.47
ΔV_q	0.35	0.70	1.10
product ratios			
PM3	77:23	87:13	92:8
experiment	79:21	90:10	96:4
distances (Å)			
"C- -C"	2.04:2.04	2.04:2.05	2.04:2.05
"C- -O_d"	2.15:2.14	2.15:2.14	2.15:2.13
O_d–O_c	3.14:3.09	3.16:3.12	3.12:3.02
O_d–O_x	4.49:5.33	4.57:4.73	4.99:5.27
O_d–O_n	5.26:3.98	5.52:3.84	5.27:3.81
O_d–S	4.67:4.49	4.76:4.26	4.90:4.45
O_d–N	3.62:3.71	3.60:3.73	3.71:3.87
imaginary freq (*i* cm^{-1})	750:753	751:750	751:753

[a] Notations are as follows: $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}(\text{disfav}) - \Delta H^{\ddagger}(\text{fav})$; $\Delta V_q = V_q(\text{disfav}) - V_q(\text{fav})$, where V_q is the potential energy of Coulombic interaction between two reactants. "C- -C" and "C- -O_d" represent the partial bonds formed in the transition states. Bond distances and frequencies for the favored and disfavored transition states are given with their ratios.



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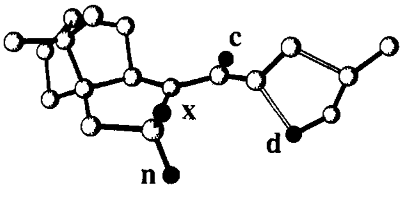
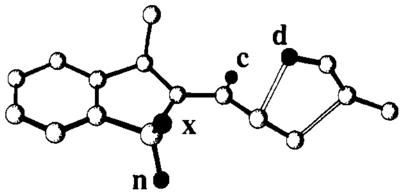


Disfavored

Figure 1. PM3-predicted geometries of the favored and disfavored transition states for the cycloaddition of MeCNO with sultam **1**. Filled circles represent oxygen atoms; "c", "d", "n", and "x" denote O_c, O_d, O_n, and O_x, respectively.

when the *ab initio* calculations are performed at the PM3 optimized geometries, the Coulombic interaction energies are strongly enhanced in the *ab initio* results compared with the PM3 results. Thus, it is expected that the optimization by *ab initio* calculations will increase the distances between the strongly charge-enhanced atoms so that the Coulombic interaction cannot be overestimated.



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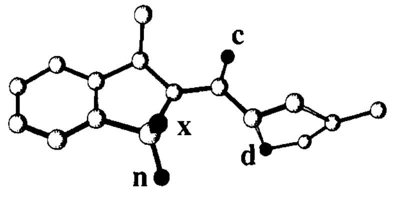

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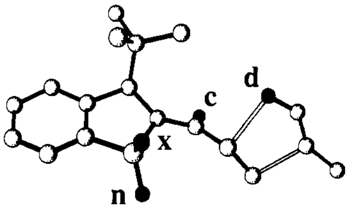
Figure 2. PM3-predicted geometries of the favored and disfavored transition states for the cycloaddition of MeCNO with sultam **2**.



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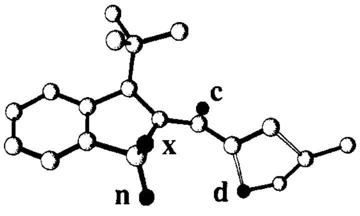


Disfavored

Figure 3. PM3-predicted geometries of the favored and disfavored transition states for the cycloaddition of MeCNO with sultam **3**.

From the PM3 results in Table II, we find no significant structural and energetic differences between the cycloadditions with the fulminic acid and acetonitrile oxide. Thus, we will mainly discuss the cycloaddition of the acetonitrile oxide with the sultam systems, for which the experimental diastereofacial selectivity data are available. However, for the isothiazolidine systems for which the experimental data are not available, we will consider only the cycloaddition with the fulminic acid.

The PM3 calculations of the transition states for the cycloaddition of acetonitrile oxide with the sultam **1** show that the activation barrier for the cycloaddition from the top face is 1.12 kcal/mol less than that from the bottom face. The calculated product ratio (87:13) is in accord with the experimental product ratio (90:10). For the cycloadditions of acetonitrile oxide with sultams **2** and **3**, the PM3 activation barriers for the cycloadditions from the top face are less than those from the bottom face by 0.72 and 1.47 kcal/mol, respectively. The calculated product ratios for **2** (77:23) and **3** (92:8) are in good agreement with the experimental product ratios for **2** (79:21) and **3** (96:4), respectively (Table II). It should be noted, however, that the entropy effect was not taken into account for the following two reasons. First, the relative free energy correction for sultam **3** was only ~0.1 kcal/mol at 298 K. Second, the PM3-predicted entropies or

Table III. PM3 Results of the Bottom-Facial Transition States Relative to the Top-Facial Ones for the Cycloadditions of Fulminic Acid (HC≡NO) with Isothiazolidine Systems **1′**, **2′**, and **3′**[a]

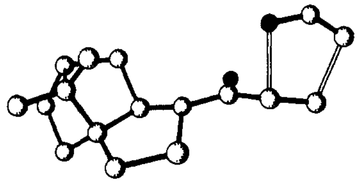
	2′(Me)	**1′**(Cam)	**3′**(*t*-Bu)
relative energies (kcal/mol)			
$\Delta\Delta H^{\ddagger}$	–0.23	0.03	0.02
ΔV_q	–0.10	–0.03	0.14
product ratios	49:51	51:49	51:49
distances (Å)			
"C- -C"	2.01:2.00	2.01:2.01	2.01:2.00
"C- -O_d"	2.18:2.18	2.18:2.18	2.18:2.18
O_d–O_c	3.25:3.17	3.24:3.15	3.25:3.14
O_d–S	4.31:4.11	4.45:4.08	4.39:4.07
O_d–N	3.50:3.69	3.51:3.73	3.51:3.73
imaginary freq (i cm^{-1})	782:784	782:784	782:784

[a] See the footnote of Table II; the favored and disfavored TSs in Table II are replaced by the top-facial and bottom-facial TSs, respectively.

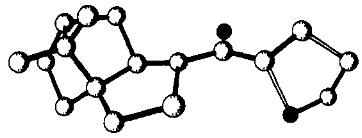
relative entropies may not be too reliable, because the PM3 parameters were originally optimized for the standard experimental enthalpies at 298 K.

The most important and intriguing question to be addressed in our discussion is why nitrile oxides favor approaching the top faces of sultams **1**–**3**. On the basis of conventional steric considerations, the favored approaching direction is from the bottom face, because the top face is a sterically more congested π-face due to the bulky groups. But our study finds that the unique diastereofacial selectivity arises mainly from the difference between the favored and disfavored transition states in the Coulombic repulsions between the sultam oxygen atoms and the nitrile oxide oxygen atom. Among the most important interatomic Coulombic interactions between sultams and nitrile oxides, the most conspicuous difference between the favored and disfavored transition states comes from the difference in the distance O_d–O_n. For the cycloaddition of the acetonitrile oxide with sultams **1**, **2**, and **3**, the distances O_d–O_n for the disfavored transition states are 3.84, 3.98, and 3.81 Å, respectively, while those for the favored ones are 5.52, 5.26, and 5.27 Å, respectively. These distance differences are the main reasons that the favored transition states have smaller activation barriers due to less Coulombic repulsions than the disfavored transition states. In addition, the difference in the distance O_d–S between the favored and disfavored transition states also strongly affects the Coulombic interaction energies between the sultams and nitrile oxides. Then, for sultams **1**, **2**, and **3**, the Coulombic interaction energy differences between the favored and disfavored transition states are 0.70, 0.35, and 1.10 kcal/mol, respectively. These should be compared with the differences in the activation barriers between the favored and the disfavored transition states, which are 1.12, 0.72, and 1.47 kcal/mol for sultams **1**, **2**, and **3**, respectively. This indicates that Coulombic interaction energies govern the activation energy barriers.

To provide more clear evidence that Coulombic interaction plays an important role in diastereoselectivity for the sultam systems, we investigated the isothiazolidine systems (**1′**–**3′**) in which the two oxygens in the sulfone group in the sultam systems were removed. The isothiazolidine systems do not have strong Coulombic repulsions such as O_d–O_n and O_d–O_x in the sultam systems. In each isothiazolidine system, the energy difference between two different transition states is very small (as shown in Table III) so that we can no longer distinguish between the favored and disfavored transition states. Thus, we define the top-facial and bottom-facial transition states for which the nitrile oxides approach from the top and bottom faces of the isothiazolidine systems, respectively. The top-facial and bottom-facial transition states for the cycloadditions of fulminic acid with the isothiazolidine systems **1′**, **2′**, and **3′** are shown in Figures 4, 5, and 6, respectively. Lack of Coulombic energy differences between the top-facial and bottom-facial transition states for the isothiazolidine systems makes the corresponding activation energy barrier differences negligible, showing no diastereofacial selectivity (Table III). This provides evidence that the diastereofacial selectivity for the sultam systems arises mainly from Coulombic interaction.

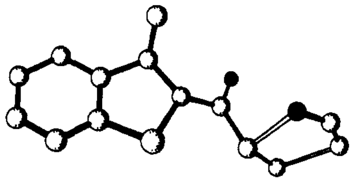


Top-facial

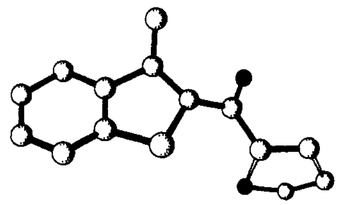


Bottom-facial

Figure 4. PM3-predicted geometries of the top-facial and bottom-facial transition states for the cycloaddition of HCNO with isothiazolidine **1′**.



Top-facial



Bottom-facial

Figure 5. PM3-predicted geometries of the top-facial and bottom-facial transition states for the cycloaddition of HCNO with isothiazolidine **2′**.

To provide a more reliable conclusion, we compare the PM3 results with the *ab initio* results. Since the sultam systems are too large for geometry optimization by HF *ab initio* calculations, the single-point HF calculations were performed at the PM3 optimized geometries using the basis sets described in the calculation method. For this reason, the absolute magnitude of the activation energy barrier difference between the favored and disfavored transition states may not be reliable, because the energies of the transition states are very sensitive to the geometries used. Indeed, as shown in Table IV, the activation barrier differences obtained from the *ab initio* calculations are very different from those predicted by the PM3 calculations. It should be recalled that the charges of O_c and N are strongly enhanced in the *ab initio* results compared with the PM3 results. Consequently, the Coulombic interaction energies are strongly enhanced in the *ab initio* calculations performed at the PM3 optimized geometries. However, the *ab initio* results with full geometry optimization will increase the distances between the

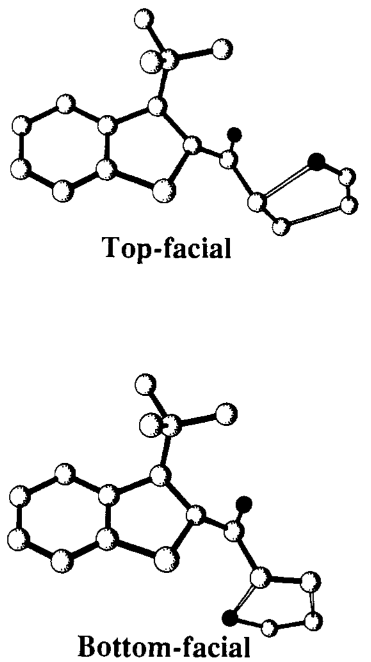


Figure 6. PM3-predicted geometries of the top-facial and bottom-facial transition states for the cycloaddition of HCNO with isothiazolidine **3'**.

Table IV. Comparison of the PM3 and *ab initio* Energies of the Disfavored Transition States Relative to the Favored Ones for the Cycloadditions of Fulminic Acid ($HC{\equiv}NO$) with Sultam Systems **1**, **2**, and **3**[a]

	2(Me)	**1**(Cam)	**3**(*t*-Bu)
PM3			
$\Delta\Delta H^{\ddagger}$	0.70	1.13	1.46
ΔV_q	0.33	0.69	1.05
ab initio			
$\Delta\Delta E^{\ddagger}$	0.67	3.31	4.16
ΔV_q	1.12	2.93	3.71

[a] The *ab initio* calculations were performed using the PM3 optimized geometries. Refer to the text for the basis set. The relative potential energies of Coulombic interaction between two reactants (ΔV_q) were obtained using the charges obtained from the natural orbital population analysis. $\Delta\Delta E^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ are the relative standard internal energy and enthalpy of activation, respectively.

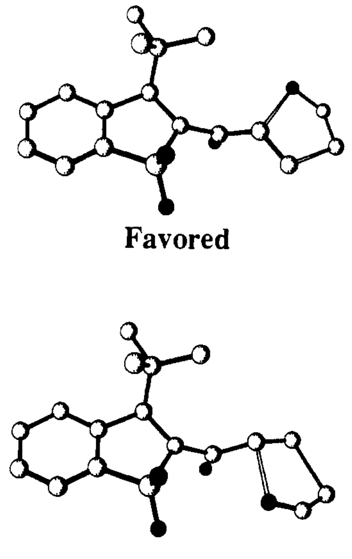


Figure 7. PM3-predicted geometries for the second lowest energy set of the favored and disfavored transition states for the cycloaddition of HCNO with sultam **3**.

strongly charge-enhanced atoms so that the Coulombic interaction cannot be overestimated. Although the interaction energy between two charges is proportional to r^{-1}, the interaction energy between two dipoles is proportional to r^{-3}. Thus, a slight distance change can reduce the Coulombic interaction energy drastically without changing the molecular structure significantly.

Although the energetics of the *ab initio* results performed at the PM3 optimized geometries are not too reliable, one should note that there is a certain correlation between the PM3 and *ab initio* activation barriers. More seriously, we investigated if for the favored and disfavored transition states the relative Coulombic interaction energies can still be closely correlated with the relative activation barriers. For this purpose, the Coulombic interaction energies were calculated using the natural orbital population analysis. In Table IV, we find that for the three sultam systems (**1**, **2**, and **3**) the Coulombic interaction energy differences (2.93, 1.12, and 3.71 kcal/mol) between the favored and disfavored transition states are strongly correlated with the activation energy differences (3.31, 0.67, and 4.16 kcal/mol). This again supports that the cycloadditions are controlled mainly by electrostatic interaction.

However, one may wonder if the relative activation barrier can be smaller than the relative Coulombic energy. The activation barrier arises from many different factors, such as Coulombic interaction, steric effect, molecular orbital change, and quantum exchange interaction. These terms are not necessarily additive, but can sometimes be subtractive with negative signs. If the Coulombic interaction energy is several kilocalories/mole larger than the activation barrier of a few kilocalories/mole, the overestimation problem can be serious. But the overestimation for sultam **2** is not likely to be serious. In particular, the *ab initio* results were obtained using the PM3 optimized geometries. If the geometries are fully optimized with *ab initio* calculations, the overestimation can be much less serious.

Now, we need to consider other possible transition states which are not listed in Tables II and III. Indeed, we located other transition states. There can be a number of transition states for large and complex molecular systems. Further, it is extremely difficult to locate all low-lying transition states without missing any. Thus, we searched for the transition states in a systematic way with the consideration of various possible orientations of the $C{=}O_c$ and $C{\cdots}O_d$ partial bonds. Namely, for a given dihedral angle of O_c–C–N–S we varied the dihedral angle of O_d–C–C–O_c from −180 to 180° in order to find the lowest energy transition-like structure which has 0 energy gradient with the pentagonal shape of –C–N–$O_d{\cdots}$C–C– within the given dihedral angle constraint. Then, the lowest energy transition-like structure was fully optimized. We continued the repetitive procedure for a different dihedral angle of O_c–C–N–S, for example, for every 30° increment. If the orientation was not energetically favorable due to the proximity of the oxygen atoms, the computation was skipped. In this way, we finally located two sets of the favored and disfavored transition states for sultam **3**. The two sets differ in the orientations of the $C{=}O_c$ bond, i.e., rotation about the nitrogen–carbonyl carbon bond. The lowest energy transition state set has the dihedral angle of O_c–C–N–S of ~145° (−139° for the favored; −147° for the disfavored), while the higher energy transition state set has that of ~90° (−98° for the favored; −83° for the disfavored), which are shown in Figure 7.

The main differences between the lowest and higher energy transition state sets are the distances of O_c–O_n and O_c–S, which are shorter in the higher energy set. Namely, the two distances for the favored transition states of the lowest energy set are 4.07 and 3.86 Å, while those of the higher energy set are 3.58 and 3.61 Å. Similarly, the two distances for the disfavored transition states of the lowest energy set are 4.23 and 3.92 Å, while those of the higher energy set are 3.44 and 3.50 Å. For the higher energy transition set the shortened distances of O_c–O_n and O_c–S increase the Coulombic repulsion and attraction, respectively; thus, these two interactions are partially canceled.

It seems that the transition structures with the dihedral angles of O_c–C–N–S which are not near ~145° and ~90° are energetically unfavorable due to the proximity of some of the negatively charged atoms of N, O_c, O_d, O_x, and O_n. However, we should address that other transition states can still be available among the energetically unfavorable conditions. Indeed, in a PM3 calculation we found one such favored transition state which is 4 kcal/mol higher than the lowest, but such transition states are energetically somewhat higher than the lowest favored and disfavored transition states so that we did not try to search for all such high-energy transition states.

With PM3 calculations, the favored and disfavored transition states of the higher energy set for sultam **3** are 1.42 and 1.92 kcal/mol higher than those of the lowest energy set. However, the corresponding single-point *ab initio* results using the PM3 optimized geometries are 13.05 and 13.76 kcal/mol higher. Such large differences sometimes can be expected due to single-point calculations at the PM3 geometries, because in the *ab initio* calculations the strongly enhanced charge of O_c disfavors the shortened distances of O_c–O_n and O_c–S. Although such a high energy difference can be somewhat reduced by the *ab initio* calculations with full geometry optimization, this transition-state set is expected to be far from the experimentally meaningful transition states. Namely, the cycloadditions via the higher energy transition states may not be possible practically. Therefore, we did not pursue locating such transition states (having the dihedral angle of O_c–C–N–S of ~90°) for sultams **1** and **2**.

We also searched for various possible transition states for the cycloadditions of the formonitrile oxides with the isothiazolidine systems in the same systematic way as investigated in the sultam systems. Owing to the lack of the two sultam oxygen atoms, we located for each isothiazolidine system only a pair of the top-facial and bottom-facial transition-state structures for which the dihedral angles of O_c–C–N–S are in the range of 149 ~ 167°. For isothiazolidine system **3'**, the dihedral angles are 152° and 160° for the top-facial and bottom-facial transition states, respectively.

IV. Concluding Remarks

Hehre et al.[14–16] have applied electrostatic interaction to be diastereofacial selectivity in Diels–Alder reactions. They claimed that the electrostatic effect is a very general determinant of the π-facial selectivity.[17] Very recently, the possible importance of Coulombic interaction in chemical reactions has also been discussed by Houk et al.[18–20] and Paddon-Row et al.[20–22] Compared with the dienes in Diels–Alder reactions, the nitrile oxides are very polar molecules. Thus, the π-face differentiation of the incoming nitrile oxides in the sultam systems is indeed a case where the Coulombic interaction is very important.

In conclusion, diastereofacial selectivity in the nitrile oxide cycloadditions with Oppolzer's chiral sultams **1–3** originates not from conventional face shielding by sterically bulky groups, but mainly from face shielding due to Coulombic interaction (repulsion) between the dipolar oxygen and the sultam oxygens. This kind of electronic shielding deserves more attention in the design of other asymmetric reactions.

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Supplementary Material Available: Tables of the Cartesian coordinates for the favored and disfavored transition-state structures of the lowest energy set for the cycloadditions of the acetonitrile oxides with sultams **1–3**, the top-facial and bottom-facial transition structures for the cycloadditions of the formonitrile oxides with isothiazolidine systems **1'–3'**, and the favored and disfavored transition structures of the second lowest energy set for the cycloadditions of the formonitrile oxide with sultam **3** (7 pages). Ordering information is given on any current masthead page.

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(14) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663.

(15) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1986**, *27*, 6041.

(16) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.

(17) Chao, T.-M.; Baker, J.; Hehre, W. J.; Kahn, S. D. *Pure Appl. Chem.* **1991**, *63*, 283.

(18) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

(19) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1499.

(20) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638.

(21) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327.

(22) Wong, S. S.; Paddon-Row, M. N. *Aust. J. Chem.* **1991**, *44*, 765.