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Roles of C−H···O=S and π-Stacking Interactions in the 2-Bromoacrolein Complex with *N*-Tosyl-(*S*)-tryptophan-Derived Oxazaborolidinone Catalyst

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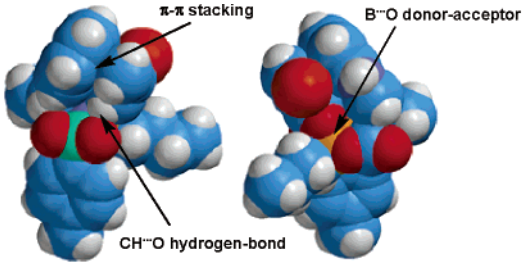

2-bromoacrolein-N-tosyl-(S)trytophan derived 1,3,2-oxazaborolidinone complex

Ab initio and density functional calculations were employed to examine the structures and binding energies of various complexes between 2-bromolacrolein and *N*-tosyl-(*S*)-tryptophan-derived *B*-butyl-1,3,2-oxazaborolidin-5-one (NTOB), a catalyst commonly used for Diels−Alder reactions. Our calculations show that the chiral oxazaborolidinone catalyst serves as a tridentate complexation agent via B···O donor−acceptor, C−H···O hydrogen-bonded, and π-stacking interactions. The most stable complex (**1TS**) is predicted to have a binding energy of −93 kJ mol^{-1} (ΔG_{298} = −29 kJ mol^{-1}). The formyl C−H···O hydrogen bond and π-stacking interaction are the key factors governing the relative stabilities of the four acrolein−NTOB complexes examined. The calculated structure and binding properties of **1TS** are consistent with the experimental results on the absorption spectrum of the acrolein−NTOB complex and the effects of substituents on the reactivity of Diels−Alder reactions. **1TS** differs from Corey's proposed model of transition-state assembly in two aspects: (1) it involves the *s-trans*-acrolein and (2) it favors a C−H···O interaction via the sulfonyl oxygen (C−H···O=S), rather than the ring oxygen (C−H···O−B). This calculated structure of the acrolein−catalyst complex provides an alternate explanation of the origin of stereoselectivity in the NTOB-catalyzed Diels−Alder reactions.

Introduction

The design of an effective chiral catalyst to achieve maximum enantioselectivity is of utmost importance in organic synthesis.[1] Oxazaborolidinone derivatives are useful catalysts for enantioselective reduction of prochiral ketones,[2] Diels−Alder cycloadditions,[2d,3,4] and Mukaiyama aldol reactions.[5] These Lewis acids are most useful for promotion of asymmetric Diels−Alder (DA) reactions

(1) (a) Corey, E. J. *Angew. Chem., Int. Ed*. **2002**, *41*, 1650. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (c) Ojima, I. *Catalytic Asymmetric Synthesis*; VHC: Berlin, 1993. (d) Williams, J. *Catalysis in Asymmetric Synthesis*; Blackwell Publishing: New York, 1999.

(2) (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun*. **1983**, 469. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Martens, J.; Wallbaum, S. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (c) Singh, V. K. *Synthesis* **1992**, 605. (d) Deloux, L.; Srebnik, M. *Chem. Rev*. **1993**, *93*, 763. (e) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed*. **1998**, *37*, 1986.

(3) (a) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc*. **1991**, *113*, 8966. (b) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc*. **1992**, *114*, 8290.

(4) (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (b) Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron: Asymmetry* **1991**, *2*, 639. (c) Seerden, J.-P.; Scheeren, H. W. *Tetrahedron Lett*. **1993**, *34*, 2669. (d) Oh, T.; Reilly, M. *Org. Prep. Proced. Int*. **1994**, *26*, 129. (e) Dias, L. C. *J. Braz. Chem. Soc*. **1997**, *17*, 245. (f) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1221. (g) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc*. **2003**, *125*, 6388. (h) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc*. **2004**, *126*, 13708.

(5) (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (b) Kiyooka, S.-I. *Rev. Heteroat. Chem.* **1997**, *17*, 245. (c) Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc*. **1998**, *120*, 6920. (d) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem*. **1999**, *64*, 5511. (e) Wang, X.; Adachi. S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T. *J. Org. Chem*. **2003**, *68*, 10046.

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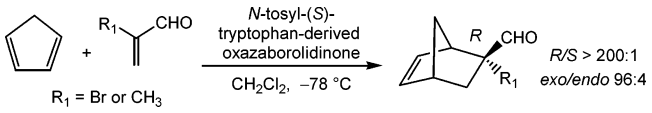

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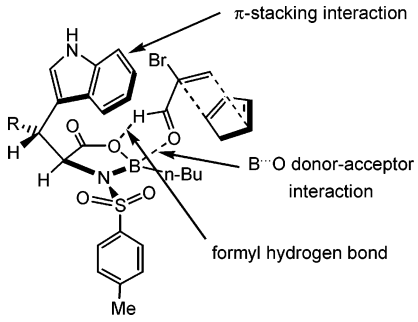

of α,β-unsaturated aldehydes with simple dienes. In particular, Corey and co-workers have shown convincingly that *N*-tosyl-(*S*)-tryptophan-derived oxazaborolidinone catalyst is able to achieve a remarkable enantioselectivity for the Diels−Alder reactions between cyclopentadiene and 2-substituted acrolein (Scheme 1).[3]

To account for the observed enantioselectivity, Corey et al. proposed a model of transition-state assembly (Scheme 2) involving the *s-cis* conformation of acrolein.[3] The salient structural features in their proposed acrolein−catalyst complex and transition-state model include (1) B···O donor−acceptor interaction, (2) a formyl C−H···O hydrogen bond, and (3) π-stacking interaction between the coordinated acrolein and the indole subunit. Their model is supported by ^{1}H NMR and UV spectroscopic experiments on the acrolein−catalyst complex.[3b] On the basis of supporting evidence from X-ray crystallographic studies of formyl−Lewis acid complexes, the formyl C−H···O hydrogen bond is proposed to be a key organizing factor in many types of Lewis acid-catalyzed enantioselective reactions.[6]

In this paper, we attempt to examine the validity of Corey's proposed model. To this end, we have investigated the structures and binding properties of complexes between 2-bromoacrolein and *N*-tosyl-(*S*)-tryptophan-derived *B*-butyl-1,3,2-oxazaborolidin-5-one (NTOB), which is the Lewis acid catalyst employed in the experimental studies,[3,4] using ab initio and density functional calculations. More importantly, a better understanding of the intermolecular forces in the acrolein−catalyst complex is essential for the future design of effective Lewis acids with high catalyst activity and enantioselectivity.[7] Ab initio studies on the coordination of formaldehyde and acrolein to smaller model systems, namely, *N*-sulfonylated oxazaborolidines[8] and oxazaborolidinone,[9] have been reported previously. However, these authors did not consider the role of π−π interactions involving the indole unit of NTOB.

Computational Methods

Geometry optimizations of various possible complexes between 2-bromoacrolein and NTOB were performed using a density functional theory (DFT) method together with the 6-31G(d) basis set, which represents a good compromise between reliability and practicality for the relatively large systems studied here. The Perdew−Wang 1991 exchange-correlation functional (PW91PW91)[10] was chosen for the DFT calculations as this functional is better suited for studying systems with long-range hydrogen-bonding forces[11] and van der Waals interactions, such as π−π interaction.[12] In particular, the PW91PW91 functional is found to perform significantly better than the hybrid DFT methods, such as B3LYP, in describing the π−π interaction.[12] It is well established that the MP2 method provides a more reliable energy prediction for systems containing π−π interaction.[12,13] Thus, the binding energies of the acrolein−NTOB complexes were obtained by single-point energy calculations at the MP2/6-31+G(d) level, based on the DFT-optimized geometries. Frequency calculations were carried out with the optimized PW91PW91/6-31G(d) geometries to verify the local energy minima as equilibrium structures and to evaluate zero-point energies (ZPEs) and thermal corrections. Unless otherwise noted, the computed binding energies correspond to the MP2/6-31+G(d) level and include (unscaled) zero-point energy corrections. The free energy differences (ΔG) were computed from the equation $\Delta G_T = \Delta H_T - T\Delta S$, where ΔS is the entropy change and $\Delta H_T = \Delta H_0 + (H_T - H_0)$. The term $H_T - H_0$ corresponds to the thermal energy at temperature T. Time-dependent density functional theory (TDDFT)[14] calculations were performed on the excitation energies and oscillator strengths of the acrolein−NTOB complexes. Atomic charges were obtained using the natural bond orbital (NBO) analysis,[15] based on the PW91PW91/6-31G(d) wave function. Onsager's self-consistent reaction field (SCRF) theory[16] was employed to investigate the solvation effect. For the solvent-effect calculations, geometry optimizations were performed at the PW91PW91/6-31G(d) level and higher level single-point energy calculations were carried out at the PW91PW91/6-31+G(d) level. Conformational analysis at the PM3 level was carried out with the Spartan program,[17]

(6) Corey, E. J.; Lee, T. W. *Chem. Commun*. **2001**, 1321.
(7) Harb, W. F.; Ruiz-López, M. F.; Coutrot, F.; Grison, C.; Coutrot, P. *J. Am. Chem. Soc.* **2004**, *126*, 6996.
(8) (a) Nevalainen, V. *Tetrahedron: Asymmetry* **1993**, *4*, 1565. (b) Nevalainen, V. *Tetrahedron: Asymmetry* **1994**, *5*, 767. (c) Uggla, R.; Nevalainen.; V.; Sundberg, M. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2725.
(9) Salvatella, L.; Ruiz-López, M. F. *J. Am. Chem. Soc*. **1999**, *121*, 10772.
(10) (a) Perdew, J. P. In *Electronic Structure of Solids '91*; Ziesche, P., Eschrig, H., Eds.; Akademie-Verlag: Berlin, 1991; p 11. (b) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *45*, 13244. (c) Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev. B* **1992**, *46*, 6671. (d) Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev. B* **1993**, *48*, 4979(E).
(11) (a) Lai, C.-C.; Shen, C.-C.; Hu C.-H. *J. Chin. Chem. Soc*. **2001**, *48*, 145. (b) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, Germany, 2000.
(12) (a) Kurita, N., Tanaka, S.; Itoh, S. *J. Phys. Chem. A* **2000**, *104*, 8114. (b) Tsuzuki, S.; Luthi, H. P. *J. Chem. Phys*. **2001**, *114*, 3949. (c) Kurita, N.; Sekin. H. *Int. J. Quantum Chem*. **2003**, *91*, 355. (d) Ye, X.; Li, Z.-H.; Wang, W.; Fan, K.; Xu, W.; Hua, Z. *Chem. Phys. Lett*. **2004**, *397*, 56.
(13) (a) Ujaque, G.; Lee, P. S.; Houk, K. N.; Hentemann, M. F.; Danishefsky, S. *Chem.—Eur. J.* **2002**, *8*, 3423. (b) Tarakeshwar, P.; Choi, H. S.; Kim, K. S. *Chem. Rev*. **2000**, *100*, 4245. (c) Hobza, P.; Havlas, Z. *Chem. Rev*. **2000**, *100*, 4253. (d) Sinnokrot, M. O.; Sherrill, C. D. *J. Phys. Chem. A* **2003**, *107*, 8377.
(14) (a) Bauernschmitt, R.; Ahlrichs, R. *Chem. Phys. Lett.* **1996**, *256*, 454. (b) Stratmann, R. E.; Scuseria, G. E.; Frisch, M. J. *J. Chem. Phys.* **1998**, *109*, 8218. (c) Casida, M. E.; Jamorski, C.; Casida, K. C.; Salahub, D. R. *J. Chem. Phys.* **1998**, *108*, 4439.
(15) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev*. **1988**, *88*, 899.
(16) (a) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 4776. (b) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Chem. Phys*. **1991**, *95*, 8991. (c) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645. (d) Kiruba, G. S. M.; Wong, M. W. *J. Org. Chem*. **2003**, *68*, 2874.
(17) *Spartan 5.0*; Wavefunction Inc.: Irvine, CA, 1997.

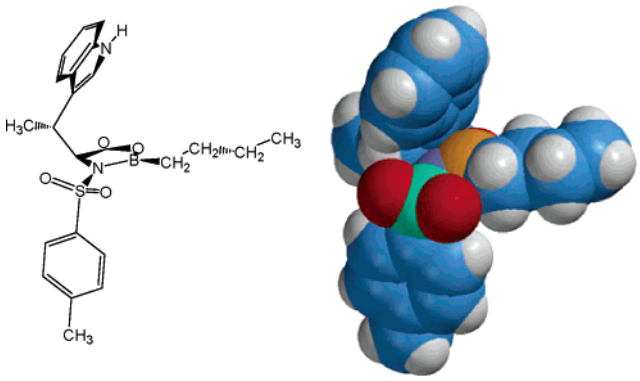

FIGURE 1. Optimized (PW91PW91/6-31G(d)) geometry of NTOB (CPK model on the right).

and all other calculations were performed using the Gaussian 98 suite of programs.[18]

Results and Discussion

NTOB Lewis Acid. Conformational analysis based on the Monte Carlo method was carried out initially at the semiempirical PM3 level to locate various possible low-lying conformations of the chiral Lewis acid NTOB. Several of the lower energy minima were further refined at the DFT level. The optimized geometry of the lowest energy structure of NTOB is shown in Figure 1. The structure has a rather rigid geometry. The oxazaborolidinone five-membered ring is essentially planar, with the oxygen atoms of the sulfonyl group lying close to the ring. The *p*-tolyl group is perpendicular to the heterocycle. Our finding here agrees well with previous theoretical studies on the conformational properties of the smaller oxazaborolidines and oxazaborolidinones.[8,9,19] Due to the presence of the bulky *N*-tosyl unit, the 3-methylindole moiety is directed toward the opposite face of the oxazaborolidinone ring. The *n*-butyl substituent on boron lies in the same plane of the heterocycle. As expected, this Lewis acid has the highest LUMO density at the boron atom, which can interact readily with the electron-rich oxygen atom of an α,*β*-enal.

2-Bromoacrolein−NTOB Complexes. The NTOB Lewis acid may serve as a tridentate complexation agent via B···O donor−acceptor, C−H···O hydrogen-bonded, and *π*-stacking interactions, as suggested by Corey et al.[3] One may envisage these nonbonded interactions in the coordination of an α,*β*-enal with NTOB. Coordination of 2-bromoacrolein to the Lewis acid and the boron center of NTOB occurs by means of its oxygen lone pair *syn* to the formyl proton via donor−acceptor interaction. The ring oxygen and one of the sulfonyl oxygens are in close proximity to the boron center. Thus, the formyl C−H proton of the coordinated acrolein may interact with either the ring oxygen (C−H···O−B) or the sulfonyl oxygen (C−H···O=S) to form a C−H···O type of hydrogen bond. The importance of the C−H···O=S type of interaction has been noted in previous theoretical investigations.[9,20] Finally, the complex can be further stabilized by *π*-stacking interaction between the indole unit of the catalyst and the coordinated acrolein. This *π*−*π* donor−acceptor interaction is expected to be strong, such as that in the indole−1,3,5-trinitrobenzene complex.[21] Nevalainen et al. have examined the possibility of *π*-stacking interaction between the phenyl group of *N*-phenylsulfonyl-1,3,2-oxazaborolidinone and coordinated acrolein, and they concluded that the *π*-stacking in the complex is essentially passive in nature.[8c] Preliminary calculations on structures with this mode of *π*-stacking are found to be significantly higher in energy, and they will not be considered further in this study. This result is, perhaps, not surprising as the phenylsulfonyl group and 2-bromoacrolein are both *π*-deficient systems.

On the basis of the optimized geometry of the NTOB catalyst (Figure 1), the three-point complexation with 2-bromoacrolein is only feasible on the face *syn* to the 3-methylindole unit. Two anchoring modes of C−H···O interactions (C−H···O−B and C−H···O=S) are envisaged for each of the two conformations of acrolein, *s-cis* and *s-trans*. This gives rise to four possible structures for coordination of 2-bromoacrolein to NTOB: **1CR**, **1CS**, **1TR**, and **1TS**. The notations **C** and **T** denote the *s-cis* and *s-trans* forms of acrolein, respectively, while the notations **R** and **S** refer to the C−H···O interaction involving the ring (CH···O−B) and sulfonyl oxygen (CH···O=S), respectively. The optimized geometries of these four complexes are depicted in Figure 2, and their computed binding energies are given in Table 1.

As evidenced in Figure 2, all four complexes are characterized by the three types of nonbonded interactions mentioned above. The B···O distances in these adducts have a rather narrow range of 1.64−1.66 Å, indicating that their strengths of donor−acceptor interaction are fairly similar. On the other hand, the C−H···O distances in the **S** complexes (with C−H···O=S interaction) are significantly shorter than those in the corresponding **R** complexes (with C−H···O−B interaction), by ∼0.20 Å (Figure 2). The corresponding C−H···O bond angles are ∼100° and ∼146° for the **R** and **S** complexes, respectively. These structural differences suggest that the sulfonyl oxygen is a better hydrogen bond acceptor than the ring oxygen. This is further supported by the electrostatic potential map of NTOB, which indicates that the sulfonyl oxygen is the most electron rich region. For both *s-trans*- and *s-cis*-2-bromoacrolein, the formation of the **S** complex is more favorable than that of the corresponding **R** complex (Table 1).

A parallel orientation between coordinated 2-bromoacrolein and the indole unit of NTOB is found in all four complexes. The calculated interplane distances, 3.16−

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(19) Nevalainen, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1449.

(20) Suárez, D.; López, R.; González, J.; Sordo, T. L.; Sordo, J. A. *Int. J. Quantum Chem.* **1996**, *57*, 493.

(21) Hanson, A. W. *Acta Crystallogr.* **1964**, *17*, 559.

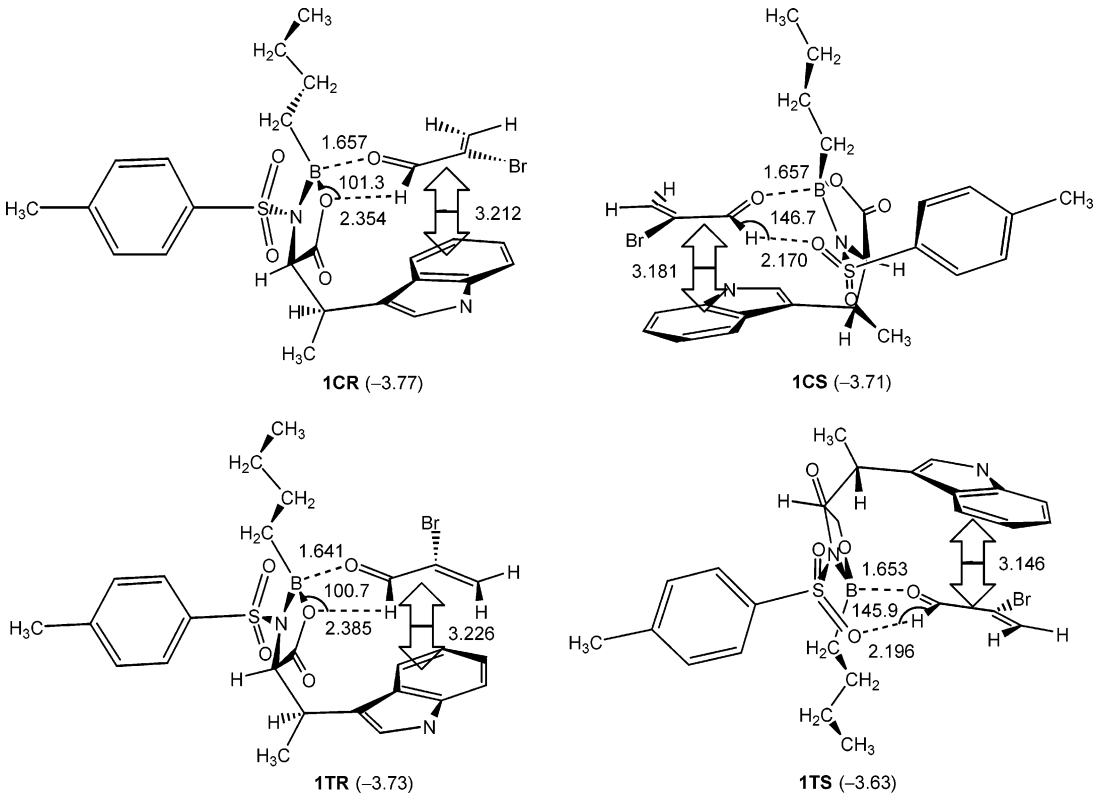

FIGURE 2. Optimized (PW91PW91/6-31G(d)) geometries of 2-bromoacrolein−NTOB complexes, bond distances in angstroms and angles in degrees. The π-stacking interplane distance (double arrow) is defined as the projection distance from the midpoint of the central C−C bond of 2-bromoacrolein onto the plane of the indole unit. The LUMO energies (eV) are given in parentheses.

TABLE 1. Calculated Relative and Binding Energies[a,b] (kJ mol^{-1}) and Dipole Moments (μ, D)[c] for the 2-Bromoacrolein−NTOB Complexes

	relative energy		binding energy $\Delta E°_0$				
complex	$\epsilon = 1.0$	$\epsilon = 8.9$[d]	$\epsilon = 1.0$	$\epsilon = 8.9$[d]	$\Delta H°_{298}$	$\Delta G°_{298}$	μ[c]
1CR	22.7 (20.2)	(20.8)	71.2 (36.6)	(33.9)	69.6	11.7	2.57
1CS	20.4 (15.8)	(16.4)	73.5 (42.0)	(39.3)	72.4	10.9	2.58
1TR	28.2 (23.3)	(21.8)	64.7 (34.6)	(29.4)	63.6	5.6	4.94
1TS	0.0 (0.0)	(0.0)	92.9 (57.9)	(51.3)	92.5	28.8	3.17

[a] MP2/6-31+G(d)//PW91PW91/6-31G(d)+ZPE level. [b] PW91PW91/6-31+G(d)//PW91PW91/6-31G(d)+ZPE values in parentheses. [c] PW91PW91/6-31G(d) values; the calculated dipole moments of NTOB nad *trans*- and *cis*-2-bromoacrolein are 3.57, 3.28, and 1.44 D, respectively. [d] SCRF calculations for dichloromethane solvent ($\epsilon = 8.9$).

3.22 Å (Figure 2), are similar to those observed in organic molecular crystals of benzene, 3.3−3.6 Å.[22] This clearly indicates that the attractive $\pi-\pi$ interaction plays an important role in stabilizing the acrolein−NTOB complexes. On the basis of the NBO analysis, the indole moiety of NTOB is found to undergo a significant decrease of electron population upon complexation, by 0.13−0.16 e, which indicates the role of the indole unit as a π-donor. The orientations of 2-bromoacrolein with respect to the indole moiety are different in these complexes. Among the four acrolein adducts, structure **1TS** is predicted to be the most stable form with a binding energy of −93 kJ mol^{-1} ($\Delta G_{298} = -29$ kJ mol^{-1}). The calculated free energy of complexation reflects the observed stability of the acrolein−catalyst complex, which is stable up to 250 K.[3b] The small free energy of interaction is also reflected in the fact that the complexation of acrolein with NTOB is rapidly reversible on the NMR time scale.[3b] Significant dipole moments are predicted for all four complexes (Table 1). The larger dipole moment of **1TR** is due to the fact that the S=O, B···O, and C=O bond dipoles are oriented in the same direction.

It is important to note that the counterpoise (CP) method[23] grossly overestimates the basis set superposition error (BSSE) in the systems examined here. This is not unexpected as the geometry of the NTOB monomer changes significantly in the complexes. For instance, the BSSE correction obtained by the CP method for **1TS** is 71 kJ mol^{-1} at the MP2/6-31+G(d) level. Therefore, we do not include the BSSE correction in our computed binding energies. Nevertheless, we believe the calculated interaction energies reported here are realistic as there is a cancellation of errors between basis set effect and BSSE correction. The use of a larger basis set increases

(22) Dahl, T. *Acta Chem. Scand*. **1994**, *48*, 95.

(23) Boys, S. F.; Bernardi, F. *Mol. Phys*. **1970**, *19*, 553.

the binding energy, while the inclusion of BSSE correction reduces the binding energy. The structure of **1TS** was also optimized with a basis set including diffusion functions, i.e., 6-31+G(d). We found that the effect of diffusion functions on the molecular geometry is minimal. This lends confidence to our calculated PW91PW91/6-31G(d) structures of the various complexes.

To investigate the influence of a dielectric medium on the structures and binding affinities of the four NTOB−acrolein complexes, self-consistent reaction field (SCRF)[16] calculations based on Onsager's reaction field model were employed. Since the experimental study was carried out in dichloromethane solvent,[3b] a dielectric constant of $\epsilon = 8.9$ was employed in the solvent-effect calculations. There are small changes in the complex geometries on going from the gas phase to the dielectric medium. The calculated relative energies of the four complexes in dichloromethane are close to those computed for the gas phase (Table 1). On the other hand, the binding energies are reduced slightly, by 3−6 kJ mol^{-1} in solution. These changes are not sufficient to alter the relative binding affinities of the four complexes, and **1TS** remains the most stable conformation in an isolated state and in dichloromethane. The smaller binding energies in the presence of a dielectric field can be attributed to the fact that the reactants (NTOB and 2-bromoacrolein) are polar molecules (Table 1).

Roles of C−H···O and $\pi-\pi$ Interactions. 1TS is calculated to be significantly more stable than the other three complexes, by 20−30 kJ mol^{-1} (Table 1). However, it is not clear which is the dominant interaction responsible for the greater stability of **1TS**. To probe further the relative importance of the C−H···O and $\pi-\pi$ interactions in the binding affinities of these adducts, we have investigated two smaller model systems, **2** and **3**. Species **2**, a C−H···O hydrogen-bonded complex between *s-trans*-2-bromoacrolein and *N*-sulfonyl-1,3,2-oxazaborolidinone, will shed light on the relative importance of the two different modes of C−H···O hydrogen bonds (C−H···O−B and C−H···O=S) in the **R** and **S** complexes. On the other hand, species **3**, a π-stacked complex between 2-bromoacrolein and indole, will indicate the relative strengths of the different $\pi-\pi$ interactions in the four acrolein−NTOB complexes (**1**).

Species **2** has two possible forms, **2R** and **2S**, which are characterized by both B···O donor−acceptor and C−H···O hydrogen-bonded interactions (Figure 3). The difference between the two structures lies in the formyl C−H···O hydrogen bond, where **2R** involves the ring oxygen while **2S** involves the sulfonyl oxygen. The optimized geometries of **2R** and **2S** are shown in Figure 3. As with the adduct **1**, the **S** conformation has shorter B···O and C−H···O bond distances than the **R** conformation. Accordingly, **2S** is calculated to have a significantly larger binding energy (MP2/6-31+G(d)//PW91PW91/6-31G(d)+ZPE) than **2R**, by 10 kJ mol^{-1}. A similar preference of the C−H···O=S interaction, by 6 kJ mol^{-1}, is calculated for the complexes involving *s-cis*-2-bromoacrolein. Thus, we confirm that the C−H···O=S interaction is more favorable than the C−H···O−B interaction in the acrolein−catalyst complexes.

The relative strengths of the $\pi-\pi$ interactions in the four acrolein−NTOB complexes **1CR**, **1CS**, **1TR**, and **1TS** were assessed by a simpler π-stacking model between 2-bromoacrolein (π-acceptor) and indole (π-donor). The fully optimized geometries (MP2/6-31G(d)) and computed binding energies (MP2/6-31+G(d)+ZPE) of the four possible adducts **3C**, **3C′**, **3T**, and **3T′** are given in Figure 4. **3C**, **3C′**, **3T**, and **3T′** represent the π-stacking unit in **1CR**, **1CS**, **1TR**, and **1TS**, respectively. First, we note that the geometries of these complexes resemble the corresponding π-stacking geometries in the acrolein−NTOB complexes. In particular, the π-stacking separation of ∼3.1 Å is readily reproduced. This indicates the $\pi-\pi$ interactions in various acrolein−catalyst complexes (**1**) are close to optimum. Structure **3T′**, which represents the π-stacking in **1TS**, has the largest binding energy of −20.9 kJ mol^{-1}. For comparison, the binding energy of a parallel-displaced benzene dimer is significantly smaller (−6.5 kJ mol^{-1}) at the same level of theory. Thus, $\pi-\pi$ interaction provides a significant contribution to the complexation energy of **1TS**. On the basis of the model calculations of **2** and **3**, we can safely conclude that both the formyl C−H···O and π-stacking interactions are key factors in governing the relative stabilities of the various acrolein−catalyst complexes.

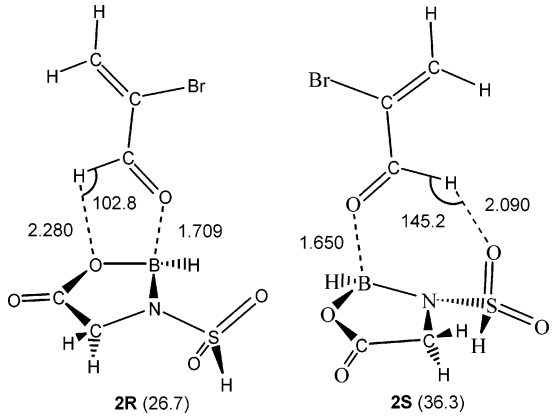

FIGURE 3. Optimized (PW91PW91/6-31G(d)) geometries of *s-trans*-2-bromoacrolein−*N*-sulfonylated 1,3,2-oxazaborolidine-5-one complexes, bond distances in angstroms and angles in degrees. The calculated binding energies (MP2/6-31+G(d)// PW91PW91/6-31G(d)+ZPE, kJ mol^{-1}) are given in parentheses.

The Lewis acidity of the coordinated acrolein can be assessed by comparing the LUMO energy and atomic charges with those of the free acrolein. The NTOB Lewis acid is expected to activate a dienophile. For 2-bromoacrolein, the LUMO energy (−3.16 and −3.05 eV for *cis* and *trans*, respectively) is lowered substantially, by 0.55−0.69 eV, upon coordination with NTOB (Figure 2). In other words, this Lewis acid can reduce the HOMO−LUMO gap between a diene and a dienophile and thereby induce an increase of the rate of the catalyzed reaction. Experimentally, the NTOB-catalyzed Diels−Alder reactions occurred readily at −78 °C,[3] which indicates that NTOB is a very efficient catalyst in lowering the activation barriers of the Diels−Alder reactions. The C−O bond length of acrolein is increased from 1.218 to 1.260 Å in the complex **1TS**. Accordingly, the charge of the carbonyl carbon changes from 0.33 to 0.35 upon complexation. These electronic changes account for the activation of acrolein by coordination to the NTOB catalyst.

Electronic Absorption Spectra. Finally, we investigate the electronic absorption spectra of the four ac-

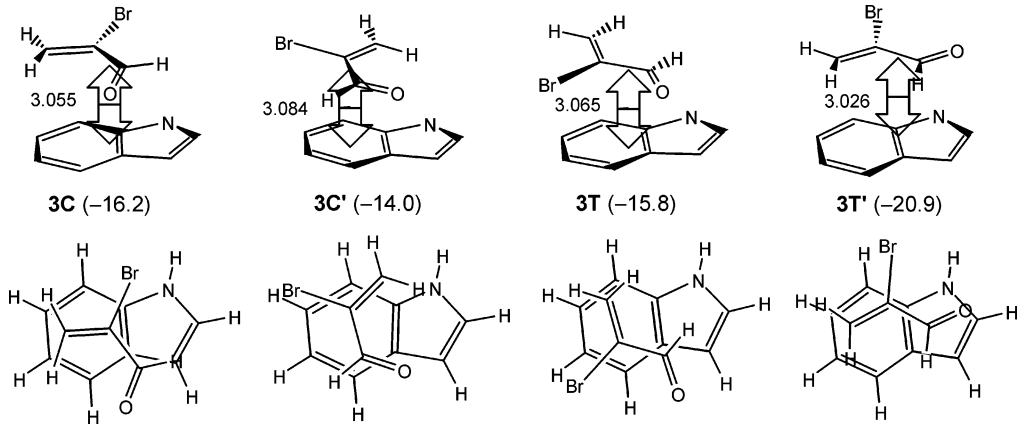

FIGURE 4. Optimized (MP2/6-31G(d)) geometries of 2-bromoacrolein−indole $\pi-\pi$ stacking complexes. Two different views (side and top) are given for each structure. The π-stacking distances are given in angstroms, and the calculated binding energies (MP2/ 6-31+G(d)//MP2/6-31G(d)+ZPE, kJ mol^{-1}) are given in parentheses.

TABLE 2. Four Strongest UV Absorptions (T_1−T_4, >350 nm) of 2-Bromoacrolein−NTOB Complexes, Calculated at the TD-PW91PW91/6-31G(d) Level[a]

	T_1		T_2		T_3		T_4	
species[b]	TE	f[c]	TE	f[c]	TE	f[c]	TE	f[c]
1CR	728	0.007	608	0.060	461	0.012	448	0.014
1CS	793	0.030	607	0.021	456	0.011	388	0.058
1TR	845	0.027	678	0.012	458	0.019	383	0.006
1TS	816	0.012	516	0.062	439	0.010	379	0.040

[a] The computed transition energies (TEs) are given in nanometers. [b] NTOB has weak UV absorptions below 350 nm: 324 (f = 0.005) and 300 (f = 0.010). [c] Oscillator strength.

rolein−NTOB complexes (**1**) using the time-dependent DFT (TDDFT) method. The uncomplexed Lewis acid does not show any absorption peak in the visible spectrum (Table 2). Upon coordination with 2-bromoacrolein, several new peaks are found in the visible absorption region (Table 2). These peaks are readily attributed to the electronic excitation through charge transfer from the indole moiety (π-donor) of NTOB to the adjacent coordinated acrolein (π-acceptor). The interpretation of charge-transfer transitions is further supported by the calculated electronic absorption spectrum of the simpler $\pi-\pi$ stacking complex **3T′**, which is characterized by two visible absorptions at 407 and 537 nm. Experimentally, Corey et al. observed a bright orange-red color, which corresponds to a broad absorption band in the 400−600 nm region, for the 2-methylacrolein−NTOB complex at 210 K.[3b] For **1TS**, the computed strongest UV absorption at 516 nm is in pleasing accord with the experimental finding. This lends strong confidence to our calculated geometries of the various acrolein−NTOB complexes and reinforces the crucial role of $\pi-\pi$ interaction in these intermolecular complexes.

A Comparison with Corey's Transition-State Model. Our calculated structures of acrolein−NTOB complexes confirm the importance of B···O donor−acceptor, C−H···O hydrogen-bonded, and π-stacking interactions in the pre-transition-state complex proposed by Corey et al.[3] However, there are two distinct features of **1TS** that differ from those of the proposed model. First, the formyl C−H proton of acrolein favors the formation of a hydrogen bond with the sulfonyl oxygen, rather than the ring oxygen. It is worth noting that the formyl proton in **1TS** is also in close proximity (2.64 Å) to the ring nitrogen, which is a good hydrogen bond acceptor. Second, the most stable complex (**1TS**) involves the *s-trans* conformation of 2-bromoacrolein, in contrast to the proposed *s-cis* complex. Corey et al. did not rule out the possibility that the catalytic Diels−Alder reaction proceeds via the *s-trans* complex.[3b] However, they argued that there is a stronger steric repulsion between the α-bromine substituent and the indole ring or a mismatch of $\pi-\pi$ interaction in the *s-trans* complex. As seen in the calculated structures of both *s-trans* complexes **1TR** and **1TS** (Figure 2), the steric repulsion appears to be minimal. In a subsequent study, Corey and co-workers have shown that the *s-trans* conformation is the predominant form for the 2-methylacrolein complex of boron trifluoride in solution and in the crystalline phase.[24]

Because of the π-stacking interaction, one face of the coordinated acrolein in the complex **1TS** is blocked (i.e., the face *cis* to the 3-methylindole moiety). As a consequence, a dienophile, such as cyclopentadiene, may approach only from the opposite face, which leads to the chiral (*R*)-bromoaldehyde product. Thus, our study here provides an alternate model to explain the high enantioselectivity in Diels−Alder reactions. In particular, the structure of **1TS** reveals that both the indole and *N*-tosyl subunits of the NTOB catalyst are crucial in understanding the enantioselectivity as they represent the anchoring points for the formyl C−H···O hydrogen bond and $\pi-\pi$ interaction. This finding is in excellent accord with the experimental results on the effects of substituents on the reactivity of catalyzed Diels−Alder reactions.[3b]

Conclusion

In summary, molecular recognition of the NTOB catalyst involves three-point binding of the Lewis acid via B···O donor−acceptor, C−H···O hydrogen-bonded, and π-stacking interactions, as proposed by Corey et al. The relative stabilities of the four 2-bromoacrolein−NTOB complexes are governed by the strengths of the formyl C−H···O hydrogen bond and the $\pi-\pi$ interaction between 2-bromoacrolein and the indole unit of the

(24) Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945.

catalyst. In agreement with experiment, these complexes are characterized by charge-transfer transitions in the visible absorption region. The most stable complex (**1TS**) differs from Corey's proposed model of transition-state assembly in two aspects: the involvement of the *s-trans*-acrolein and the preference of the C—H···O═S hydrogen-bonded interaction. The calculated geometry of **1TS** provides an alternate explanation to the observed high enantioselectivity in Diels−Alders reactions.

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Supporting Information Available: Tables S1, S2, and S3, Cartesian coordinates and absolute energies of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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