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The Application of the Formyl C–H--O Hydrogen Bond Postulate to the Understanding of Enantioselective Reactions Involving Chiral Boron Lewis Acids and Aldehydes.

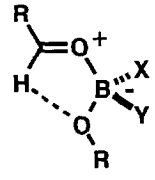
E. J. Corey,* and Jeffrey J. Rohde

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Summary: *A number of noteworthy enantioselective reactions involving a variety of chiral boron Lewis acids and aldehydes can be rationalized in terms of the occurrence of formyl CH--O hydrogen bonds in the transition states and the additional three-dimensional organization which they provide.*

The preceding paper in this issue[1] presents a simple explanation for a conformational preference of complexes of formyl compounds with boron Lewis acids in which a hydrogen bond holds the formyl CH in proximity to an oxygen or fluorine attached to boron. This novel type of hydrogen bond, illustrated in **1**, is potentially a determinant of molecular geometry, not only in the solid state where its existence is supported directly by X-ray diffraction data, but also in reactions in solution. The purpose of this paper is to show how such hydrogen bonds between coordinated formyl and oxygen substituents at boron can help in the understanding of enantioselectivity in reactions accelerated by chiral Lewis acids.

We recently reported[2] that the cationic chiral Lewis acid **2** is an extraordinarily powerful catalyst for Diels-Alder reactions of substituted acroleins with a wide range of 1,3-dienes. Under optimal conditions Diels-Alder adducts were obtained with enantiomeric purities in the range 90-98%.[2] It was pointed out that the stereochemical course of these highly enantioselective reactions could be understood in terms of a transition-state assembly such as that shown in **3** for the reaction of 2-bromoacrolein and cyclopentadiene. In transition structure **3**, the formyl hydrogen is placed in proximity to the oxygen substituent on boron and held there by a C–H--O hydrogen bond to the equatorial oxygen lone pair. Indeed, this C–H--O hydrogen bond in the aldehyde-Lewis acid complex was an important design element in the selection of catalyst **2** for study. Thus, the concept of the formyl CH--O hydrogen bond led to the development of a useful new chiral catalyst and also to a specific arrangement for the transition-state assembly which correctly predicted the absolute configuration of the Diels-Alder product.[2,3] It should be noted that, although the diene has partially added to the α,β-double bond of the dienophile in transition-state assembly **3**, the formyl carbon retains substantially all of its positive charge, so that no loss of formyl CH--O hydrogen bonding in the transition state need occur.



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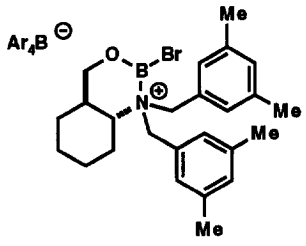

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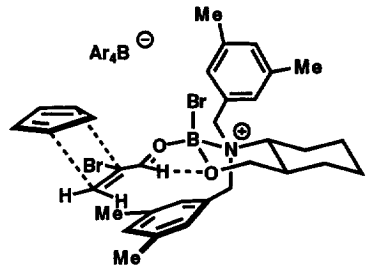
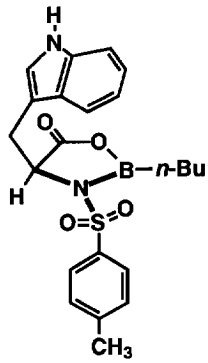


3 Ar = C_6H_3-3,5-$(CF_3)_2$

We have previously reported that the (*S*)-tryptophan derivative **4** catalyzes the Diels-Alder reaction of cyclopentadiene with 2-bromoacrolein to form one of the two possible enantiomeric adducts with >200 : 1 enantioselectivity.[4] The transition state for this reaction, as indicated by detailed mechanistic studies, is ideally arranged for formyl CH--O hydrogen bonding, as shown in **5**.[4] Thus, the formyl CH--O hydrogen bond, though not suggested in the original analysis,[4] could represent an additional factor which contributes to the high degree of enantioselectivity that is observed in this system.

Yamamoto and colleagues have introduced a chiral acyloxyborane (CAB) Diels-Alder catalyst prepared by reaction of the mono 2,6-diisopropoxybenzoate ester of tartaric acid with H_3B•THF.[5] Based on NMR NOE studies Yamamoto *et al.*[6] have proposed that diene addition to the complex **6** may give rise to the predominating Diels-Alder adduct by the addition of the diene to the sterically less shielded (front) face of the α,β-double bond.[6] However, their data are also consistent with an alternative structure of the complex (**7**) which would lead to the *enantiomer* of the predominant Diels-Alder adduct, and no reason is given as to why this pathway would be disfavored. On the other hand, consideration of the formyl CH--O hydrogen bonded analogs of complexes **6** and **7**, that is structures **8** and **9**, provides a simple reason for the observed enantiomeric preference. Structure **9** should be disfavored relative to **8** because it allows only *one* hydrogen bond which involves the much less basic carboxylate oxygen.

Formyl CH--O hydrogen bonding effects can also be used to rationalize a remarkable early example of a catalytic enantioselective Diels-Alder reaction which was discovered by Koga and coworkers.[7] The catalyst for this reaction, which is produced by reaction of equimolar amounts of (–)-menthol and $AlCl_3$ and which is



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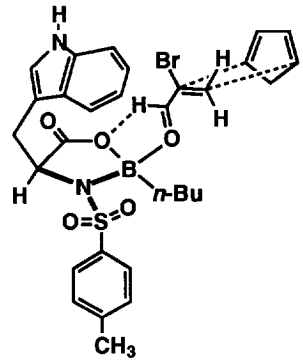

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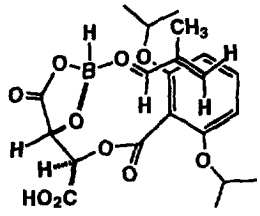

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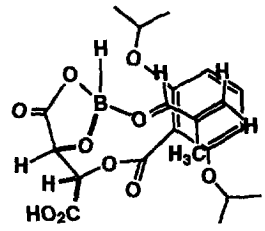

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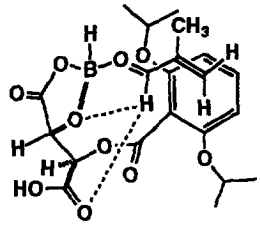

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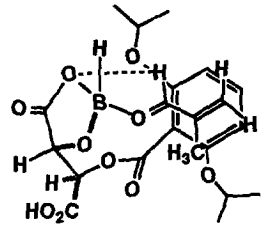

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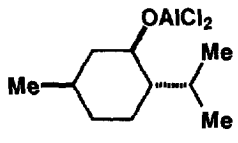
presumably the alkoxyaluminum dichloride **10**, induces the addition of 2-methylacrolein to cyclopentadiene at -78 °C to form **11** as the predominating enantiomer (57% ee).[7] No satisfactory explanation for this preference has been given thus far. Indeed, the problem is a daunting one because of the many rotational degrees of freedom which are possible in the transition state and because of the modest level of enantioselectivity (only 3.7 : 1). A simple rationalization is possible in terms of formyl hydrogen bonded structures **12** and **13** each of which involves a different oxygen lone pair. If reaction via transition state **12** assembly occurs face selectively as shown (because of steric screening by isopropyl), a predominance of the observed product **11** would be expected. On the other hand, addition of cyclopentadiene to the front (a) and rear (b) faces of the α,β-double bond of complex **13** should be equally likely. Therefore, a slightly greater degree of reaction via **12** (selective for **11**) than via **13** (non selective) could lead to the observed 3.7 : 1 predominance of enantiomer **11**.

The formyl CH--O hydrogen bond model is also applicable to other types of enantioselective reactions. For example, it leads to an interesting interpretation of the Roush enantioselective allylboration of aldehydes.[8]



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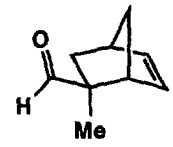

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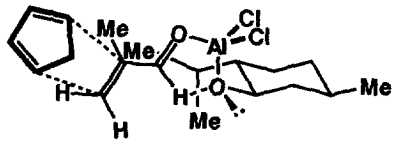

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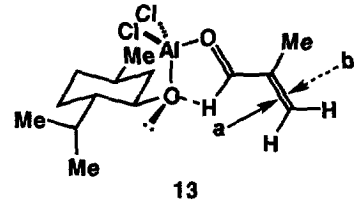

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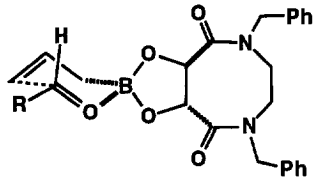
Roush has proposed the allylboration pathway via **14** is preferred with the *R,R*-tartaric bislactam derivative shown. The alternative (diastereomeric) transition state **15** has been considered to be disfavored because of the lone pair repulsions which are indicated. Such lone-pair repulsive effects are not strongly precedented. The formyl CH--O hydrogen bond model predicts that the complex shown in **16** should be preferred, because of the possibility of a stronger bifurcated (double) hydrogen bond over the alternative **17**, in which only a single hydrogen bond is possible.



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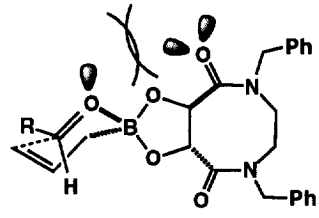

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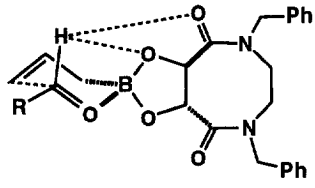

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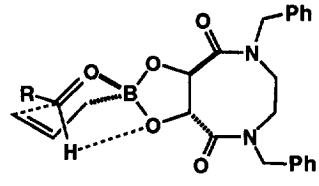

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In conclusion, a number of examples of noteworthy enantioselective reactions have been analyzed in this paper to determine the possible involvement of formyl CH--O bonding as a determinant of stereoselectivity. The model successfully predicts the predominating stereochemical pathway in each case. Although the importance of such formyl C–H--O hydrogen bonds must be regarded as only a working hypothesis at this time, the simplicity, clarity, and success of the model indicate that it could turn out to be both useful and valid.[9]

References and Notes

1. Corey, E. J.; Rohde, J. J.; Fischer, A.; Azimioara, M. D., preceding paper, this issue.
2. Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502.
3. Other design considerations included (1) the use of the π-electron rich 3,5-dimethylbenzyl substituents on nitrogen to allow neighboring π-aromatic group stabilization of the positive charge at the formyl carbon atom in the transition state and also steric screening at one face of the coordinated dieneophile, and (2) the expectation that the *s-trans* rotomer of the coordinated dienophile would react more rapidly than the *s-cis* form with which it is in rapid equilibrium. The analysis leading to the second of these considerations is similar to that presented previously.[4a]
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8. See Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.
9. This research was supported by grants from the National Institutes of Health, the National Science Foundation and the Eli Lilly Co.

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