The Origin of 1,4-Asymmetric Induction in the Additions of Chiral Alcohols to Ketenes

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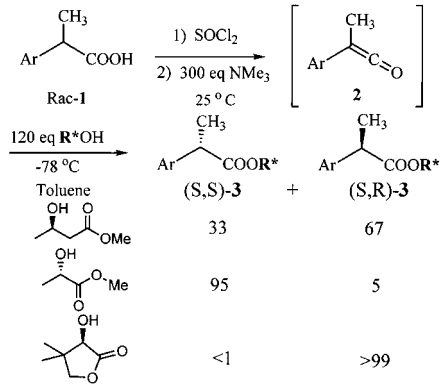
Diastereoselective additions of chiral alcohols to ketenes have been known since 1919,[1,2] but a particularly useful class of reactions of this type was discovered by Larsen et al. at Merck in 1989.[2] As shown in Scheme 1, the reactions of α-hydroxy esters and lactones with aryl alkyl ketenes proceed with high stereoselectivity; the products can be hydrolyzed to give optically active arylpropionic acid antiinflammatory drugs. Such high 1,4-asymmetric induction (up to 99%) is rare, and no mechanism that rationalizes the direction or magnitude of the stereoselectivity has been proposed, even though many additional examples have been reported.[3] We have explored this reaction with quantum mechanical calculations and provide a quantitative model that accounts for the origin of stereoselectivity and all of the experimental observations made on this reaction. The unusual 1,4-asymmetric induction[4] is the result of the steering of enolate protonation by electrostatic and hydrogen-bonding interactions involving the carbonyl oxygen at the stereogenic center and the trialkyammonium ion that protonates the enolate carbon.

The reaction was found to give maximum stereoselectivity at −78 °C in hydrocarbon solvents. It is first-order in ketene, amine, and chiral alcohol, with a $k_H/k_D \approx 4$ for deuterated alcohols. Several mechanisms have been proposed for the addition of alcohols to ketenes.[5−8] These include cyclic transition states for direct addition to the alkene[5−7] and acyclic transition states for initial addition of alcohol to the carbonyl group to form an enol intermediate.[1b,8] The catalytic effect of amines has also been explained by the initial attack of amine on the carbonyl[1i,9] or a base-catalyzed addition of alcohol to the ketene.[5,10] Of these mechanisms, we favor alcohol addition to form either a zwitterion or enol under the experimental conditions. Protonation or tautomerization gives the ester product. We have explored variations on this last mechanism theoretically with (*S*)-methyl lactate, methyl phenyl ketene, and trimethylamine in the gas phase. The conditions are not too different from the reaction in toluene solvent ($\epsilon = 2.38$).

Scheme 1. Merck Process for the Stereoselective Addition of Chiral Alcohols to Ketene



There have been a variety of previous computational studies of nucleophilic additions to ketenes.[11] The most relevant is the study of ketene hydration.[12] Several groups have shown that water adds to the C═O to give an enol, followed by tautomerization to the acid. The computed results reproduced closely the experimental energy of activation.[13]

All stationary points were fully optimized at the B3LYP/6-31G* level[14] using Gaussian 98[15] and characterized by frequency analysis at the same level. The reported energies include zero-point energy corrections scaled by 0.9806.[16] All transition states were further characterized by analysis of the normal modes corresponding to their imaginary frequencies and, in the case of the addition transition state, by intrinsic reaction coordinate (IRC) calculations. The structures and relative energies of reactants, intermediates, and transition states along the lowest-energy pathway are shown in Figure 1. The stereoisomeric transition states and intermediates are not shown, but their energies are given in the figure.

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(1) (a) Weiss, R. *Mh. Chem.* **1919**, *40*, 391. (b) Anders, E.; Ruch, E. *Angew. Chem. Int Ed. Engl.* **1973**, *12*, 25−29. (c) Jaehme, J.; Rüchardt, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 885. (d) Salz, U.; Ruchardt, C. *Tetrahedron Lett.***1982**, *23*, 4017−4020. (e) Bellucci, G.; Berti, G.; Bianchini, R.; Vecchiani, S. *Gazz. Chim. Ital.* **1988**, *118*, 451. (f) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem.* **1991**, *103*, 490. (g) Fehr, C. *Angew. Chem.* **1996**, *108*, 2726. (h) Donohoe, G.; Satchell, D. P. N.; Satchell, R. S. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1671. (i) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. J. Am. Chem. Soc.* **1999**, *121*, 2637−2638.

(2) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.***1989**, *111*, 7650.

(3) (a) Calmes, M.; Daunis, J.; Jacquier, R.; Natt, F. *Tetrahedron* **1994**, *50*, 6875−6880. (b) Camps, P.; Gimenez, S. *Tetrahedron Asymmetry* **1995**, *6*, 991−1000. (c) Calmes, M.; Daunis, J.; Mai, N.; Natt, F. *Tetrahedron Lett.* **1996**, *37*, 379−380. (d) Calmes, M.; Daunis, J.; Mai, N.; Natt, F. *Tetrahedron* **1997**, *53*, 13719−13726. (e) Calmes, M.; Daunis, J.; Mai, N. *Tetrahedron Asymmetry* **1997**, *8*,1641−1648.

(4) The 1,4-asymmetric induction in enamine alkylations has previously been described theoretically: Lucero, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 826.

(5) Brady, W. T.; Vaughn, W. L.; Hoff, E. F. *J. Org. Chem.* **1969**, *34*, 843−845.

(6) Tille, A.; Pracejus, H. *Chem. Ber.* **1967**, *100*, 196−210.

(7) Lillford, P. J.; Satchell, D. P. N. *J. Chem. Soc. B* **1968**, 889−897.

(8) Jahme, J.; Ruchardt, C. *Tetrahedron Lett.* **1982**, *23*, 4011−4014.

(9) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000,** *121*, 7831−7832.

(10) (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9−22. (b) Pracejus, H.; Matie, H. *J. Prakt. Chem.* **1964**, *24*, 195−205. (c) Samtleben, R.; Pracejus, H. *J. Prakt. Chem.* **1972**, *314*, 157−169. (d) Pracejus, H.; Leska, J. *Z. Naturforsch.* **1966**, *21B*, 30−32. (e) Pracejus, H. *Fortschr. Chem. Forsch.* **1967**, *8*, 493−553.

(11) (a) Raspoet, G.; Nguyen, M. T.; Kelly, S.; Hegarty, A. F. *J. Org. Chem.* **1998**, *63*, 9669−9677. (b) Raspoet, G.; Nguyen, M. T.; McGarraghy, M.; Hegarty, A. F. *J. Org. Chem.* **1998**, *63*, 6878−6885. (c) Raspoet, G.; Nguyen, M. T.; McGarraghy, M.; Hegarty, A. F. *J. Org. Chem.* **1998**, *63*, 6867−6877. (d) Nguyen, M. T.; Raspoet, G.; Vanquickenborne, L. G. *J. Chem. Soc., Perkin Trans. 2* **1999**, 813−820. (e) Fang, D.-C.; Fu, X.-Y. *J. Mol. Struct.(THEOCHEM)* **1998**, *455*, 59−68.

(12) (a) Skancke, P. *J. Phys. Chem.* **1992**, *96*, 8065. (b) Duan, X.; Page, M. *J. Am. Chem. Soc.* **1995**, *117*, 5114. (c) Xie, J. F.; Yu, J. G.; Feng, W. L.; Liu, R. Z. *J. Mol. Struct.(THEOCHEM)* **1989**, *60*, 249−256. (d) Ruelle, P. *Chem Phys.* **1986**, *110*, 273. (e) Nguyen, M. T.; Raspoet, G.; Vanquickenborne, L. G. *J. Phys. Org. Chem.* **2000**, *13* (1), 46−56. (f) Guthrie, J. P. *Can. J. Chem.* **1999**, *77* (5/6), 934−942. (g) Nguyen, M. T.; Raspoet, G. *Can. J. Chem.* **1999**, *77* (5/6), 817−829.

(13) Mackie, J. C.; Doolan, K. R *Int. J. Chem. Kinet.* **1984**, *16*, 525−541.

(14) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(15) 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.; 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. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

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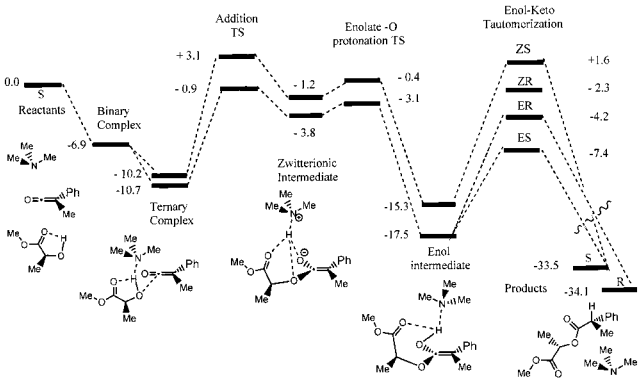

Figure 1. Energies (kcal/mol) of intermediates and transition states on the pathway for addition of (*S*)-methyl lactate to methyl phenyl ketene catalyzed by trimethylamine.

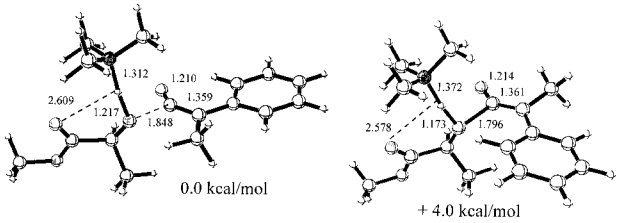

Figure 2. Addition transition states.

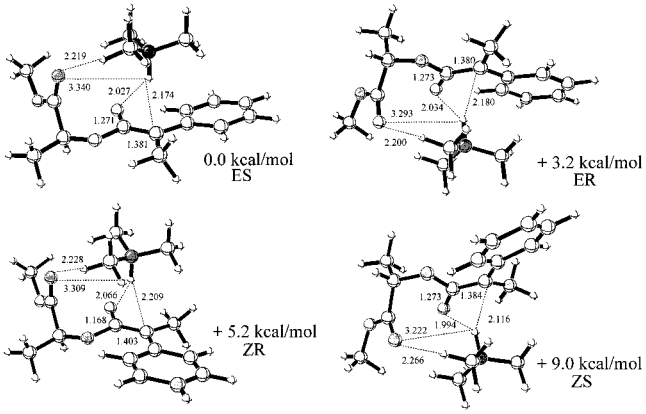

Figure 3. Transition states for enol−keto tautomerization.

The ketene, amine, and alcohol form a termolecular complex in the gas phase. The addition transition states shown in Figure 2, are 10−13 kcal/mol above this complex and involve nucleophilic addition to the ketene carbonyl, assisted by deprotonation of the alcohol by trimethylamine. The addition occurs in the plane of the ketene substituents and is 4.0 kcal/mol lower for approach *cis* to the methyl than for attack *cis* to the phenyl group. The phenyl group is nearly planar and presents substantial steric hindrance to attack.[17] This step is rate-determining and is expected to give rise to the observed primary kinetic isotope effect. It leads to a zwitterion with trimethylammonium hydrogen-bonded to the three oxygen atoms. A transition state for protonation of the enolate oxygen connects this zwitterion with the enol intermediate bearing trimethylamine hydrogen-bonded to the enolic OH.

The last step in the reaction involves the deprotonation of the enol and transfer of the proton to the carbon to form the ester product. The transition states calculated for this process resemble ion pairs of the trimethylammonium ion poised above the enolate anion. There are four such transition states shown in Figure 3. These are designated **ES**, **ER**, **ZR**, and **ZS** where the first letter represents the stereochemistry around the enol double bond and the second letter specifies the absolute chemistry of the newly created stereocenter. The lower-energy E enol, formed from attack of the alcohol *cis* to the methyl substituent, can have proton transfer along the top of the enolate to form the SS ester, or along the bottom of the enolate, via transition state **ER**, to form the SR ester. The former is 3.2 kcal/mol lower in energy. The transition states involving the Z enol also prefer proton transfer along the face of the enolate near the ester group.

The key to stereoselectivity is the lower energy of the E enol and corresponding transition states, and the electrostatic attraction between the lactate carbonyl and the trimethylammonium ion. Figure 3 shows the distance from the carbonyl-O to the trimethylammonium proton, but stabilization arises from interaction of the whole trimethylammonium group which bears the positive charge, with the C═O dipole. The shortest distance from the carbonyl-O to a methyl-H is only 2.2 Å.

The stabilizing interaction is another example of an important C−H···O hydrogen bond.[18,19] In order for proton transfer to occur along the bottom face of the enolate, either this stabilization must be sacrificed, or the lactate must rotate into the unfavorable conformation shown in the transition states, **ER** and **ZS**, in Figure 3. These conformations suffer from repulsion between the α-methyl group of the lactate and the enolate oxygen, as well as the unfavorable conformation about the bond from the stereogenic center to the ester carbon.

This model accounts for the preferred stereoisomer, the kinetic isotope effect, the fact that stereoselectivity is only high in nonpolar solvents, and the special role of small trialkylamine bases. Polar solvents would disrupt the tight ion-pair transition state and decrease steering of the proton transfer along one face of the enolate by the lactate ester. The trimethylammonium is ideal for C−H···O═C hydrogen bonding. The model also indicates why steric bulk of the alkyl substituent (e.g., pantolactone, the last entry in Scheme 1) at the stereogenic center increases the stereoselectivity. This increases the energies of transition states for proton transfer "below" the enolate plane, by forcing the quaternary center into the crowded region near the carbonyl group. The precise nature of the aryl group on the other hand is unimportant, since even a phenyl produces essentially one addition pathway, and additional bulk on the aryl group will mostly reside away from the area where nucleophilic attack occurs. Our model for the remarkable 1,4-asymmetric induction observed in this example uncovers a new factor controlling stereoselectivity and provides a guide to how stereoselective protonations might be achieved in other cases.

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(16) Wong, M. W. *Chem. Phys. Lett.* **1996**, *256*, 391−399.
(17) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron*. **1986**, *42*, 2587−2613 and references therein.
(18) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750−4755 and references therein.
(19) Raymo, F.; Stoddart, J. F.; Bartberger, M. D.; Houk, K. N., submitted for publication and references therein.