Modeling Chemical Reactivity. 8. Asymmetric Induction in [3,3] Sigmatropic Rearrangements

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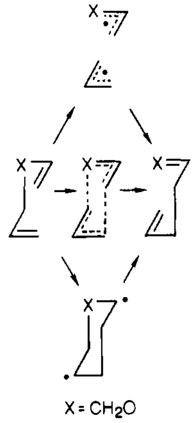
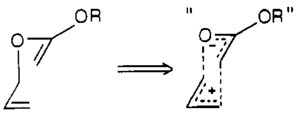
Description of the transition state for [3,3] sigmatropic migration in terms of interacting allyl-like fragments allows elaboration of diastereofacial selectivity on the basis of electrostatics. Specifically, stereoselectivity may be assigned by matching the more electron-rich face of the "nucleophilic" allylic component with the more electron-poor face of the "electrophilic" component in a chairlike transition structure. Experimental data on diastereofacially selective Ireland-Claisen rearrangements provide support.

[3,3] sigmatropic migrations, among them the Cope and Claisen rearrangements, provide a powerful means for constructing carbon-carbon bonds[1] and are increasingly employed in asymmetric synthesis.[2-4] [3,3] sigmatropic migrations are generally thought to proceed in a concerted fashion,[5] the amount of bond breaking and bond making in the transition structure depending on skeletal substituents,[6] i.e.



Substitution on one or both fragments, while giving rise to the possibility of diastereomeric products, enhances the dipolar nature of the transition state[7] by altering the inherent ability of the fragments to support charge. As the dipolar character increases, it is reasonable to anticipate that electronic biases will compete with steric interactions, perhaps to the point of dominating, in diastereomeric transition structures. Thus, selectivity rules developed to account for stereochemistry of nucleophilic[8] and electrophilic[9] additions to chiral olefins, and for diastereofacial selectivity in Diels-Alder cycloaddition reactions,[10] should be applicable to the description of diastereofacial preferences of [3,3] sigmatropic processes[11,12] of appropriately substituted 1,5-dienyl substrates.

This paper considers stereoselectivity in the Ireland modification of the Claisen rearrangement.[13] The working hypothesis that the underlying skeleton adopts a chairlike transition structure[14] and may be conceptually divided into a nucleophilic "ester enolate" allylic component and an electrophilic "hydrocarbon" allylic fragment, i.e.



is consistent with substituent effects on rearrangement kinetics[6,7] and is in accord with greater bond breaking than bond making in the transition state.[15] As a consequence,

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(1) For reviews, see: (a) Bennett, G. G. *Synthesis* **1977**, 589. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Jefferson, A.; Scheinmann, F. *Q. Rev., Chem. Soc.* **1968**, *22*, 391.

(2) For more recent reviews, see: (a) Hill R. K. In *Asymmetric Synthesis*; Morrison, J. D. Ed.; Wiley: New York, 1984; Vol. 3, p 503. (b) Ap Simon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157.

(3) For example, see: (a) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1118. (b) Morrow, D. F.; Culbertson, T. P.; Hofer, R. M. *Ibid.* **1968**, *32*, 361. (c) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* 1982 *104*, 2198. (d) Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* 1982, *47*, 5420. (e) Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, *24*, 4535. (f) Kurth, M. J.; Yu, C.-M. *Ibid.* **1984**, *25*, 5003. (g) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443. (h) Kurth, M. J.; Yu, C.-M. *J. Org. Chem.* **1985**, *50*, 1840. (i) Kurth, M. J.; Decker, O. H. W. *Ibid.* **1985**, *50*, 5769. (j) Kallmerten, J.; Gould, T. J. *Ibid.* 1986, *51*, 1152. For related work on [2,3] migrations, see: (k) Mikami, K.; Fujimoto, K.; Kasuga, T.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 6011. (l) Mikami, K.; Takahashi, O.; Kasuga, T.; Nakai, T. *Chem. Lett.* **1985**, 1729.

(4) (a) Kametani, T. *Heterocycles* 1982, *19*, 205. (b) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984**, *25*, 5263. (c) Hatakeyama, S. Saijo, K.; Takano, S. *Ibid.* **1985**, *26*, 865.

(5) For a detailed theoretical study, see: (a) Osamura, Y.; Kato, S.; Morokuma, K.; Feller, D.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1984**, *106*, 3362. See also: (b) Dewar, M. J. S.; Healy, E. F. *Ibid.* **1984**, *106*, 7127.

(6) (a) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693. (b) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142. (c) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733. (d) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636 and references cited therein. (e) Hwu, J. R.; Anderson, D. A. *Tetrahedron Lett.* **1986**, *27*, 4965. (f) Burrows C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984. (g) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877.

(7) (a) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160. (b) Gajewski, J. J.; Jurayi, J.; Kimbrough, D. R. Gaude, M. E. Ganem, B.; Carpenter, B. K. *Ibid.* **1987**, *109*, 1170.

(8) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399.

(9) (a) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7396. (b) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *Ibid.* **1987**, *109*, 650. (c) Kahn, S. D.; Hehre, W. J. *Ibid.* **1987**, *109*, 666. (d) Chamberlin, A. R.; Mulholland, R. L.; Jr.; Kahn, S. D.; Hehre, W. J. *Ibid.* **1987**, *109*, 672.

(10) (a) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663. (b) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1986**, *27*, 6041.

(11) See also the discussion of regiochemistry in ref 2a, p 510.

(12) For related studies on facial selectivity in [1,5] sigmatropic migrations, see: Kahn, S. D.; Okamura, W. H.; Hehre, W. J. submitted for publication in *J. Am. Chem. Soc.*

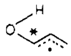
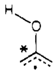
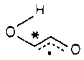
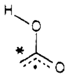
(13) (a) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (b) Ireland, R. E.; Thaisrivong, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. (c) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933. (d) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Ibid.* **1982**, *47*, 3941. (e) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. (f) Burke, S. D.; Fobare, W. F. Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (g) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177.

(14) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.

(15) Tritium isotope effects in the rearrangement of chorismic acid have been interpreted as indicative of a partly dissociative mechanism. Addadi, L.; Jaffe, E. K.; Knowles, J. R. *Biochemistry* **1983**, *22*, 4494.

0022-3263/88/1953-0301$01.50/0

Table I. Atomic Charges for the Terminal Carbon Atoms in Allylic Radicals[a]

allylic radical	mulliken charge[b]	Löwdin charge[c]	natural charge[d]
	−0.391	−0.176	−0.353
	+0.165	+0.062	+0.172
	−0.433	−0.238	−0.432
	−0.429	−0.176	−0.364
	+0.127	+0.057	+0.160
	−0.441	−0.206	−0.388

[a] As calculated from UHF/3-21G wave functions. Terminal carbon atoms (C_1 or C_6) are starred. [b] Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833, 1841, 2338, 2343. [c] Löwdin, P. O. *Phys. Rev.* **1955**, *97*, 1474. [d] Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.

the "stereoelectronically" preferred mode of rearrangement will be that in which the more electron-rich face of the ester enolate approaches the more electrophilic face of the remaining allylic component.

Computational Methods

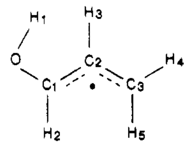
While questions of reaction asymmetry may, in principle, be investigated by locating all possible diastereotopic transition structures, such an approach is presently not practical for systems of the size dealt with here.[16] This fact, together with the presumed "dissociative nature" of Claisen rearrangements,[7,15] suggested that mechanistic insight could be gleaned from investigation of the component allylic fragments.

All calculations were performed by using unrestricted Hartree–Fock (UHF) theory and the 3-21G basis set.[17] Optimum geometries either were taken from the Carnegie–Mellon Archives[18] or are provided in Chart I. Ab initio calculations were performed with the GAUSSIAN 85 program system[19] as implemented on Harris H800 and CDC Cyber 180/830 digital computers.

Results and Discussion

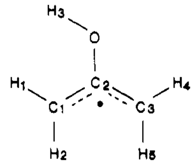
The scission of the transition state for [3,3] sigmatropic rearrangement in a 1,5-dienylic system is a formal construct, intended only to convey the inherent imbalance in the bond making and bond breaking involved between the interacting terminii of the two participating allylic moieties. For example, kinetic isotope effects for the parent Claisen rearrangement[6a] indicate a "reactant-like" transition structure, with bond breaking more advanced than bond making. These characteristics become more pro-

Chart I. Optimized Structures[a] **for Allylic Radicals at the UHF/3-21G Level**



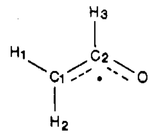
1-hydroxyallyl radical (E = −190.25932)

$C_1{-}C_2 = 1.378$ $C_1{-}C_2{-}C_3 = 124.1$ $H_1O{-}C_1{-}C_2 = 0.0$
$C_2{-}C_3 = 1.391$ $O{-}C_1{-}C_2 = 125.0$
$C_1{-}O = 1.383$ $H_2{-}C_1{-}C_2 = 123.2$
$C_1{-}H_2 = 1.069$ $H_3{-}C_2{-}C_1 = 117.9$
$C_2{-}H_3 = 1.077$ $H_4{-}C_3{-}C_2 = 121.1$
$C_3{-}H_4 = 1.071$ $H_5{-}C_3{-}C_2 = 121.2$
$C_3{-}H_5 = 1.074$ $H_1{-}O{-}C_1 = 112.8$
$O{-}H_1 = 0.965$



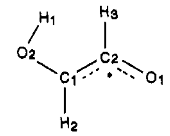
2-hydroxyallyl radical (E = −190.26128)

$C_1{-}C_2 = 1.381$ $C_1{-}C_2{-}C_3 = 123.6$ $H_3{-}O{-}C_2{-}C_1 = 0.0$
$C_2{-}C_3 = 1.390$ $H_1{-}C_1{-}C_2 = 122.1$
$C_1{-}H_1 = 1.073$ $H_2{-}C_1{-}C_2 = 120.2$
$C_1{-}H_2 = 1.070$ $O{-}C_2{-}C_1 = 114.9$
$C_2{-}O = 1.391$ $H_4{-}C_3{-}C_2 = 119.8$
$C_3{-}H_4 = 1.070$ $H_5{-}C_3{-}C_2 = 120.6$
$C_3{-}H_5 = 1.070$ $H_3{-}O{-}C_2 = 112.5$
$O{-}H_3 = 0.964$



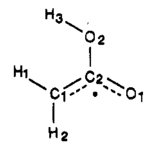
oxallyl radical (E = −151.45153)

$C_1{-}C_2 = 1.383$ $C_1{-}C_2{-}O = 122.1$
$C_2{-}O = 1.300$ $H_1{-}C_1{-}C_2 = 120.9$
$C_1{-}H_1 = 1.071$ $H_2{-}C_1{-}C_2 = 112.0$
$C_1{-}H_2 = 1.071$ $H_3{-}C_2{-}C_1 = 119.2$
$C_2{-}H_3 = 1.076$



1-hydroxyoxallyl radical (E = −225.88999)

$C_1{-}C_2 = 1.374$ $C_1{-}C_2{-}O_1 = 121.6$ $H_1{-}O_2{-}C_1{-}C_2 = 0.0$
$C_2{-}O_1 = 1.295$ $H_2{-}C_1{-}C_2 = 121.7$
$C_1{-}H_2 = 1.067$ $H_3{-}C_2{-}C_1 = 118.8$
$C_2{-}H_3 = 1.079$ $O_2{-}C_1{-}C_2 = 124.8$
$C_1{-}O_2 = 1.365$ $H_1{-}O_2{-}C_1 = 114.0$
$O_2{-}H_1 = 0.966$



2-hydroxyoxallyl radical (E = −225.90188)

$C_1{-}C_2 = 1.413$ $C_1{-}C_2{-}O_1 = 122.4$ $H_3{-}O_2{-}C_2{-}C_1 = 0.0$
$C_2{-}O_1 = 1.245$ $H_1{-}C_1{-}C_2 = 122.3$
$C_1{-}H_1 = 1.071$ $H_2{-}C_1{-}C_2 = 118.2$
$C_1{-}H_2 = 1.068$ $O_2{-}C_2{-}C_1 = 120.1$
$C_2{-}O_2 = 1.371$ $H_3{-}O_2{-}C_2 = 114.6$
$O_2{-}H_3 = 0.963$

[a] Energies in hartrees, bond lengths in angstroms, and angles in degrees.

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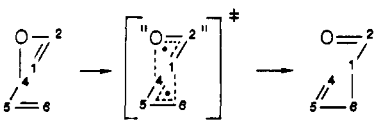
[16] Transition structure searches without symmetry constraints, on systems with greater than four or five non-hydrogen atoms, with nonminimal basis sets, are at the limits of existing computational resources. In this regime, it is common to construct transition structure models (cf. ref 25) or use empirical methods such as molecular mechanics for structural minimizations. See: Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 955 and references cited therein.

[17] Binkely, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

[18] Whiteside, R. A.; Frisch, M. J.; Binkley, J. S.; DeFrees, D. J.; Schlegal, H. B.; Krishnan, R.; Pople, J. A. *Carnegie–Mellon Quantum Chemistry Archive*; 3rd ed.; Department of Chemistry, Carnegie-Mellon University, Pittsburgh, PA, 15213.

[19] Hout, R. F., Jr.; Francl, M. M.; Kahn, S. D.; Dobbs, K. D.; Blurock, E. S.; Pietro, W. J.; McGrath, M. P.; Steckler, R.; Hehre, W. J. University of California, Irvine, to be published.



nounced upon substitution at C2 with electron donors.[6c] The lack of solvent effects on the rate of rearrangement of allyl vinyl ether[6a] and its 2-trimethylsilyl derivative[6c] contrast with large solvent effects observed in reactions of more highly substituted systems.[7]

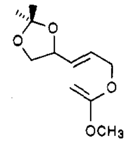
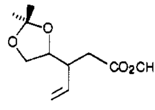
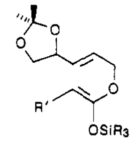
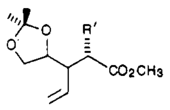
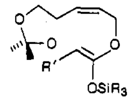
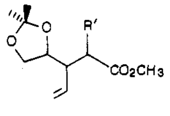
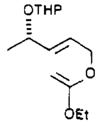
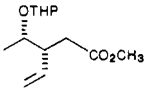
Calculations (Table I) on the putative allylic fragments involved in [3,3] sigmatropic rearrangements suggest that while the radicaloid moieties are formally neutral, the terminal carbon on the oxygen-containing fragment (C_1) is more negatively charged than the analogous carbon on the hydrocarbon framgent (C_6). This result, which is independent of the methodology used to assess atomic charge,[20] suggests that charge imbalance between the interacting terminii does not require that there be actual charge separation in the transition state.

The data in Table I show that substitution on the central carbon in oxallyl radical with alcohol functionality (as a model for OR and $OSiR_3$ groups employed experimentally[3,4,7,13] accentuates the difference in charge on C_1 and C_6 relative to the parent Claisen. This is consistent with solvent effects (on reaction rates) upon skeletal substitution and provides support for the notion of increased dipolar character along the reaction coordinate.[7] Therefore, the conceptual dissection of [3,3] sigmatropic rearrangements of allyl enol ethers into relatively nucleophilic and electrophilic components, i.e., "ester enolate" and "hydrocarbon" allylic fragments, respectively, is straightforward, and a logical extension of the experimental and computational results discussed thus far.

The experimental observation that electron-donor substituents at C_1 (O^-, NH_2, F) and C_2 ($OSiR_3$, NH_2, CR_2^-) accelerate the rates of rearrangement of allyl vinyl ethers[6,7] is mirrored by increased charge separation between the interacting carbon terminii (see Table I). This correlation suggests that greater electronic complementarity gives rise to accelerated reaction rates in the class of sigmatropic rearrangements discussed here. In further support of such a hypothesis, diminished reaction rates are observed for substitution by electron-donor groups (OR, $CH_2Si(CH_3)_3$) at C_5, following from increased charge on C_6 in the hydrocarbon fragment, i.e., greater charge neutrality between the two allylic moieties. Calculated charges for Claisen rearrangement with a C_6 methoxy substituent (Table I) suggest increased dipolar character of the transition state (increased charge separation between the carbon terminii) relative to that for the parent system, in accord with the noted rate enhancement.

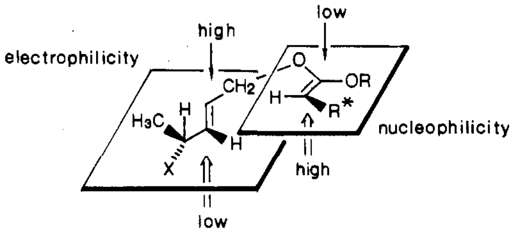
The noted effects of electron-withdrawing groups on reaction rate,[7b–d] while not subjected to calculation, are in full accord with the present analysis.[21] In particular, cyano substitution at C_5 is expected to render C_6 more electron poor relative to the oxallyl fragment, leading to a rate enhancement due to increased charge imbalance between the interacting terminii. Further evidence for the link between charge imbalance and reaction rate may be found in Diels–Alder chemistry. Cycloadditions involving electron-rich dienes and electron-poor dienophiles occur faster than processes in which the cycloaddends are of comparable electronic demand.[22]

Table II. Experimental Stereoselectivity of Claisen Rearrangements Involving Chiral Allyl Enol Ethers[a]

allyl enol ether	major product	selectivity	"ester enolate" approach[b]	ref
		2:1	anti	4a
		1.3:1–4.4:1[c]	anti	4b
		1.4:1–9:1[c]	anti	4b
		3:1	anti	4c

[a] Allylic chirality where a heteroatom is part of the chiral center. [b] With respect to the allylic heteroatom, from an H-eclipsed conformer. See text for discussion. [c] Varies with R′.

As a consequence of the latent "dipolar" nature of Claisen rearrangements, especially in Ireland–Claisen substrates, selectivity rules developed for nucleophilic[9] and electrophilic[10] additions to chiral allylic substrates should also be applicable for the assignment/prediction of stereoselectivity in this ubiquitous class of [3,3] sigmatropic migrations; that is, the preferred stereochemistry of rearrangement follows from the matching of the more electron-rich face of the "nucleophilic" ester enolate with the more electron-poor face of the "electrophilic" allylic olefin, i.e.



X = electron-rich group

in a manner that is strictly analogous to the matching of the more reactive diene and dienophile faces to assign diastereofacial selectivity in Diels–Alder cycloadditions.[10,12] Note that when R* = H, the selectivity is due only to the biases of the allylic (hydrocarbon) component. Conversely, when X is neither significantly electron-rich nor electron-poor, e.g., alkyl or aryl groups, selectivity either will

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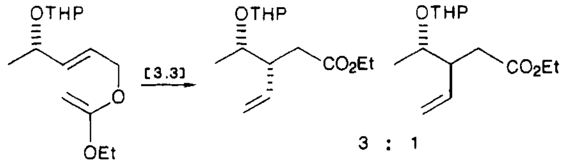
(20) For a general discussion of population analysis, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; p 25.

(21) Because substituents at C_4 are not coplanar with $C_5{=}C_6$ in the rearranging substrates, they cannot be modeled with the "dissociative" constructs discussed herein. However, alkoxy substitution on C_4 should favor an axial position (anomeric effect) in a chairlike transition structure, from which the low-lying σ_{co}^* should function as an electron-withdrawing group, cf. ref 25.

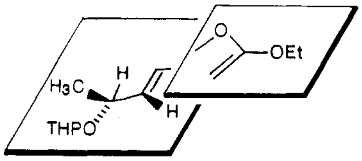
(22) For reviews, see: (a) Herndon, W. C. *Chem. Rev.* **1972**, *72*, 157. (b) Epiotis, N. D. *J. Am. Chem. Soc.* **1973**, *95*, 5621. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (d) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1975. (e) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F., *Tetrahedron* **1977**, *33*, 523. (f) Matatoshi, K. *Can. J. Chem.* **1979**, *57*, 2564. (g) Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (h) Gleiter, R.; Bohm, M. C.; *Pure and Appl. Chem.* **1983**, *55*, 237.

arise because of steric dictates of the hydrocarbon fragment[23] or will be under the control of the stereoelectronic biases of the "ester enolate" component.

While quite limited, the experimental data (Table II) support the assertions of the electrostatic basis of rearrangement stereoselectivity. Hatakeyama et al.[4c] have recently observed that allylic alcohols (protected as THP ethers) undergo stereospecific Ireland ester enolate Claisen rearrangement, yielding a 3:1 mixture of diastereomers, i.e.



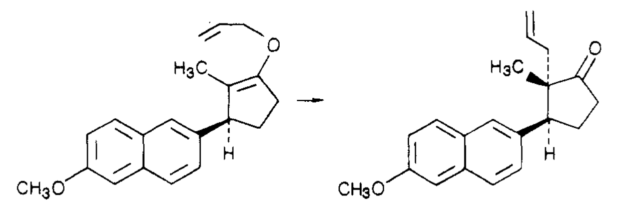
This result is consistent with the electrostatic bias of the allylic ether toward addition of an electron-rich (nucleophilic) "ester enolate" fragment, wherein approach anti to the allylic oxygen is favored. Note that rearrangement



is assumed to occur from a conformation in which the allylic CH bond eclipses C=C.[24] This conformation maximizes the electron-withdrawing ability of the adjacent CO bond,[25] thereby maximizing the relative electrophilicity of the already "electron-poor" allylic hydrocarbon component.[26] Support for this assignment of reactive conformer is provided by the work of Cha and Lewis,[4b] who have found that rearrangement of both cis and trans allylic glycolate esters leads to similar distributions of stereoisomers with cis substrates slightly more selective (see Table II). This has been cited elsewhere[9d] as evidence for participation of hydrogen-eclipsed conformers (in additions involving allylic alcohols and ethers) and argues for the assignment of this form as the more reactive conformer.[26]

The delicate balance between electronic and steric biases in directing overall selectivity is well evidenced by the work of Cha and Lewis,[4b] who have observed a strong dependence of product distributions on the degree of substitution of the silyl enol ether moiety, although in all cases, electronic dictates appear to prevail. On the other hand, steric effects are obviously responsible for the stereochemistry reported by Horeau and co-workers,[27] whereby rearrangement occurs preferentially anti to an allylic naphthyl group (on C_6) despite the electron-rich character of the aromatic ring.

It has already been noted[4c] that the observed selectivity is consistent with the "inside-alkoxy" effect proposed by Houk.[25] This is surprising, as the "inside-alkoxy" model was developed for electrophilic additions, with the conformational preference for allylic oxygen functionality (giving rise to the asymmetric bias) a consequence of the



electron deficiency of the olefin component as the transition structure is approached. It is difficult to rationalize how the approach of an electron-rich olefinic center (the "ester enolate") depletes electron density of the C_5–C_6 double bond. Rather, the "inside-alkoxy" model suggests that oxygen should adopt the "outside" position,[28] with the incoming carbon terminus (leading to the formation of a C_1–C_6 bond) and the bulky allylic alkyl substituent maintaining an antiperiplanar relationship.[29] This leads to the incorrect assignment of product stereochemistry. It is perhaps worth noting that the observed stereoselectivities[4] fall in line with a "Felkin-type" model,[30] where the allylic oxygen plays the role of the "large" group, and hydrogen the "small" group.

Conclusions

Discussion of stereoselectivity in [3,3] sigmatropic migrations, particularly Claisen rearrangements, is facilitated through the conceptual dissection of the rearranging skeleton into "nucleophilic" and "electrophilic" components. Inspection of neutral allylic radicals reveals that such an analysis does not require charge separation, i.e., C_4–X_3 bond heterolysis, per say, in the transition structure. Rather, the indication is that, for many systems, the asymmetry of the rearranging framework gives rise to one component being more electron-rich (nucleophilic) than the other.

Assignment of migration asymmetry follows from the electrostatic dictates of the two allylic components, wherein the more electrophilic face of the relatively electron-poor component combines with the more nucleophilic face of the relatively electron-rich component. For allylic alcohols and ethers on the "electrophilic" component, this involves addition of the nucleophiliuc "ester enolate" anti to the electron-rich allylic oxygen from the more reactive (most electrophilic) conformer in which the allylic CH bond eclipses C=C. Full confirmation of the underlying hypothesis, that *electrostatic dictates operating at the initial stages of reaction select the highly reactive species, which then proceed to low energy transition structures*, will require a painstaking mapping of the reaction coordinate from reactants to products, although for "reactant-like" transition structures, as is presumed for the rearrangements dealt with here,[15] such a hypothesis is entirely reasonable.

The experimental studies to date have not succeeded in identifying systems and/or conditions where [3,3] sigmatropic rearrangement proceeds with a high degree of

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(23) Perrin, C. L.; Faulkner, J. *Tetrahedron Lett.* **1969**, 2783.

(24) This is known to be a low energy form in 3-buten-2-ol. See: (a) Smith, Z.; Carballo, N.; Wilson, E. B.; Marstokk, K.-M.; Møllendal, J. *J. Am. Chem. Soc.* **1985**, *107*, 1951. (b) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1985**, *26*, 3647.

(25) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(26) The more reactive forms will dictate product distributions in kinetically controlled reactions. See: (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. See also: (c) De Tar, D. F. *J. Org. Chem.* **1986**, *51*, 3749.

(27) Horeau, A.; Lorthioy, E.; Guette, J.-P. *Compt. Rend., Ser. C* **1969**, *269*, 558.

(28) The "outside" orientation of an allylic oxygen allows σ^*_{CO} to act as an electron-withdrawing group, and gives rise to the most favorable diastereotopic transition structure leading to non-"inside-alkoxy" selectivity.[25]

(29) (a) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. (b) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Mareda, J.; Mueller, P. H.; Houk, K. N. *Ibid.* **1982**, *104*, 4974. (c) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *Ibid.* **1982**, *104*, 7162.

(30) (a) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (c) Cherest, M.; Felkin, H. *Ibid.* **1968**, 2205. (d) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (e) Anh, N. T. *Fortschr. Chem. Forsch.* **1980**, *88*, 145. See also: (f) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. (g) Anh, N. T.; Thanh, B. T. *Nouv. J. Chem.* **1986**, *10*, 681.

asymmetric induction upon incorporation of a chiral substituent at the olefinic centers (C_1, C_5, C_6). In the hope of assisting such a goal, we offer the following predictions: (1) Replacement of the C_6 allylic oxygen with other electron-rich atoms, e.g., N, S, P, and halogens, will give rise to a similar sense of selectivity. (2) Replacement of the C_6 allylic oxygen with an electropositive group, such as trimethylsilyl, will result in a reversed sense of diastereofacial control, i.e., approach of the "ester enolate" syn to silyl, from a hydrogen-eclipsed conformation. (3) C_5 substituent effects on *diastereofacial selectivity* will mirror those seen for analogous C_6 substitution. (4) Transposition of the allylic chirality at C_5 or C_6 to C_1 (both geometric isomers) will result in an opposite sense of diastereofacial selectivity, provided that there are similar conformational preferences about the two allylic centers.

Finally, we suggest that evaluation of ground-state conformer reactivity via molecular electrostatic potentials provides a powerful tool for assessing reaction energetics early along the reaction coordinate, where stereoselectivity in kinetically controlled asymmetric transformations may be addressed.[8-10,12] While unlikely to provide quantitative descriptions of resultant product distributions (as in rigorous transition-structure studies), reactivity models based on Coulombic potentials allow discussion of the means by which electronic asymmetry affects the reactivity of chiral substrates.

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The Transient Species in Radical Chlorination in Benzene Solvent

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Although all data on selectivity in alkane chlorination in complexing solvents such as benzene are consistent with two chain carriers, a low selectivity intermediate (LSI) and high selectivity intermediate (HSI), there is controversy as to their nature. Data and arguments are reviewed concluding that there are no valid reasons for rejecting a $\mathrm{Cl}^{\bullet}$–benzene π complex (πC) as the HSI. Data in which intermediates are trapped by maleic anhydride or excess Cl_2 are too fragmentary and contradictory to identify the HSI, although chemical intuition suggests that trapping could involve a small concentration of chlorocyclohexadienyl radicals (CCH) also present in the system. The best basis for identifying the HSI are the transient spectra reported by Ingold et al., and there is no convincing reason for rejecting their identification of it as πC.

The selectivities observed in free radical chlorinations are strikingly enhanced when they are carried out in benzene, other aromatic media, and a few other solvents, most notably CS_2.[1,2] The phenomenon is well-known, and Russell's original interpretation in terms of the formation of a $\mathrm{Cl}^{\bullet}$–solvent π complex showing higher selectivity than uncomplexed $\mathrm{Cl}^{\bullet}$[1] has been generally accepted, although for many years little more was published on the matter.

In 1983 interest was revived by a brief communication by Skell,[3] who reported that selectivities also depended on substrate concentration, increasing markedly as this was descreased. He proposed that, in addition to free $\mathrm{Cl}^{\bullet}$ and its π complex, a σ complex, i.e., in the case of benzene the chlorocyclohexadienyl radical, was involved in the reaction. The incipient controversy gained momentum in 1985 when Ingold and co-workers[4] confirmed Skell's selectivity data for 2,3-dimethylbutane (DMB) in benzene but showed that all data were consistent with a kinetic scheme involving only two species of distinguishable selectivity. They further investigated the transients involved in the reaction by a series of elegant experiments involving fast laser spectroscopy, assigned rate constants to the steps in their scheme, and, from observed spectra and the insensitivity of their observed kinetics to O_2, concluded that the high selectivity intermediate (HSI) was indeed Russell's π complex, while the low selectivity intermediate (LSI) is uncomplexed $\mathrm{Cl}^{\bullet}$. Skell[5] has now published his data in detail and accepts the form and rate constants of Ingold's analysis but identifies the HSI as the chlorocyclohexadienyl radical (CCH) with the LSI being free $\mathrm{Cl}^{\bullet}$ and its π complex (πC), considered to have similar selectivities. His most significant argument (of several) involves data on the competition between alkane chlorination and two other long-known reactions of the Cl_2–benzene system: the formation of hexachlorocyclohexane at high Cl_2 concentrations, and the induced conversion of maleic anhydride to 2-chloro-3-phenylsuccinic anhydride.[6] Although neither reaction has had definitive study, both have long been considered to involve the chlorocyclohexadienyl radical as a plausible intermediate[7] and accordingly in Skell's scheme should act as traps for the HSI.

In this paper I review these trapping experiments and some of Skell's other arguments to see if there are, in fact, valid criteria other than Ingold's fast spectroscopic data for identifying the HSI. My conclusion is that there are not. The trapping data yield only fragmentary and inconsistent results when analyzed in terms of the model,

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(1) Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 2977; **1958**, *80*, 4987, 4997.

(2) Walling, C.; Mayahi, M. F. *J. Am. Chem. Soc.* **1959**, *81*, 1485.

(3) Skell, P. S.; Baxter, H. N., III; Taylor, C. K. *J. Am. Chem. Soc.* **1983**, *105*, 120.

(4) Bunce, N. J.; Ingold, K. U.; Landers, J. P.; Lusztyk, J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5464.

(5) Skell, P. S.; Baxter, H. N., III; Tanko, J. M.; Chebolu, V. *J. Am. Chem. Soc.* **1986**, *108*, 6300.

(6) Ecke, G. G.; Buzbee, L. R.; Kolka, A. J. *J. Am. Chem. Soc.* **1956**, *78*, 79.

(7) Walling, C. *Free Radicals in Solution*; Wiley: New York, 1957; pp 308–310.

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