zation and hence was not a viable synthetic intermediate.

All of the new[10] compounds **1** → **5** were characterized by NMR, IR, and mass spectrometry.[11] Compounds **1** and **5** could be distinguished from their *Z* isomers by the significantly larger vicinal coupling constants of the vinyl hydrogens for the *E* configuration in the ^{1}H NMR.

The activation parameters for Claisen rearrangement of **1-6** were determined by using dilute (typically 5×10^{-3} M) solutions in anhydrous, degassed, di-*n*-butyl ether. Analyses were performed by following the disappearance of starting material using an analytical high-pressure liquid chromatograph equipped with variable wavelength UV detector and digital integrator. In each case control experiments confirmed a complete mass balance and showed no detectable side reactions. Activation parameters were calculated from the Eyring equation by using rate constants determined at five temperatures (six temperatures for **6**). All of the compounds exhibited good first-order kinetics over several half-lives. The results are summarized in Table I.

Detailed theoretical interpretations of these results are given in the following communication, but a few points are sufficiently striking to be made here.

Both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for **6** are somewhat lower than the values found in an earlier investigation.[12] Part of the discrepancy can be attributed to the difference in reaction media (di-*n*-butyl ether solution vs. gas phase) although we note that the new value for $\Delta S^{\ddagger}$ (-15.9 ± 1.5 cal/(mol K)) is more in line with the activation entropies for other [3,3]-sigmatropic migrations (from −9 to −20 cal/(mol K))[1a,13,14] than was the previous value (−7.7 cal/(mol K)).[12]

The effect of the nitrile substituent, which we assume to be primarily electronic in origin, is quite substantial, covering a range of nearly 2500 in k_{rel} at 100 °C (between **5** and **3**). It is particularly interesting that an acceptor substituent at the α position of the vinyl ether function (compound **2**) causes a rate enhancement since a donor substituent at that location apparently has a similar effect.[1a,15] This unusual (non-Hammett) behavior is in accord with our qualitative model for substituent effects on pericyclic reactions.[3]

Experiments to determine the effect of a methoxy substituent on the rate of the aliphatic Claisen rearrangement are in progress. The qualitative results of these experiments are predicted in the following communication.

Acknowledgment. Support of this work by the NIH (grant GM 27022) is gratefully acknowledged. We thank Professor M. F. Semmelhack for helpful suggestions on the synthesis of **4**.

Supplementary Material Available: Details of the kinetics for rearrangement of compounds **1-6** (13 pages). Ordering information is given on any current masthead page.

(10) Syntheses of both **1** and **2** have been claimed (Movsum-Zade, E. M.; Mamedov, M. G.; Shikhiev, I. A. *Zh. Org. Khim.* **1976**, *12*, 1687-1689). No proofs of structure except elemental analyses were given. Curiously, an incorrect elemental composition was both calculated and observed for **2**.

(11) **1**: ^{1}H NMR ($CDCl_3$) δ 7.23 (d, J = 13 Hz, 1 H), 5.8-6.2 (m, 1 H), 5.2-5.5 (m, 2 H), 4.70 (d, J = 13 Hz, 1 H), 4.44 (m, 2 H); IR 2240, 1620 cm^{-1}; CI-MS, m/e (M + 1) 110. **2**: ^{1}H NMR ($CDCl_3$) δ 5.75-6.15 (m, 1 H), 5.22-5.48 (m, 2 H), 5.01 (d, J = 3 Hz, 1 H), 4.88 (d, J = 3 Hz, 1 H), 4.34 (m, 2 H); IR 2240, 1620 cm^{-1}; CI-MS, m/e (M + 1) 110. **3**: ^{1}H NMR ($CDCl_3$) δ 6.50 (dd, J = 7, 14 Hz, 1 H), 5.8-6.25 (m, 1 H), 5.5-5.95 (m, 2 H), 5.15 (m, 1 H), 4.64 (dd, J = 3, 14 Hz, 1 H), 4.44 (dd, J = 3, 7 Hz, 1 H); IR 1625 cm^{-1}; CI-MS, m/e (M + 1) 110. **4**: ^{1}H NMR ($CDCl_3$) δ 6.38 (dd, J = 7, 14 Hz, 1 H), 6.00 (m, 2 H), 4.30 (m, 2 H), 4.22 (dd, J = 2.5, 14 Hz, 1 H), 4.15 (dd, J = 2.5, 7 Hz, 1 H); m/e (M + 1) 110. **5**: ^{1}H NMR ($CDCl_3$) δ 6.77 (dt, J = 3.5, 16 Hz, 1 H), 6.54 (dd, J = 7, 14 Hz, 1 H), 5.67 (dt, J = 2.5, 16 Hz, 1 H), 4.36 (dd, J = 2.5, 3.5 Hz, 2 H), 4.25 (dd, J = 2.5, 14 Hz, 1 H), 4.15 (dd, J = 2.5, 7 Hz, 1 H); IR 2225, 1620 cm^{-1}; CI-MS, m/e (M + 1) 110.

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(13) Wehrli, R.; Schmid, H.; Belluš, D.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 1325-1356.

(14) Willcott, M. R.; Cargill, R. L.; Sears, A. B. *Prog. Phys. Org. Chem.* **1972**, *9*, 25-98.

(15) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.

Substituent Effects on the Aliphatic Claisen Rearrangement. 2. Theoretical Analysis

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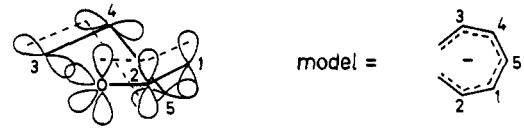
We have recently described a simple theoretical model that gives a good qualitative description of substituent effects on most thermal pericyclic reactions.[1] Our approach has been to focus on the π electrons of the various species involved and then to use simple Hückel molecular orbital (HMO) theory to evaluate the effect of a substituent on the transition state and the reactant(s). Transition states are modeled by the π-isoconjugate ground-state structure[1-3] while, at the zeroth level of approximation, π-donor substituents are represented by a carbanion and π- acceptors by a carbonium ion.[1] The difference in HMO π-electron energy between the transition state and reactant models (ΔE_π) is then compared for the reaction of interest and its unsubstituted analogue. This procedure yields the parameter $\Delta\Delta E_\pi$ whose sign and (in the case of neutral hydrocarbons) magnitude represent the predicted effect of the substituent on the activation enthalpy of the reaction. Thus if $\Delta\Delta E_\pi$ is negative (in absolute β units), the substituent is predicted to decrease $\Delta H^{\ddagger}$ with respect to that for the unsubstituted analogue whereas a positive $\Delta\Delta E_\pi$ means that the substituent should increase $\Delta H^{\ddagger}$. Surprisingly, given the crudeness of the model, there is a quantitative correlation between the calculated $\Delta\Delta E_\pi$ and the experimental $\Delta\Delta H^{\ddagger}$ for pericyclic, radical, and biradical reactions of unsaturated hydrocarbons.[3] This quantitative agreement presumably means that the basic approach is valid and, we assume, suitable for making qualitative predictions in heteroatomic pericyclic reactions.

In an analysis of the aliphatic Claisen rearrangement one begins by replacing the π-donor oxygen of the allyl vinyl ether by a carbanion. Such an approximation will, of course, quantitatively overestimate the importance of the oxygen lone pair but can be expected to give qualititatively correct results.[1] The π electrons of the unsubstituted reactant are therefore represented by an allyl anion and an isolated ethylene. The model for the transition state depends upon the geometry of the real activated complex. If the reaction proceeds through a chair conformation (A), then the oxygen lone pair that was in conjugation in the reactant will become almost orthogonal to the pericyclic array of orbitals in the transition state. On the other hand, the conjugation can be maintained if the transition state adopts a half-chair conformation (B) similar to that of cyclohexene. The orbital connectivity of A can be modeled by a phenyl anion whereas B is better modeled by a heptatrienyl anion because the orthogonality of orbitals on oxygen prevents completion of a cycle.[4]

A



B

(1) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877-1884.

(2) Wilcox, C. F., Jr.; Carpenter, B. K.; Dolbier, W. R., Jr. *Tetrahedron* **1979**, *35*, 707-711.

(3) Wilcox, C. F., Jr.; Carpenter, B. K. *J. Am. Chem. Soc.* **1979**, *101*, 3897-3905.

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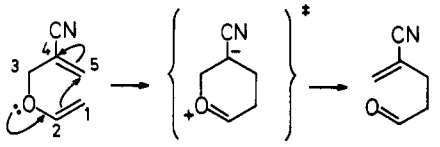
Table I. Predictions of Qualitative Substituent Effects on the Aliphatic Claisen Rearrangement[a]

substituent location	$\Delta\Delta E_\pi$ D	A
1	−	+
2	−	−
3	−	−
4	+	(±)[b]
5	+	+

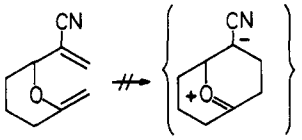
[a] D represents a π-donor substituent, and A represents a π acceptor. A negative sign means that the substituent should lower $\Delta H^\ddagger$ while a positive sign means that the substituent should raise $\Delta H^\ddagger$. [b] See text for explanation.

Presumably A is the less strained conformation and so preferable under normal circumstances.[5] However, B might become important when there is an acceptor substituent at the 4 position because it would then allow a stabilized zwitterionic contribution to the transition state.



If one carries out the HMO calculations to determine the sign of $\Delta\Delta E_\pi$, it turns out that the two transition-state models (phenyl anion and heptatrienyl anion) lead to the same qualitative predictions of substituent effects for all cases except that of an acceptor at the 4 position. As expected, the model for the half-chair conformation B leads to a prediction of lower activation enthalpy for this case (compared to unsubstituted allyl vinyl ether) whereas the model for conformation A leads to a prediction of higher activation enthalpy. The results are summarized in Table I.

The predictions for a π-donor substituent can be expected to apply to such groups as methoxy, trimethylsiloxy, and dimethylamino. We are carrying out experiments to test the predictions using the methoxy substituent. As reported in the preceding communication we have now completed the experimental tests for the acceptor series using a cyano substituent. Comparison of the experimental $\Delta\Delta H^\ddagger$ values with the predictions in Table I shows agreement for positions 1–3 and 5. The experimental observation of a reduction in $\Delta H^\ddagger$ caused by a cyano group at position 4 might be indicative of adoption of the half-chair conformation in this case. The large negative $\Delta S^\ddagger$ observed for the rearrangement of the 4-cyano derivative would be consistent with some solvent ordering caused by increased charge separation. We plan to test our hypothesis by investigating the effect of a cyano group on the rearrangement of 2-methylene-5-vinyltetrahydropyran. In this case the half-chair conformation is inaccessible (as can be seen from the anti-Bredt nature of the zwitterionic formulation), and so the substituent should increase $\Delta H^\ddagger$ if our hypothesis is correct.



As always, the fact that the experimental observations so far are consistent with our theoretical predictions does not necessarily prove that the model is correct. Indeed there has recently been proposed a quite different model for substituent effects on the Claisen and Cope rearrangements. This approach[6,7] recognizes that the two extreme biradical structures for a [3,3]-sigmatropic shift can be connected with each other and with the transition state by a vibration that is orthogonal to the reaction coordinate. Substituents might change the position and energy of the reaction transition state by selective stabilization of one of the biradical extremes. The effect of a group such as cyano would then be discussed in terms of its radical stabilizing properties rather than its acceptor properties. A quantitative formula has been proposed for this kind of surface and has been applied to a variety of [3,3]-sigmatropic rearrangements.[7c,d] It is clearly of interest, then, to see whether our new experimental results are consistent with this alternative model.

Unfortunately, we had some difficulty in finding all of the necessary thermochemical parameters required to do the calculations, but some conclusions can be drawn for compounds **3–5** (numbered according to the location of the cyano group). Using a value of 9 kcal/mol for the radical stabilizing energy of a cyano group[7c] and ignoring any resonance stabilization between the substituent and a C=C double bond,[8] one calculates differences in $\Delta G^\ddagger$ (523 K) between **3–5** and the unsubstituted compound of −4.0, −3.3, and −4.0 kcal/mol, respectively. The experimental values are −4.0, −1.7, and +1.5 kcal/mol. It seems unlikely that the 5.5-kcal/mol error in the calculated $\Delta G^\ddagger$ for **5** could be attributed to a steric effect since the sterically much larger methyl group has at most a 1-kcal/mol effect at the corresponding location in a Cope rearrangement.[9] If one attempts to correct the fault by introducing a 5.5-kcal/mol CN/C=C resonance stabilization energy, then the calculated $\Delta\Delta G^\ddagger$ values become −5.1, +0.8, and +1.3 kcal/mol. Now the fit to the Claisen rearrangement data is better, but, unfortunately, these parameters are no longer consistent with cyano substituent effects on the Cope rearrangement. Thus the $\Delta G^\ddagger$ calculated for the [3,3]-sigmatropic migration of 2,5-dicyano-3-methyl-1,5-hexadiene is 10.3 kcal/mol higher than the observed value.[6]

In attempting to locate the problem with the quantitative model for [3,3]-sigmatropic rearrangements we noticed the curious fact that the cyclically delocalized structure that is normally considered to be an important contributor to the description of the transition state for a pericyclic reaction has no place in the calculations. Since the position and energy of the transition state in this model are completely determined by the energies of the four extrema in the More-O'Ferrall Jencks diagram,[7c,d] it follows that the same energy must be calculated for the transition states of orbital symmetry allowed and forbidden reactions. The model further leads to the prediction of identical substituent effects on allowed and forbidden reactions.[7c] Neither of these predictions is in accord with the experimental facts.[2,10] We emphasize that this is a flaw in the mathematical representation of the surface and not in the underlying physical concept, which we believe to be fundamentally sound. A reformulation that would allow explicit inclusion of the delocalized structure would remove the orbital symmetry problems and might improve the precision of the quantitative calculations.

In summary, then, we note that qualitative predictions about substituent effects on the aliphatic Claisen rearrangement can apparently be made by focusing on the delocalized model for the

(4) This is similar to the so-called pseudopericyclic transition state defined by Lemal (Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325–4327).

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(7) (a) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 6268–6270. (b) Gajewski, J. J.; Conrad, N. D. *Ibid.* **1979**, 2747–2748. (c) Gajewski, J. J. *Ibid.* **1979**, 4393–4394. (d) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142–148. (e) An extended version of the original formula can apparently encompass allowed concerted and biradical mechanisms[7d] but could not, we believe, differentiate between allowed concerted and forbidden concerted transition states.

(8) The values of $\Delta G^\ddagger_{BB}$ and $\Delta G^\ddagger_{BM}$ used to explain the Cope rearrangement of 2,5-diphenyl-1,5-hexadiene[7c] indicate that resonance interactions between the phenyl groups and the C=C double bonds were ignored. Stabilization of an allyl radical by 2-phenyl substitution was also apparently ignored.[7c] We began our attempts to fit the cyano substituent effects by making similar assumptions.

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transition state and that explicit inclusion of such a structure is probably necessary for a proper quantitative description of substituent effects on [3,3]-sigmatropic migrations or other pericyclic reactions.

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Transition-Metal Binding Site of Bleomycin. A Synthetic Analogue Capable of Binding Fe(II) to Yield an Oxygen-Sensitive Complex

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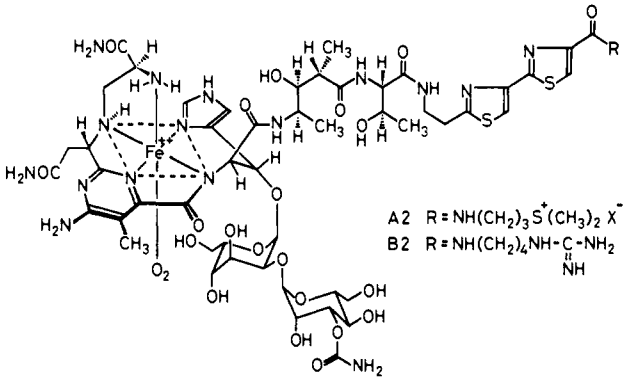
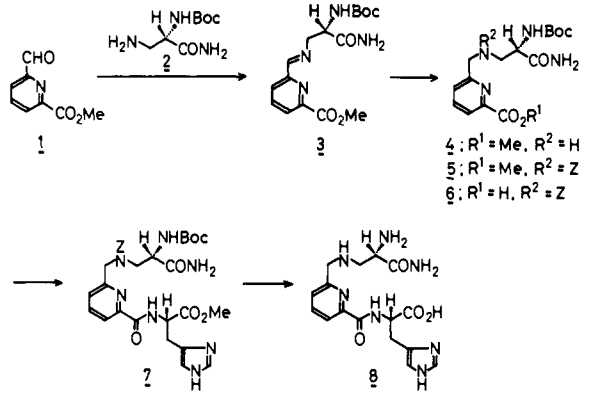
Bleomycin (BLM) is an antitumor antibiotic clinically used in the treatment of squamous cell carcinoma and malignant lymphoma.[1] In addition to its medicinal importance, BLM has attracted a great deal of structural[2] and synthetic[3-6] studies because of the unique structure and interesting biological activity. The mechanism by which the drug exhibits antitumor activity is currently under active investigation, and two important capabilities of BLM are considered essential. BLM is capable of producing strand breaks in DNA[1] and binding Fe(II) to yield an oxygen-sensitive complex, BLM-Fe(II).[7] A number of possible transition-metal binding sites of BLM were proposed on the basis of



The proposed structure for bleomycin-Fe(II) complex[8a]

Scheme I



theoretical and spectroscopic studies.[8] Among them, the X-ray structural analysis[9] of the Cu(II) complex of P-3A isolated from a culture broth of BLM demonstrated the most direct evidence for the metal binding site, and an acid hydrolysis product of BLM-Co(III) was recently shown to be analogous to the structure of P-3A-Cu(II).[10] However, these complexes are biologically inactive and do not activate molecular oxygen. We wish to report the first successful synthesis of an analogue of the pyrimidine moiety of BLM capable of binding Fe(II) to yield an oxygen-sensitive complex at physiological values of pH.

During our synthetic study[4] of BLM, a strategy was developed for the elaboration of the pyrimidine moiety of BLM, affording pyrimidoblamic acid as a key intermediate to the total synthesis of bleomycin aglycon.[5] The synthetic approach has been considered to provide the most reliable evidence for the controversial transition-metal binding sites of BLM and now extended to the synthesis of the analogue of the pyrimidine moiety of BLM. The key features of the approach include (1) simplification of the pyrimidine nucleus of BLM to pyridine nucleus, (2) use of a simplified side chain, [((*S*)-2-amino-2-carbamoylethyl)amino]-methyl group, (3) use of histidine for β-hydroxyhistidine of BLM, and (4) the assembly of such fragments to provide a simplified analogue which corresponds to the amine-pyrimidine-imidazole region of BLM.

Thus, methyl 6-formylpyridine-2-carboxylate (**1**)[11] was treated with (*S*)-3-amino-2-[(*tert*-butoxycarbonyl)amino]propionamide (**2**)[4] in an equal molar ratio in CH_3CN in the presence of an activated molecular sieve at 25 °C for 12 h (Scheme I). The resulting Schiff base **3** was hydrogenated in the presence of 5% Pd-C in MeOH, affording yellow foam **4** upon workup and chromatography on silica gel (eluted with 9:1 CH_2Cl_2-MeOH) (**4**: 60% yield from **1**, $[\alpha]^{20}_D$ +36.2° (*c* 1, $CHCl_3$); $M^+ + 1$, 353). Then, the secondary amino group of **4** was protected with the benzyloxycarbonyl group (*Z*), since it was found that the secondary amino group caused difficulty in the peptide formation between **4a** ($R^1 = R^2 = H$) and histidine methyl ester. Treatment of **4** with a little excess of benzyl chloroformate in the presence of 0.1 N NaOH in CH_2Cl_2 (3 h, 25 °C) afforded colorless foam **5** upon workup and chromatography on silica gel (eluted with 9:1 CH_2Cl_2-MeOH) in 88% yield (**5**: $[\alpha]^{20}_D$ +77.7° (*c* 1, $CHCl_3$); M^+, 486). Condensation of **5** with histidine methyl ester[12] was carried out smoothly. Methyl pyridine-2-carboxylate derivative **5** was hydrolyzed (0.1 N LiOH, 30 min at 0 °C and then 1 h at

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