was ±0.02 pK units in most cases. Inexplicably, 5-bromoisophthalic acid gave a value of pK_2 significantly higher than that of the other 5-halo compounds, despite repeated redeterminations and checks of the compound's identity and purity. It is possible that incomplete solubility is the cause since a similar effect was noted in the case of 5-methylisophthalic acid, where low solubility is clearly a major problem. For these two acids we calculated pK_2 from a Hammett plot of the well-behaved compounds. In order to have sufficient data to make such a calculation, we determined pK values for a number of other 5-substituted isophthalic acids, not all of which were used as catalysts. The data for such compounds and for the 2-methoxy derivative are given in Table III. References for the pK values of the other acids are given in the tables.

Materials. Many of the acids are commercially available. The isophthalic acids, except for the 2-methoxy derivative, had been previously prepared in this laboratory.[12] Tetramethylsuccinic acid was obtained by hydrolysis of its dimethyl ester, which was prepared from methyl 2-methylpropanoate by the method of Inaba and Ojima.[13] 2,3-Dimethylsuccinic acid[14] was prepared from methyl butanoate by the same method. The (±) and meso forms were separated by crystallization from benzene, with the meso form being the less soluble component. Further recrystallization of the separated fractions from water gave the pure meso compound, mp 211–212 °C, and the (±) form, mp 133–134 °C.

The monomethyl esters of 3-methylglutaric and 3,3-dimethylglutaric acids were synthesized by the methanolysis of the corresponding anhydrides.

2-Methoxyisophthalic acid was prepared by the aqueous permanganate oxidation of 2,6-dimethylanisole: yield 97%; mp 220–222 °C. Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 55.19; H, 4.20. We thank Dr. K. Nagarajan for the preparation of this compound.

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Registry No. $C_6H_5CHOHCO_2^-$, 769-61-9; $CH_3OCH_2CO_2^-$, 20758-58-1; $HOCH_2CO_2^-$, 666-14-8; $C_6H_5CH_2CO_2^-$, 7631-42-7; $CH_3CO_2^-$, 71-50-1; $CD_3CO_2^-$, 21845-14-7; $CH_3(CH_2)_2CO_2^-$, 461-55-2; $(CH_3)_2CHCO_2^-$, 5711-69-3; $CH_3CH_2CO_2^-$, 72-03-7; c-$C_6H_{11}CO_2^-$, 3198-23-0; $(CH_3)_3CCH_2CO_2^-$, 22402-43-3; $(CH_3)_3CCO_2^-$, 29650-96-2; acetone, 67-64-1; 2-methoxyisophthalate dianion, 119695-34-0; 5-bromoisophthalate dianion, 119695-35-1; 5-iodoisophthalate dianion, 119695-36-2; isophthalate dianion, 42966-02-9; 5-methylisophthalate dianion, 119695-37-3; phthalate dianion, 3198-29-6; 3-methylglutarate dianion, 68124-57-2; succinate dianion, 56-14-4; 3,3-dimethylglutarate dianion, 20187-45-5; *meso*-2,3-diethylsuccinate dianion, 119695-38-4; (±)-2,3-diethylsuccinate dianion, 119695-39-5; diethylmalonate dianion, 63238-97-1; tetramethylsuccinate dianion, 119695-40-8; 5-hydroxyisophthalic acid, 618-83-7; 5-methoxyisophthalic acid, 46331-50-4; 5-fluoroisophthalic acid, 1583-66-0; 5-nitroisophthalic acid, 618-88-2; 2,6-dimethylanisole, 1004-66-6.

Mechanistic Implications of 1,3,2λ⁵-Dioxaphospholanes in the Mitsunobu Reaction

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Recently, we reported a highly chemoselective monobenzoylation of unsymmetrical 1,2-diols (i.e., 1,2-propanediol and 1-phenyl-1,2-ethanediol), affording both the *kinetically* and *thermodynamically* least stable secondary benzoate.[1] This monobenzoylation occurs with either of two reagent formulations, triphenylphosphine (TPP) and benzoyl peroxide (BPO) or TPP, diethyl azodicarboxylate (DAD), and benzoic acid (BA). The latter characterizes the reagent formula popularized by Mitsunobu and co-workers.[2a] In both systems, formation of 1,3,2λ⁵-dioxaphospholane **1** emerges as the key intermediate. Hydrogen-bonding interactions and ultimately proton transfer to the least hindered oxygen of **1** initiates chemoselective ring opening to form largely the C-2 secondary phosphonium salt. Finally, benzoate anion nucleophilic displacement of triphenylphosphine oxide (TPPO) affords predominantly the C-2 benzoate with inversion of configuration at the C-2 carbinol stereocenter (Scheme I).

Table I. Chemoselective Benzoylations of 1,2-Diols Using the Mitsunobu Reaction

diol	benzoates,[a] % secondary	primary	di
1,2-propanediol	88	10	2
1-phenyl-1,2-ethanediol	96	2	2

[a] See the Experimental Section for the details of the analytical analyses.

The mechanistic discernment of the Mitsunobu reaction with respect to the initial redox chemistry has received substantial documentation.[2] Quite recently, Walker and co-workers[3] proposed that the order of addition of alcohol and acid to betaine **2** has a profound effect on the reaction pathway, implying potential duality of mechanism. For example, addition of 2 equiv of a generic alcohol, ROH, to betaine **2** liberates diamine **3** and ultimately affords σ⁵-dioxaphosphorane **4** (Scheme II, path a). Addition of HX effects loss of 1 equiv of ROH to give oxaphosphonium salt **6**. In the alternative route (Scheme II, path b), the acid, HX, is added initially to betaine **2**, effecting immediate protonation and affording phosphonium salt **5**, which upon addition of the alcohol undergoes an apparent slow conversion to oxaphosphonium salt **6** with no formation of intermediate dialkoxyphosphorane **4**. Walker et al. based their conclusions on inspection of the ^{31}P NMR spectrum, which indicates only the presence of phosphonium salt **6**.

The experiments described below are designed to test this suggestion by employing unsymmetrical 1,2-diols as probes to detect the formation of 1,3,2λ⁵-dioxaphosphorane intermediates directly as well as through the identity and product ratios of the resulting diastereomeric benzoates. The predictions are (i) if benzoate substitution at C-1 predominates, the presence of a 1,3,2λ⁵-dioxaphospholane would seem unlikely while (ii) an abundance of C-2 benzoate substitution *requires* the intermediacy of a 1,3,2λ⁵-dioxaphospholane.

Results and Discussion

When 1 equiv of benzoic acid is added to a mixture of TPP and DAD in tetrahydrofuran (THF) solvent followed by the addition of an unsymmetrical 1,2-diol, a high product ratio favoring the C-2 benzoate is observed (see Table I).[4] We believe the preponderance of the C-2

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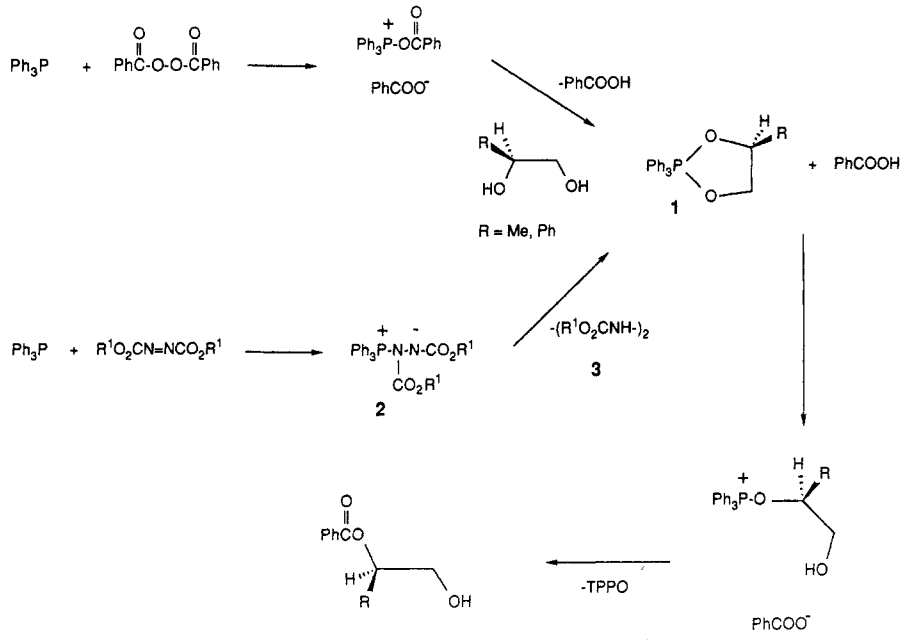
(2) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876. (c) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557. (d) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767.

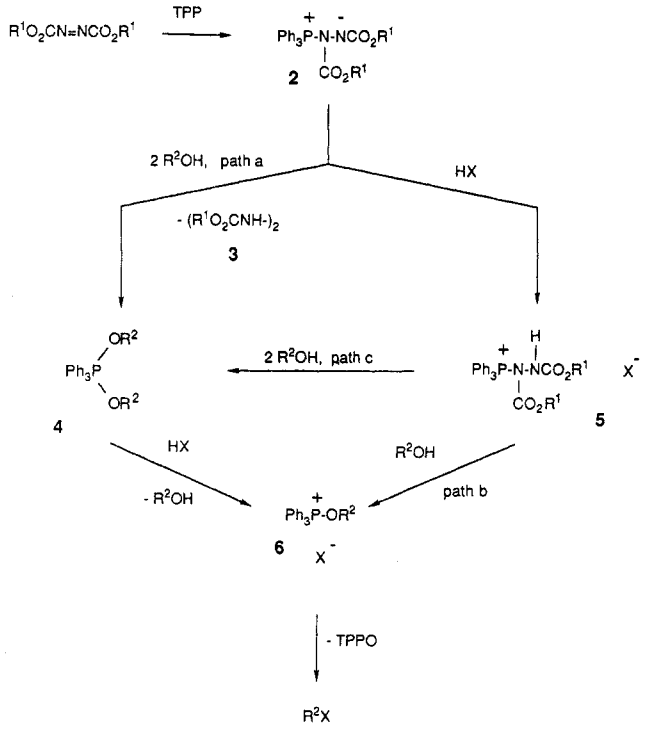
(3) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235.

0022-3263/89/1954-2485$01.50/0

Scheme I



Scheme II



benzoate can only be formed through the intermediacy of a 1,3,2λ⁵-dioxaphospholane (i.e., the cyclic analogue of **4**) with subsequent ring opening by "hydrogen bonding–protonation" at the least hindered oxygen initiated by benzoic acid to give largely the C-2 oxyphosphonium salt (i.e., Scheme II, path c).

To corroborate the presence of oxaphosphorane intermediates, similar reactions were monitored by application of low-temperature (−78 °C) ^{31}P NMR spectroscopy. When equimolar quantities (0.5 mmol) of TPP and DAD were admixed in a 10-mm NMR tube with 1 mL of anhydrous tetrahydrofuran (and 0.5 mL of C_6D_6 as a deuterium NMR lock reference signal), betaine **2** (R^1 = Et) was observed at δ +44 ppm[5] along with a small quantity of triphenylphosphine oxide (TPPO) at δ +30 ppm. Addition of an equivalent (0.5 mmol) of benzoic acid in THF (1 mL) causes replacement of the δ +44 ppm resonance with one occurring at δ +51 ppm, attributable to the conjugate acid phosphonium salt **5** (R^1 = Et).[6] On addition of an equivalent of 1,2-propanediol (R = Me), the δ +51 ppm resonance is initially replaced by a δ −37 ppm resonance characterizing 1,3,2λ⁵-dioxaphospholane[7] **1** (R = Me) with subsequent appearance of two minor peaks at δ +62.0 and δ +63.5 ppm corresponding to the two regioisomeric phosphonium salts **8** and **9**. The presence and direct observation of 1,3,2λ⁵-dioxaphospholane **1** is consistent with the product analysis and the mechanistic rationale presented in Scheme III.

Interestingly, the δ −37 ppm resonance is subsequently transformed into a broader peak at δ −31 ppm. The latter resonance is believed to characterize a benzoic acid–1,3,2λ⁵-dioxaphospholane complex, **7**, existing only in concentrated solutions (0.8 M).[8] Dilution, resulting from the addition of more solvent (5 mL of anhydrous tetrahydrofuran), causes the δ −31 ppm resonance to shift to δ −37 ppm. In fact, throughout the course of this investigation, the δ −31 ppm resonance could not be observed in diluted solutions (<0.26 M). The 6 ppm downfield ^{31}P NMR shift attributed to complex **7** (δ −31 compared to δ −37 observed for **1**) is rationalized in terms of charge polarization at the phosphorus atom caused by hydrogen bonding. Here, the developing positive charge on oxygen translates to a partial positive charge on phosphorus and ultimately a deshielding effect in the ^{31}P NMR. Any associative involvement between 1,2-dicarbethoxyhydrazine **3** (R^1 = Et) and 1,3,2λ²-dioxaphospholane **1**, which might cause 6 ppm deshielding of the resonance attributable to

(4) The secondary/primary benzoates ratios are slightly higher than those described in our earlier report[1] and may reflect a temperature dependence of the proton transfer process.

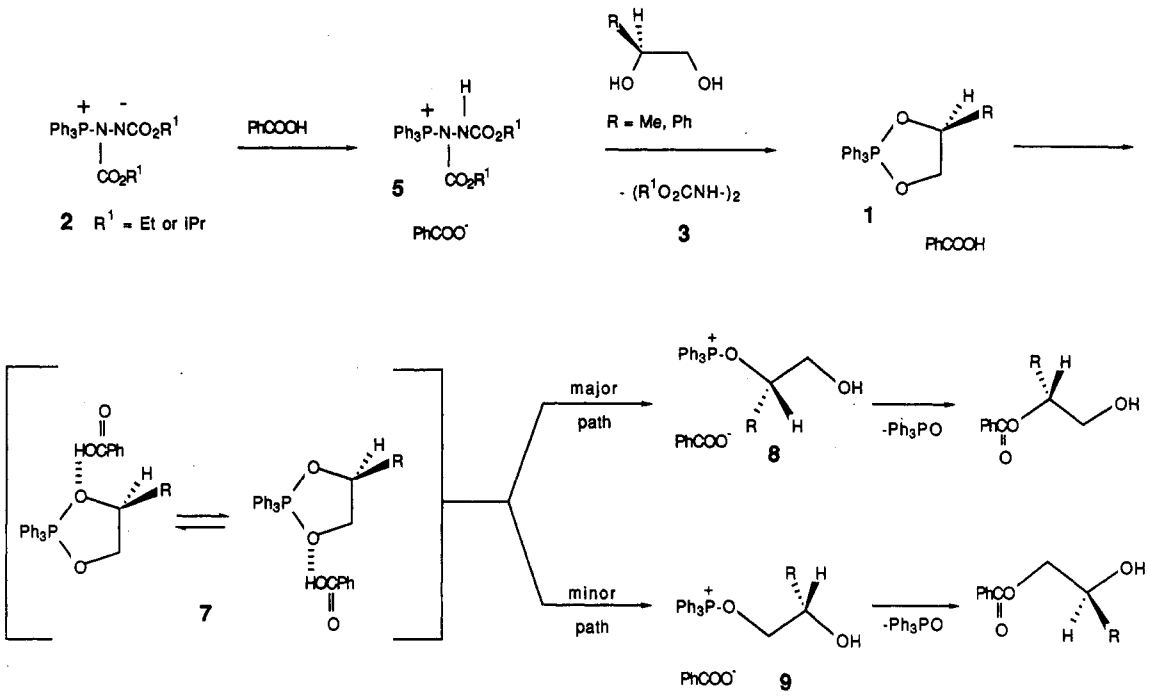
(5) ^{31}P NMR δ +44.9 ppm (THF solvent).[2d]

(6) ^{31}P NMR δ +53.1 ppm (THF solvent).[2d]

(7) ^{31}P NMR δ −37.2 ppm (toluene solvent). See: Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1986**, *106*, 7681.

(8) Similar coordination of lithium cations with sterically congested 1,3,2λ⁵-dioxaphospholanes has been postulated to promote a facile cyclodehydration process. See: (a) Murray, W. T.; Evans, S. A., Jr. *Nouv. J. Chim.*, in press. (b) Murray, W. T.; Evans, S. A., Jr. *J. Org. Chem.*, in press.

Scheme III



1 at δ 37 is excluded since complex 7 is observed at ^{31}P NMR δ −31 ppm when 1 is prepared independently[9] and admixed with benzoic acid at low temperature. From the ^{13}C NMR spectrum of complex 7, coupling ($^1J_{PC}$ = 117 Hz) between the phosphorus atom and the ipso carbons is observed and this time-averaged value is interpreted in terms of a trigonal-bipyramidal conformer having a single apical phenyl group and two equatorial phenyls as proposed by Jenkins.[10] This suggests that the basic 1,3,2λ^5-dioxaphospholane substructure is intact. As stated previously, we believe that the high stereoselective ring opening of cyclic dioxaphospholane 1 is not simply due to protonation at the least hindered oxygen but rather through hydrogen bonding visualized as benzoic acid coordinating to the ethereal P–O oxygen.

There is no doubt that 1,3,2λ^5-dioxaphospholane 1 (δ −37 ppm) is present as a stable intermediate. Walker's conclusion that no phosphoranes were formed when acid is *first* added to betaine 2 may be due to the inability of a bulky secondary alcohol to form a stable σ^5-dioxaphosphorane in the presence of an acid of low pK_a (i.e., trifluoroacetic acid). Correspondingly, in our hands, the presence of diethoxy- and diisopropoxytriphenylphosphorane [R^2 = Et and *i*-Pr, respectively, in 4] were observed by low-temperature (−78 °C) ^{31}P NMR spectroscopy when ethanol and 2-propanol were added to phosphonium ion 5. Specifically, when 1 equiv of benzoic acid (0.5 mmol) is added to an equimolar quantity (0.5 mmol) of TPP and DAD [or diisopropylazodicarboxylate (DIAD) and TPP with 2-propanol] in anhydrous tetrahydrofuran, phosphonium salt 5 (R^1 = Et) and benzoate anion (e.g., X = $C_6H_5COO^-$) are formed. Addition of 2 equiv (1.0 mmol) of anhydrous ethanol initiates the immediate disappearance of 5 and the appearance of σ^5-dioxaphosphorane 4 plus oxaphosphonium ion 6 (R^2 = Et). Diethoxytriphenylphosphorane (4, R^2 = Et)[11] is characterized by a ^{31}P NMR resonance at δ −54.0 ppm[11b] and one for the corresponding oxaphosphonium salt 6 (R^2 = Et) at δ +62.5 ppm. Similarly, when 2-propanol is added to phosphonium ion 5 (R^1 = *i*-Pr) [prepared by reaction of diisopropylazodicarboxylate (DIAD)[12] with TPP, followed by protonation with benzoic acid] a *trace* of diisopropoxytriphenylphosphorane 4 (R^2 = *i*-Pr) is observed at δ −49.6 ppm [^{31}P NMR δ −48 ppm (THF);[2b] δ −49.6 ppm (THF)[2c] with the more intense ^{31}P NMR resonance at δ +58.9 ppm corresponding to phosphonium salt 6 where R^2 = *i*-Pr.

We conclude that oxaphosphoranes of type 1 and 4 are certainly formed and directly observable in the Mitsunobu reaction even *when the acid is added before the alcohol.* The mechanistic rationales involving 1,2-diols and simple alcohols follow Scheme III and Scheme II, path c, respectively, and not necessarily via Scheme II, path b, as proposed by Walker and co-workers. It seems conceivable that an equilibrium probably exists between σ^5-dioxaphosphorane 4 and oxaphosphonium salt 6 where Arbusov decomposition of 6 is rate-limiting. Qualitatively, the decreasing stability of σ-dioxaphosphoranes in the presence of acid appears to follow the order: 1,3,2λ^5(cyclic) > primary > secondary, which might be viewed as evidence in support of the equilibrium concept. Coupling this trend with the observations of Walker et al. suggest that the stronger acid (i.e., CF_3COOH) would be expected to shift this equilibrium in favor of oxaphosphonium ion 6. Finally, the chemoselectivity arising from the use of the unsymmetrical 1,2-diol system can be employed to detect

(9) The bisphosphoranylation of 1,2-propanediol is easily initiated with diethoxytriphenylphosphorane in toluene solvent at 25 °C. Two equivalents of ethanol and toluene solvent are removed under vacuo to afford 1,3,2λ^5-dioxaphospholane 1. See: Kelly, J. W.; Evans, S. A., Jr. *J. Org. Chem.* **1986**, *51*, 5490.

(10) Acyclic dialkoxytriphenylphosphoranes having *three* equatorial phenyl groups in the trigonal-bipyramidal conformation exhibit larger coupling constants ($^1J_{P-C} \approx 175$ Hz) between the ipso ^{13}C carbon and phosphorus compared to 2,2,2-triphenyl-1,3,2λ^5-dioxaphosphorane (1) ($^1J_{P-C} \approx 120$ Hz). See: Von Itzstein, M.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 437.

(11) (a) Denney, D. B.; Denney, D. Z.; Wilson, L. A. *Tetrahedron Lett.* **1968**, 85. (b) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 5210.

(12) The use of diisopropyl azodicarboxylate (DIAD) instead of diethyl azodicarboxylate (DAD) minimizes possible complications caused by exchange reactions involving the diol and the ethyl ester of DAD.[2c] Finally, the corresponding phosphonium ion 5, resulting from reaction of TPP and DIAD, exhibits a ^{31}P NMR resonance at δ +49.8 ppm.

formation of dioxaphosphorane intermediates through product analyses of the diastereomeric benzoates after treatment with benzoic acid.

Experimental Section

Although diethyl azodicarboxylate, benzoic acid, 1,2-propanediol, and styrene glycol are commercially available, benzoic acid was recrystallized from solvent, and the diols were distilled before use. Triphenylphosphine was recrystallized from a solution of methanol and petroleum ether. The regioisomeric benzoates from 1,2-propanediol and styrene glycol have been previously prepared and characterized.[1]

Reaction of Benzoic Acid, Triphenylphosphine, and Diethyl Azodicarboxylate with 1,2-Diols. Benzoic acid (0.5 mmol, 0.061 g) was added to a cold (0–5 °C) solution of triphenylphosphine (0.5 mmol, 150 mg) and diethyl azodicarboxylate (0.5 mmol, 0.08 mL) in anhydrous tetrahydrofuran (5 mL) under an argon atmosphere. After 5 min, the diol (0.5 mmol) was added. The solution was allowed to warm to ambient temperature with continuous stirring for 1 h. The solvent was removed (rotary evaporator), and relative product ratios were determined by HPLC analyses employing a Spherisorb silica column and 10% tetrahydrofuran–90% hexanes as eluents.

Acknowledgment is made to The University of North Carolina-Research Council and the National Science Foundation (CHE-87-20270) for supporting our research programs. We are also grateful to M & T Chemicals, Inc., for supplying us with generous samples of triphenylphosphine. Finally, we are especially grateful to one of the referees for insightful comments and valuable suggestions in the redrafting the current manuscript.

An AM1 and MNDO Theoretical Study of the Diels–Alder Reaction between β-Angelica Lactone and Cyclopentadiene

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The Diels–Alder reaction has been the subject of numerous experimental and theoretical studies. There has been much recent interest in the means of predicting or controlling regioselectivity and stereoselectivity in these reactions. Several groups have treated these subjects both theoretically and experimentally.

Molecular orbital studies of the Diels–Alder reaction have been performed using both ab initio and semiempirical methods.[1] A particularly controversial problem has been that of the extent of synchronicity in these reactions. This problem has been discussed in several papers. Most recently, Bernardi et al.[2] have concluded (based upon MCSCF calculations) that there are two distinctly different reaction paths for synchronous and asynchronous reactions, in accord with a previous suggestion by Dewar.

Clearly, ab initio calculations at this level are much too expensive to be applied to the problems of regio- and stereoselectivities that are faced in the laboratories of synthetic organic chemists. Semiempirical MO calculations have been applied to these problems with varying degrees of success. One of the major problems has been to determine whether or not closed-shell RHF calculations are adequate for the predictions of the properties under discussion. Dewar has reported that RHF calculations tend to favor synchronous reaction paths.[1a] He also has reported that the effects of substituents upon the activation energies are not well described at this level, at least for cyano-substituted dienophiles. On the other hand, optimization of complex transition states using configuration interaction (CI) would be quite expensive, even at the semiempirical level. Recently, we have found that AM1 adequately describes the face selectivity for the Diels–Alder reactions of several chiral dienes, even at the closed-shell, RHF, level.[3]

Another approach to modeling the reactivity of complex Diels–Alder reactions involves using a model for the transition state and calculating the interactions in that model as one varies the substituents in the system. Houk has reported several studies of this nature.[4]

In this paper, we use the AM1 and MNDO semiempirical Molecular orbital methods to model the reaction between β-angelica lactone and cyclopentadiene. This reaction has been studied experimentally by Ortuño et al.,[5] who also studied several other similar Diels–Alder reactions.[6] Although α,β-unsaturated carbonyl compounds have found wide application in Diels–Alder chemistry, α,β-butenolides have only recently been exploited. The butenolides are a potentially useful set of synthons for the preparation of various natural products. For this reason,

Table I. Energetics for the Reactions of β-Angelica Lactone with Cyclopentadiene[a]

		MNDO		AM1	
face	exo/endo	H_f	H_{act}	H_f	H_{act}
H	endo	20.0	52.4	9.6	31.0
H	exo	19.2	51.6	8.2	29.6
methyl	endo	21.6	53.9	12.9	34.3
methyl	exo	20.9	53.3	10.5	31.9
cyclopentadiene		32.1		37.1	
β-angelica		−64.5		−58.4	

[a] All energies in kilocalories per mole.

Table II. Partial Bonds in Transition States[a]

		MNDO		AM1	
face	exo/endo	bond a	bond b	bond a	bond b
H	endo	3.014	1.625	2.151	2.105
H	exo	3.022	1.615	2.167	2.103
methyl	endo	1.614	2.961	2.133	2.125
methyl	exo	1.607	2.998	2.157	2.114

[a] All distances are in angstroms.

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