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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Received December 13, 1988

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.

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.

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,

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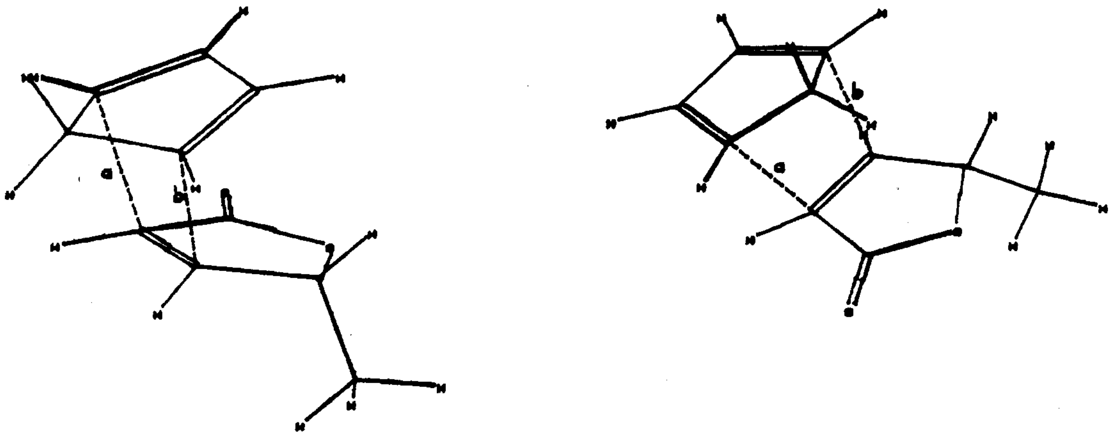
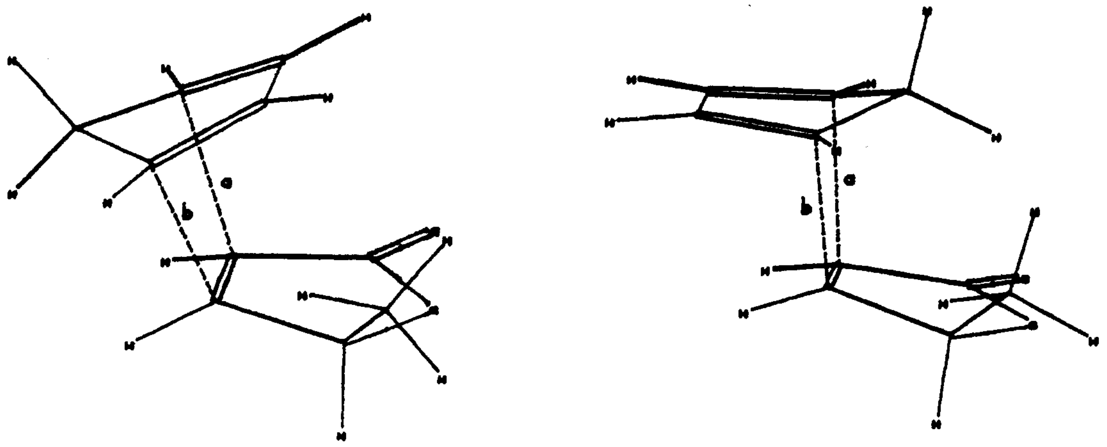


H-side endo

H-side exo



methyl-side endo

methyl-side exo

Figure 1. Transition state structures. Structures represented are those optimized with AM1. Table II gives the values for the bonds being formed (a and b) for both MNDO and AM1.

it is particularly useful to determine the applicability of semiempirical models to the reactivity of these systems.

Methods

The AM1[7] and MNDO[8] approximations to molecular orbital theory have been employed using the AMPAC computer program. The transition state for each reaction was determined with complete optimization of all internal coordinates. The RHF, closed-shell, ground state was used in all cases. Force calculation on the transition states were performed to verify that they had one, and only one, negative force constant. The activation enthalpies were calculated by difference from the correspondingly calculated enthalpies of the fully optimized reactants in their ground states.

Results and Discussion

The results are summarized in Tables I and II.

As can be readily seen, the MNDO method predicts barriers that seem much too high. Although the activation enthalpies have not been specifically determined for these reactions, 51.6–53.9 kcal/mol is clearly inconsistent for reactions that are run in the laboratory at 110 °C or lower. MNDO also predicts the exo adduct to be favored over the endo, in disagreement with the experimental observation of 3:1 endo:exo. On the other hand, MNDO is successful in predicting the face selectivity, correctly predicting attack on the less hindered face of β-angelica lactone.

AM1 is clearly more successful in predicting the activation energies (29.6–34.3 kcal/mol) for the Diels–Alder reactions that we are considering in this study. The exo adduct is once again predicted to be favored over the endo, counter to experimental observation. Face selectivity is correctly predicted as with MNDO.

The most striking differences between the transition states calculated using the two methods is the marked asynchronicity suggested by the MNDO calculations. In contrast, the AM1 transition states are relatively symmetrical. Previous calculations by Dewar have shown MNDO to predict extremely unsymmetrical transition states for Diels–Alder reactions, even for butadiene + ethylene. AM1 (RHF), on the other hand, predicts the butadiene/ethylene transition state to be symmetrical. The (seemingly) artifactual behavior of MNDO has been attributed by Dewar to an overestimation of the repulsive interactions between atoms at intermediate (somewhat longer than bonding) distances. While extremely asynchronous reaction paths have been suggested for Diels–Alder reactions that could involve extremely well stabilized diradicals (as when cyano-substituted dieneophiles are used), extreme asychronicity seems unlikely in the present case.

Both AM1 and MNDO predict the exo transition state to be favored over the endo. As this is not in accord with

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Table III. AM1 Energetics for Several Diels-Alder Reactions[a]

		transition state			
		H_f		H_{act}	
diene	dienophile	endo	exo	endo	exo
butadiene	maleic anhydride	−25.4	−26.8	21.0	19.7
cyclopentadiene	maleic anhydride	−13.8	−14.9	25.5	24.4
cyclopentadiene	cyclopentadiene	108.5	107.3	34.4	33.2

[a] AM1 heats of formation for the reagents: butadiene, 29.9; cyclopentadiene, 37.1; maleic anhydride, −76.4.[12]

the experimental observations, we decided to further investigate the exo/endo selectivity. First, we calculated the relative energies of the endo and exo transition states using the MMX molecular mechanics program[9] with inclusion of π-interactions, using bond orders of 0.4 and 0.5 for the bonds that are forming in the transition state. MMX, also, predicts the exo transition state to be of lower energy (0.9 and 1.0 kcal/mol for bond orders of 0.4 and 0.5, respectively). We then investigated the effect of imposing synchronicity upon the reaction. When a MNDO calculation is performed with the constraint of synchronicity (both bonds being formed constrained to be equal), the endo structure is 1.0 kcal/mol more stable than the exo. This observation loses much of its significance when one considers that the energies of these structures are 8–10 kcal/mol higher than the optimized transition states, which in turn, are already much too high to agree with experimental observation. The only molecular orbital study in which the transition states have been directly calculated suggests that the endo transition states are favored over the exo.[10] Unfortunately, the transition states in question were not completely optimized. We have optimized one of the transition states from ref 10 (dimerization of cyclopentadiene). The activation energies are approximately 30 kcal/mol lower than the reported values for this reaction. The exo transition state was predicted to be favored in this case as well as two others (see Table III), contrary to the previous report. The transition states were symmetrical for all of these reactions except for the dimerization of cyclopentadiene where the partial bonds differed by 0.28 and 0.11 Å for the endo and exo transition states, respectively.

One should consider the possibility that the experimental preference for the endo product might be due to the differences between the condensed phase environment at elevated pressure in which the experiments were performed and the low-pressure gas phase that are modeled by the calculations. Pressure is known to affect the product distributions of Diels–Alder reactions.[11] It is worthy of note that even at 1 atm of pressure, the internal pressure within the solution can be quite high. It is possible that the preference for endo product often (but not always) observed in solution might be largely due to the differences in the volume of activation for the endo and exo adducts. If this is the case, these differences will not be manifest in theoretical modeling of gas-phase reactions. While the present calculations are not at a sufficiently high level to allow one to conclude that the endo preference is due to these effects, the three methods used here are in reasonable internal agreement both qualitatively and quantitatively. Careful determination of the activation parameters of gas-phase retro-Diels–Alder reactions could provide evidence in this domain.

Conclusion

Although some discrepancies remain to be clarified (such as the endo/exo selectivity), AM1 (but not MNDO) seems to be a reasonably well suited method for modeling Diels–Alder reactions. In addition, RHF calculations seem adequate, at least for reactions that are not likely to progress via a diradical mechanism.

Acknowledgment. This work was supported in part by grants from the U.S.–Spain Cooperative Research Program, "Comision Asesora de Investigacion Cientifica y Tecnica" (PB85-0244), and the PSC-BHE.

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[12] These results are in agreement with those reported in ref 7. They do not agree with some values given in ref 10.

Pathway of the Aluminum Chloride Induced Isomerization of *N*-(2-Hydroxyethyl)-2-phenylbenzylamine Hydrochloride

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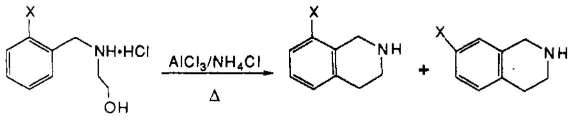
Received April 26, 1988

In previous work, we reported that the ring closure of **1b** in an aluminum chloride–ammonium chloride melt produced the 8-substituted 1,2,3,4-tetrahydroisoquinoline **2** (X = Cl) without any appreciable isomerization (eq 1).[1] When we applied the aluminum chloride cyclization to **1a**, however, we obtained 7-substituted 1,2,3,4-tetrahydroisoquinoline **3** (X = Ph) as the major product. This rearrangement raised two questions. Firstly, does the reorientation occur before or after cyclization? Secondly, is the migrating group the phenyl ring or the aminoalkyl side chain, or are both species involved in the transformation?



(1)

1a: X=Ph
1b: X=Cl
2
3

To address these questions, we explored the chemistry of *N*-(2-hydroxyethyl)-2-phenylbenzylamine hydrochloride (**1a**). Substituent-group migration occurred very readily in this compound (135 °C), whereas chlorination or cylization required more drastic temperature conditions (>180 °C). In fact, we were able to isomerize **1a** to obtain a mixture of *N*-(2-hydroxyethyl)-3- and -4-phenylbenzyl-

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