nitrogen at −10 °C for 2 h and then allowed to warm to 20 °C overnight. Aqueous workup as described for compounds **14–16**, followed by column chromatography on silica, eluent cyclohexane/toluene (3:1 v/v), gave the products. There were obtained the following:

Compound 17: an orange oil: 40 mg (26%); MS (DCI) 513 ($M^+ + 1$); NMR (δ_H, $CDCl_3$) 6.39 (2 H, s), 6.32 (4 H, s), 2.83 (4 H, t, J = 7.0 Hz), and 1.95 (2 H, pentet, J = 7.0 Hz).

Compound 18: an orange solid: 17 mg (11%); mp 124–126 °C; MS (DCI) 527 ($M^+ + 1$); NMR (δ_H, $CDCl_3$) 6.36 (2 H, s), 6.32 (4 H, s), 2.75 (4 H, m), and 1.74 (4 H, m). Anal. Calcd for $C_{16}H_{14}S_{10}$: C, 36.5; H, 2.7. Found: C, 36.3; H, 2.5.

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A Theoretical Study of Intramolecular Diels–Alder and 1,3-Dipolar Cycloaddition Stereoselectivity Using ab Initio Methods, Semiempirical Methods, and a Tandem Quantum Mechanic–Molecular Mechanic Method

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Diels–Alder and nitrile oxide intramolecular cycloadditions were studied using several methods. The structures found using all methods are similar when the forming bonds lengths are constrained, but the stereochemical predictions are quite different. The experimental stereochemical differences found for the parent Diels–Alder reactions forming 6-5 and 6-6 systems are rationalized. When the addends are linked by three methylene groups (formation of a five-membered ring), the strain in the transition structure (TS) causes the addends to twist about the forming bonds, resulting in a skewed TS as compared to the intermolecular TS. However, when the addends are linked by four methylene groups (formation of a six-membered ring), there is little strain in the TS, and the addends do not twist.

Introduction

The primary goal of this investigation was to determine the origins of the stereochemical preferences found for intramolecular nitrile oxide (INOC) and Diels–Alder (IDA) cycloadditions. This was accomplished by locating transition structures for the parent systems. The secondary goal was to determine a method for locating these transition structures that will satisfy both the necessary requirements for accuracy and cost. To do this, a tandem quantum mechanics (QM)/molecular mechanics (MM) methodology was evaluated. Interest in the intramolecular Diels–Alder cycloadditions arises from the wealth of available experimental results[1,2] and the utility of this type of reaction in synthesis. For two decades this reaction has been used for the formation of the hydrindan (5-6) and decalin (6-6) ring systems in the synthesis of natural products. The stereoselectivity of the 1,3,8-nonatrienes differs considerably from that of the 1,3,9-decatrienes depending on the substitution pattern (Table I). The study also included several examples of intramolecular nitrile oxide cycloadditions. This reaction is used for the synthesis of five- and six-membered rings fused to the heterocyclic isoxazoline ring.[3] Here no stereoisomers are possible in the absence of substituents, but the degree of flexibility of the forming five-membered ring will influence the stereoselectivity in substituted cases.

Both types of cycloadditions have been scrutinized previously[4] through the use of QM and MM. The previous approach involved QM to determine the intermolecular transition structure (TS) of the reaction and parameters

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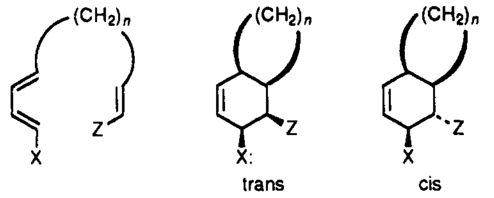
Table I. Stereoselectivities of Some Intramolecular Diels–Alder Cycloadditions of 1,3,8-Nonatriene and 1,3,9-Decatriene Systems



substituents		nonatrienes (n = 3)			decatrienes (n = 4)		
X	Z	T (°C)	trans:cis	$\Delta\Delta G^{\ddagger}$ [a]	T (°C)	trans:cis	$\Delta\Delta G^{\ddagger}$ [a]
H	H	190	25:75[b]	–1.0	190	47:53[b]	–0.1
H	CO_2Et	150	60:40[c]	0.3	155	51:49[d]	0.0
i-Pr	CO_2Et	150	72:28[c]	0.8	155	50:50[d]	0.0
Et_2N	CO_2Et	60	85:15[e]	1.1	40	55:45[e]	0.1
i-Pr	$CO_2Et\cdot AlCl_2Et$	25	>98:2[c]	>2.3	22	88:12[d]	1.2

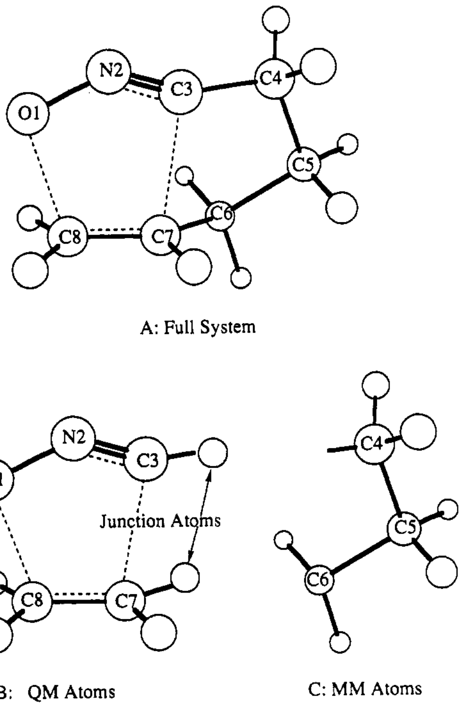
[a] $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$ (cis) – $\Delta G^{\ddagger}$ (trans) (kcal/mol). [b] Reference 2a. [c] Reference 2b. [d] Reference 2c. [e] Reference 2d.

to be used for MM2.[5] The side chain and/or substituents are then added to the TS, and the stabilities of isomeric TSs are determined by MM2. This method requires the reparameterization when substituents alter the basic TS geometry. The development of the parameters associated with forming and changing bonds is problematical in this method.

One possible improvement is a tandem QM/MM method, QUEST.[6] QUEST calculates the portion of the system undergoing bonding changes by QM and simultaneously calculates the remaining parts of the system with MM.

This partitioning is attractive because MM methods are several orders of magnitude less time-consuming than QM procedures. Early use of this approach involved the combination of semiempirical and empirical techniques.[7] This combination of methods was used in the investigation of electronic properties of model visual pigments[7a,b] and the investigation of strain energy of Michaelis complex and ionic intermediates in the carbohydrate hydrolysis by lysozyme.[7c] Recently, it has been shown that an empirical valence bond or a semiempirical approach could be effectively combined with MM to simulate complex systems.[7d–f]

Ab initio QM has also been combined with MM to investigate a variety of complex systems, such as the charge state of the His-Cys catalytic diad in papain,[8a] proton transfer in TIM,[8b] and the amide hydrolysis in solution and in trypsin.[8c] However, the ab initio QM/MM studies have not effectively coupled the geometry optimization of both methods as had the earlier semiempirical QM/MM approaches. Singh and Kollman rectified this with the development of a procedure for the coupling of G80 (UCSF)[9] and AMBER 3.0[10] which is called QUEST.[6] QUEST was applied to the study of the $CH_3Cl + Cl^-$ S_N2 exchange reaction and the gas-phase protonation of polyethers.[6]



A: Full System

B: QM Atoms C: MM Atoms

Figure 1. (A) Reaction scheme for the 1,3-dipolar nitrile oxide intramolecular cycloaddition. A representation of the intramolecular nitrile oxide cycloaddition with heavy atoms numbered. (B) The QM atoms and the junction atoms (darkened). The junction atoms are hydrogens which are added to satisfy the valences. (C) The MM atoms.

Several methods were employed in this study. QUEST was initially used because of a lack of computational resources; however, when resources became available ab initio studies were carried out. The new semiempirical methods, AM1[12] and PM3,[13] have been evaluated in these systems using MOPAC.[14] This allows for a comparison of many commonly used methods to QUEST.

Methods

Quest. The QUEST calculation has two phases. Phase 1 involves the development of an initial MM model for the

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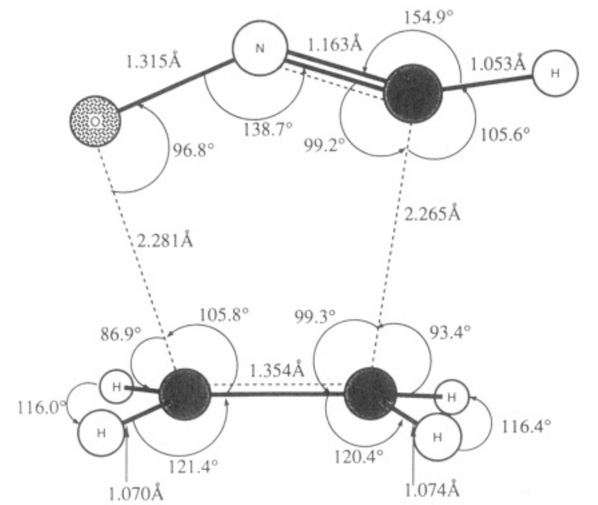

Figure 2. The 3-21G fulminic acid–ethylene transition structure.

entire intramolecular TS. The MM model is then refined and used as a starting point for the tandem QM/MM calculations. Phase 2 involves the development and refinement of the tandem model and splitting the molecule into QM and MM parts. Phase 1 involves constructing a model of the TS in internal coordinates using the PREP module in AMBER 3.0.[10] A topology file is then created using the EDIT and PARM modules. In order to create a topology file, parameters must exist for all bonds, angles, and torsions. Since parameters for the forming and changing bonds do not exist, these parameters are input based on the intermolecular TS. For example, consider the intramolecular nitrile oxide TS shown in Figure 1. There are no parameters for the equilibrium bond length, angles, or dihedral angles for the atoms associated with the forming and changing bonds, atoms 1–3, 7, and 8. An estimate for these parameters can be obtained from the 3-21G optimized intermolecular TS shown in Figure 2.[4b] Along with these equilibrium bond lengths and angles, the MM force constants used are those associated with product atom types. The parameters for the dihedral angles are less obvious, but since all of the heavy atoms in the TS lie in one plane, parameters are included to maintain this planarity and the ethylene unit is given reactant type dihedral parameters with about half the magnitude of the standard rotational barrier. The van der Waals (VDW) parameters come from the standard reactant types. The partial charges are usually calculated using the Gaussian-80 electrostatic routine (ESP),[15] but because of the nonpolarity of the MM part of the system, they were set equal to zero. This model is then refined for a given set of forming bond distances and used as an initial set of coordinates and forces for the tandem QM/MM procedure.

Phase 2 starts by specifying which atoms are "quantum mechanical" (QM set, atoms associated with 1–3, 7, and 8 (Figure 1)), which are "molecular mechanical" (MM set, atoms associated with 4–6), and which are "junction dummy atoms" (hydrogen replacing the carbons at 3 and 7 (Figure 1)). The junction atoms are necessary to satisfy the valences of the QM system and are the interface between the two systems. Starting from the refined coordinates generated in phase 1, gradients are calculated for the QM atoms including the junction atoms. The MM gradients from the previous optimization (those generated in phase 1) influence the QM gradients through the junction atoms. For example, C3 has a contribution to its gradient from the C3–C4 bond, the C3–C4–C5 angles, and the C3–C4–C5–C6 dihedral angle. The QM gradients are also affected by the van der Waals component of the nonbonded interactions with the remaining MM atoms but not with the electrostatic component of the nonbonded interactions, since the charges are set equal to zero. These combined gradients are used to optimize the geometry of the QM atoms until the root mean square (RMS) gradient on these atoms is less than some specified threshold. At this point, the MM atoms can be energy optimized while keeping the QM atoms fixed. This is the completion of one cycle for the tandem optimization, which is repeated until the charge in the structure and the energy achieve the desired threshold. In addition, simulated annealing can be performed on the MM atoms to search for other local energy minima in the MM surface.

The junction dummy atoms are part of the QM calculation and are influenced by gradients from the remaining QM atoms. The motion of the junction atoms is restricted by the presence of gradients on C3 from the MM gradients (see Figure 1). That is, in the QM system the gradient calculated for centers 2–3–4 is for N2–C3–H4. This gradient is averaged with the N2–C3–C4 from the MM gradient. Thus, the overlaps in the two gradient matrixes are averaged. In principle, one could attempt to correct for this duplication by appropriately scaling such gradients empirically, but such corrections are likely to lead to rather small effects on the calculated energies and geometries.

MM force constants involving one of the QM atoms must be set equal to zero, (e.g. C13–C3–C4 and C15–C13–C3–C4). This ensures that the total energy for any system is not overestimated by calculating an MM energy for the QM atoms, and it eliminates any need for estimated parameters. The optimization was then conducted on the QM atoms holding the forming bond lengths fixed. The calculation was run for 20 optimization cycles. If a significant change in the geometry of the QM atoms occurs, the MM atom positions were reoptimized while the QM atoms were held fixed. The QM optimization was then continued with the new position for the side chain. This iterative procedure was terminated once the change in energy for four successive cycles was less than 0.3 kcal/mol. This criterion was chosen because the usual criteria are difficult to satisfy because of gradient overlap. Since the forming bonds are fixed during the QM optimization, the "authentic" TS is not determined, but rather only one point on the potential energy surface. However, these model structures do relay some information as to the nature of the authentic TS.

Ab Initio TS. The INOC model TS determined by QUEST was used as a starting point. Each structure was optimized using G86[16] employing the 3-21G basis set while holding the forming bonds fixed. These stationary points were then refined to transition structures by using the OPT=(TS,CALCALL) method. The same procedure was used for locating the IDA TS, but in these cases both the STO-3G and 3-21G basis sets were used.

Semiempirical TS. The IDA 3-21G TS determined by the full ab initio methods was used as a starting point for the AM1[12] and PM3[13] studies. These structures were then optimized holding the forming bonds fixed. The resulting structures were then used as an initial point for the TS searching algorithm in MOPAC.[14] Every attempt made failed due to the formation of two negative eigenvalues.

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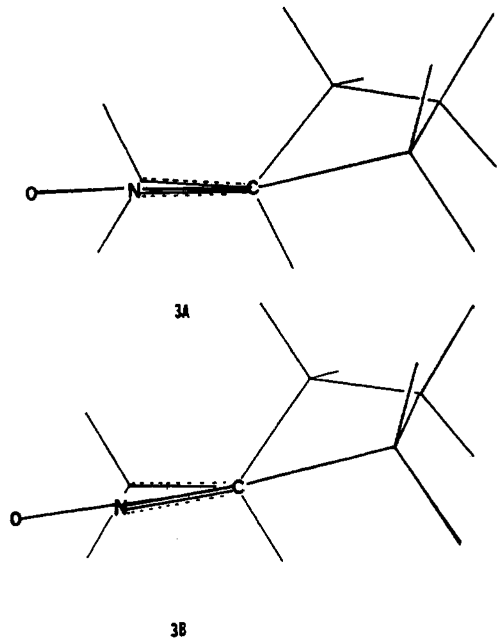

3A

3B

Figure 3. The two starting structures used for the QUEST optimization of the nitrile oxide cycloaddition. Structure 3A is the result of using rigid parameters and structure 3B is the result of using flexible parameters. The O1–C15–C13–C3 dihedral angles for 3A and 3B are 4.8° and 8.0°, respectively.

A manual search was undertaken by varying each forming bond independently from 1.8 to 2.4 Å. This procedure also led to no obvious potential surface leading to a TS. The only indication from the manual search was that the TS would be very unsymmetrical.

Results

Quest. Calculations were initiated on the fulminic acid–ethylene TS with a side chain consisting of three methylenes. In phase 1, two sets of parameters were employed to test the dependency of the initial model TS on the final tandem optimized model TS. The first parameter set maintained a rigid structure that only allowed for a slight twist after MM optimization, 3A, as shown in Figure 3. The second parameter set did not restricted the planarity of the fulminic acid–ethylene moiety; a weak bond stretching force constant, approximately one-sixth of the product value, was given to the forming C–O bond. These parameters were chosen because they gave a great deal of flexibility to the model TS and also gave a reasonable starting structure. The resulting structure after MM minimization, 3B, is shown in Figure 3. The major differences between 3A and 3B is that the latter is twisted more, causing the forming C–O bond in 3B to be stretched out to 2.5 Å. For the QM optimization, both model TSs were given the same forming bond lengths, 2.3 Å for C–C and 2.5 Å for C–O. These distances were chosen empirically and were only used for test purposes. For the TS models the bond lengths were modeled after those of the intermolecular TS.[4a]

The outcome of the initial nitrile oxide optimization starting from structures 3A and 3B was that both starting structures converged to similar structures. After 60 QM optimization cycles, the equilibrium bond lengths, bond angles, and dihedral angles are within 0.05 Å, 1.0°, and 2.0°, respectively. This result indicates that the final results are not dependent on the accuracy of the model structure chosen to start the tandem optimization. However, it is every important that the starting structure must be close to the model TS or it will not converge to the model TS.

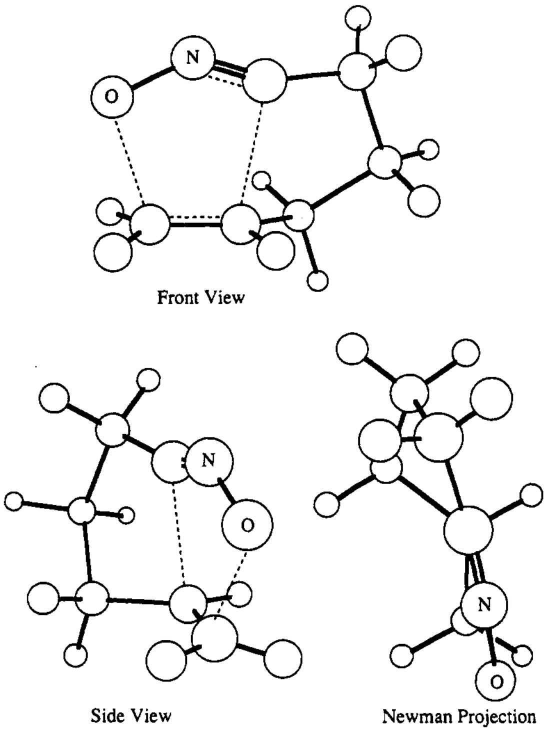

Figure 4. The front, side, and top views of the QUEST optimized nitrile oxide structure with forming C–C and O–C bond lengths at 2.265 and 2.18 Å, respectively. The O1–C8–C7–C3 dihedral angle is 13.4°. The top view is a Newman projection down the forming C–C bond.

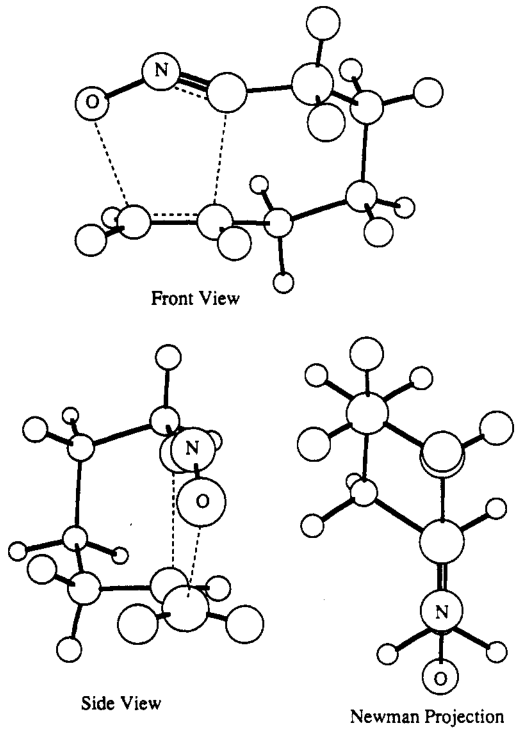

Figure 5. The front, side, and top views of the QUEST optimized nitrile oxide structure with forming C–C and O–C bond lengths of 2.265 and 2.181 Å, respectively. The O1–C8–C7–C3 dihedral angle is 2.1°. The top view is a Newman projection down the forming C–C bond.

The starting structures containing side-chains with three and four methylene units were optimized using AMBER 3.0[10] with the parameters used to optimize 3B. The forming bond distances were both set to those found for the intermolecular TS, shown in Figure 2. The QM was then run for 40 optimization cycles. The resulting struc-

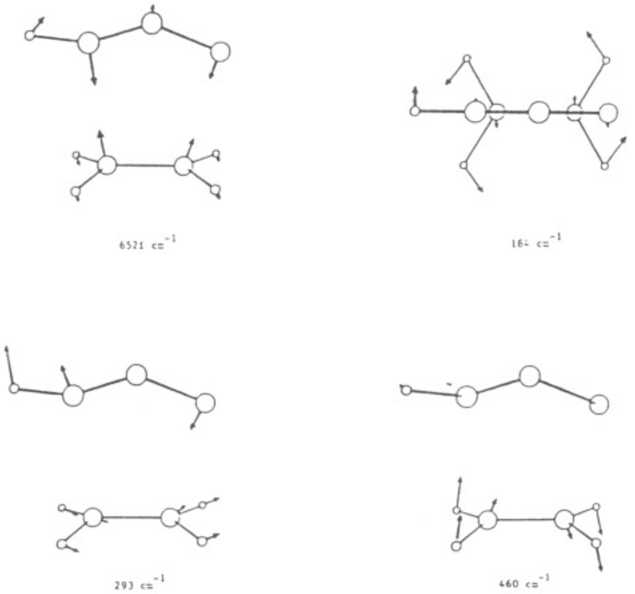

Figure 6. The imaginary and three lowest energy vibrational modes for the 3-21G intermolecular fulminic acid–ethylene transition structure.

tures show different amounts of twist motion, Figures 4 and 5. The results of the two different TS calculations suggest that the influence of the side chain on the TS can be expressed as a function of two overlapping gradients. The stress that is present for the forming of the five-membered ring is apparent from the distortion in the QM atoms. The structure is no longer planar, but is twisted by 13°. The O1–N2–C3–C4 dihedral angle is not 180°, as is the case for the intermolecular TS, but is now 160° (Figure 4). By contrast, the structure associated with the formation of the six-membered ring is distorted very little. The structure is twisted by approximately 2°, and the O1–N2–C3–C4 dihedral is 178° (Figure 5). The twisting motion was expected based on the low-energy vibrational modes found for the intermolecular TS (Figure 6).[46]

For the intramolecular Diels–Alder systems, the division of the atoms into QM and MM groups is performed in the same fashion as for the nitrile oxide cases. The QM atoms are those atoms associated with the intermolecular TS, and the MM atoms are those atoms in the side chain. The junction atoms (hydrogens) are substituted for those carbon atoms which connect the intermolecular TS and the side chain in order to satisfy the valences for the QM calculations. In phase 1, the parameters for the atoms involved with forming the changing bonds are based on the STO-3G butadiene–ethylene TS[17a] with the forming bond length being set at 2.2 Å. The forming bond stretching force constants were set equal to half the product value. The dihedral angle for the changing bonds were given reactant values, and all of the dihedral angles associated with the forming bonds were set equal to zero. As before, a model for the TS were built and refined by AMBER 3.0.[10] In phase 2, the parameters associated with the QM atoms are set equal to zero. The tandem optimization is carried out as previously described, but in these cases the QM calculations used the STO-3G basis set.

The resulting QUEST structures for the nonatriene and decatriene are given in Figures 7 and 8, respectively. The ΔE for nonatriene is 1.1 ± 0.5 kcal/mol favoring the cis structure (endo TS), and the ΔE for decatriene is 0.2 ± 0.5 kcal/mol favoring the cis structure (Table II). The error limits are estimated based on the 0.3 kcal/mol errors

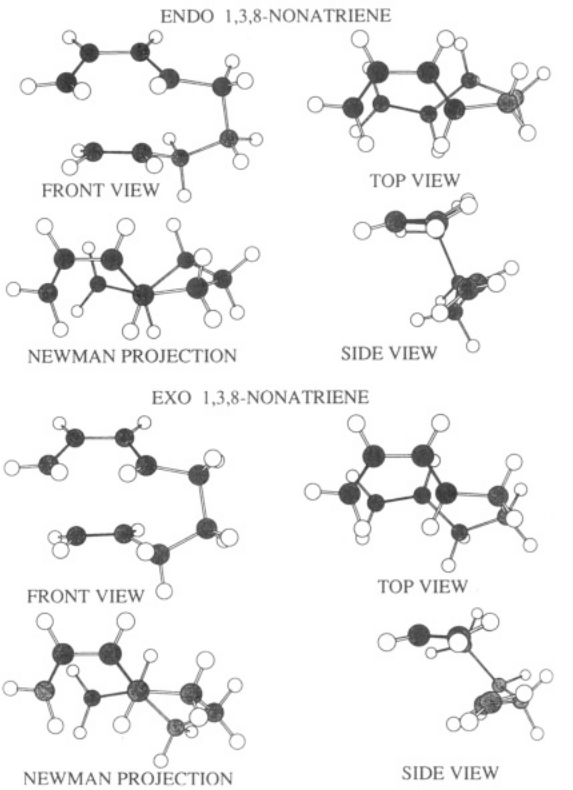

Figure 7. Front, side, and top views, and a Newman projection along the interior forming C–C bond for the QUEST-optimized 1,3,8-nonatriene structures with forming C–C bond lengths of 2.2 Å. The exo (bottom) and endo (top) structures give trans and cis products, respectively.

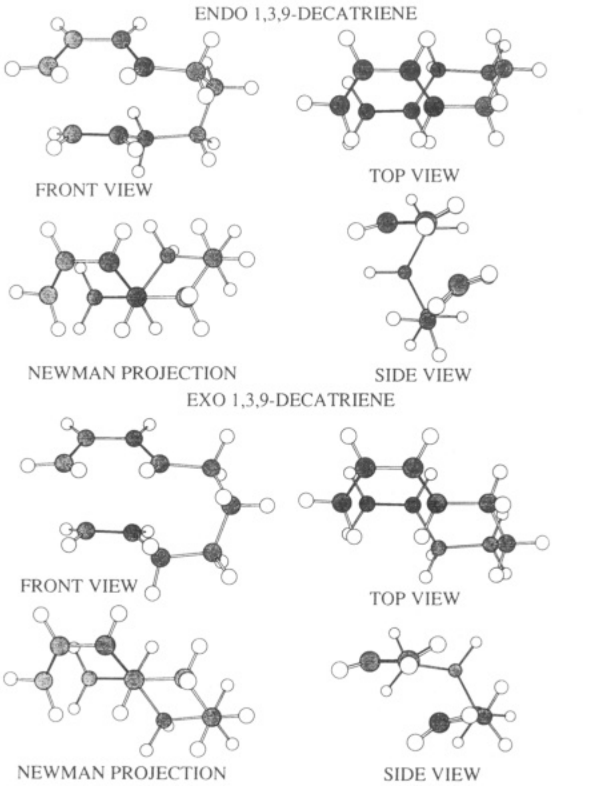

Figure 8. Front, side, and top views, and a Newman projection along the interior forming C–C bond for the QUEST-optimized 1,3,9-decatriene structures with forming C–C bond lengths of 2.2 Å. The exo (bottom) and endo (top) structures give trans and cis products, respectively.

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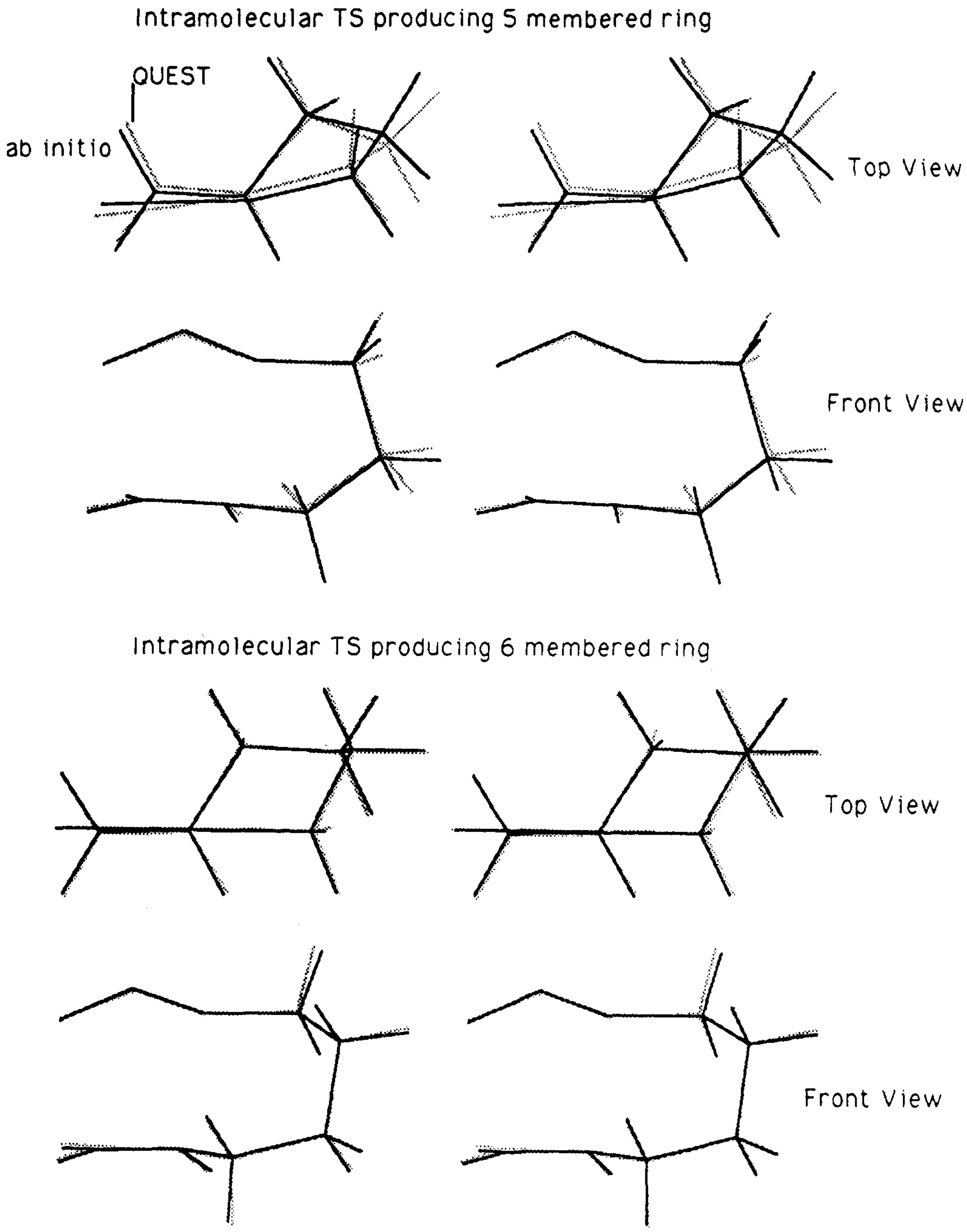

Figure 9. A top stereoview of the superimpositions of the 3-21G (dark) and QUEST (light) TS. The top overlay is of the system forming a five-membered ring (RMS deviation in the heavy atom of 0.11 Å) and the bottom overlay is of the system forming the six-membered ring (RMS deviation in the heavy atom of 0.06 Å).

associated with the QUEST optimization. The ΔE determined for these systems can only be interpreted qualitatively. The nonatriene system always favors endo, while the decatriene system shows no significant selectivity.

The forming five-membered ring of nonatriene exerts more stress on the TS than does the forming six-membered ring of decatriene, which is obvious from Figures 7 and 8. The nonatriene structures are twisted more than the decatriene structures, and the twisting motion is very similar to that found in earlier MM2 studies.[6] However, the *cis*-nonatriene structure is not twisted as much as expected. The butadiene–ethylene moiety is similar to the intermolecular TS. That is, the obtuse angle of attack and the pyramidalization at the termini of the addends is nearly the same (Figures 7 and 8).[17]

As predicted, the interior forming bond is a pivot which forces the exterior forming bond to move in an endo fashion (destabilizing) for the trans TS and in an exo (stabilizing) fashion for the cis TS.[4] Even the subtle effects found in the earlier MM2 modeling are realized in these models. That is, the *cis*-decatriene TS has a slight twist which is the result of relieving VDW strain between C3 and C6, not ring strain as it is in the nonatriene system.[4] This is also reflected in the MM energies for both cases being higher for the cis TSs, indicating that the side chain has more strain in it and/or more nonbonded interaction with the QM atoms. However, the QM energies for both systems favor the cis TS, reflecting the electronic destabilization of the exo TS.

Ab Initio TS. To check the validity of the QUEST results for INOC systems, the 3-21 G TS were located. (The TS geometries are given in full in the supplementary material.) The similarity between the QUEST and the 3-21G TSs is striking, as shown in Figure 9. The ab initio TSs show the same degree of deformation about the C=N bond and twisting about the forming bonds as do the QUEST TSs. There are no major discrepancy between the TSs in the degree of pyramidalization of the ethylene or

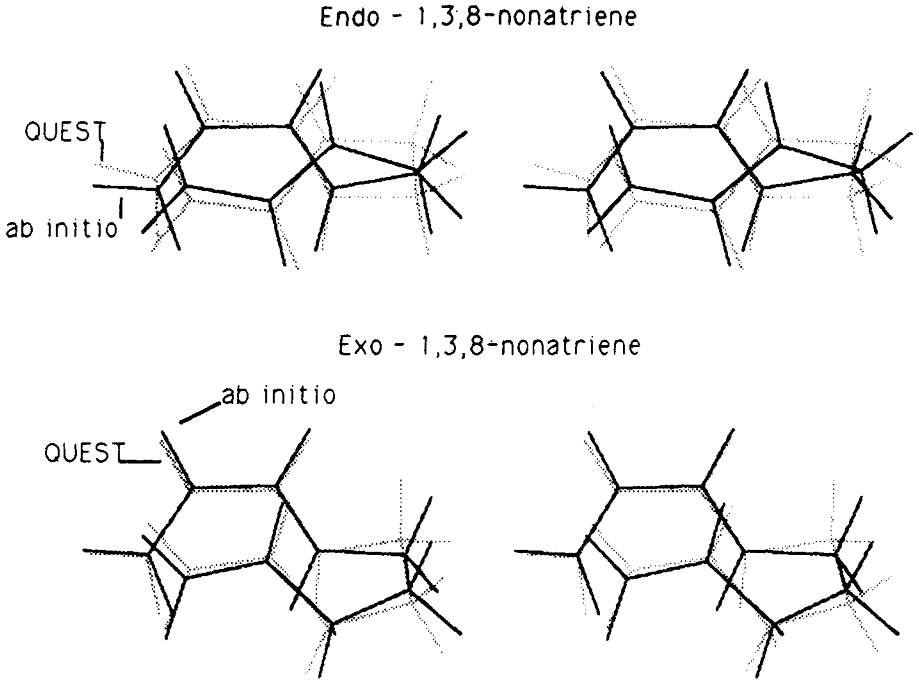

Figure 10. Top stereoviews of the superimpositions of the 3-21G (dark) and QUEST (ligh) 1,3,8-nonatriene transitions structures (RMS deviation in the heavy atom for the endo and exo TS of 0.27 and 0.17 Å, respectively).

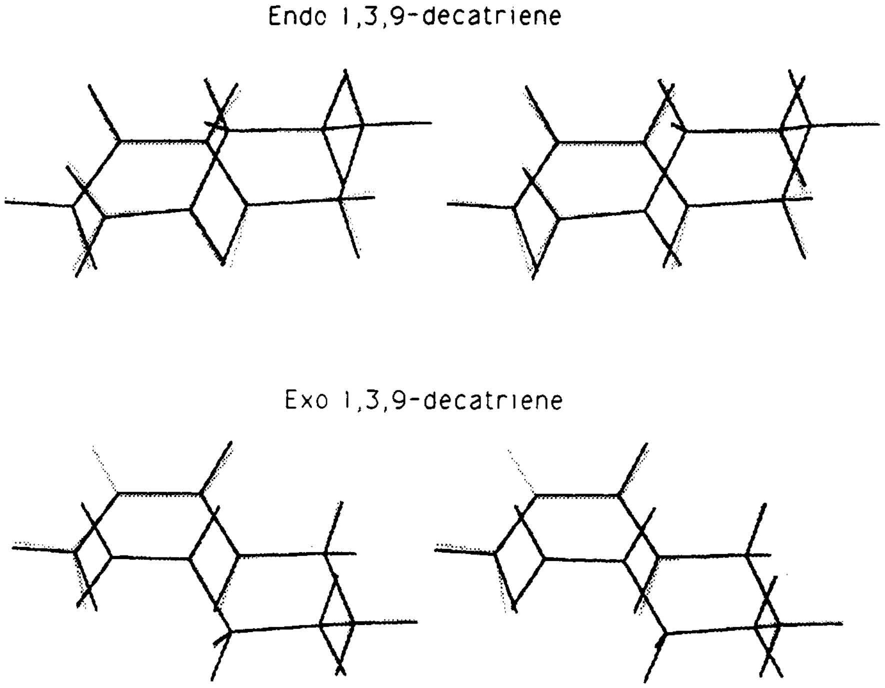

Figure 11. Top stereoviews of the superimpositions of the 3-21G (dark) and QUEST (light) 1,3,9-decatriene transitions structures (RMS deviation in the heavy atom for the endo and exo TS of 0.04 and 0.04 Å, respectively).

the bending about the fulminic acid moiety. The only significant difference is the forming bond lengths which differ by less then 0.07 Å. The difference in the forming bond length is due to the fact that the QUEST calculations were not TS searches and were based on the intermolecular TS.

To check the validity of the QUEST results for IDA systems, the STO-3G and 3-21G TSs were located. (The TSs geometries are given in full in the Supplementary Material.) The TSs found using QUEST and full ab initio methods are compared in Figures 10 and 11. The bond lengths, angles, and dihedral angles found are similar regardless of the method or level used. The strained TS relieves stress through a twist motion about the forming bonds which is consistent with the low-energy vibrational modes found for the intermolecular TS.[17] The twist for the nonatriene systems is 8–15° and the twist for the decatriene systems is 1–3°.

The ΔE for the 6-5 and 6-6 systems at the STO-3G, 3-21G, and 6-31G* levels are given in Table II. The usual basis set dependence found for the accuracy of the activation energies are reflected in the ΔE found for these systems. At the lowest level of theory, the ΔE is only in qualitative agreement with experiment, but at the higher levels of theory, the ΔE is in excellent agreement with experiment. Again, the ΔEs should be interpreted in view of the experimental data, no significant selectivity in the decatriene system, and a strong preference for the cis

Table II. Relative Energies[a] (kcal/mol) of the QUEST and ab Initio Intramolecular Transition Structures of 1,3,9-Decatriene and 1,3,8-Nonatriene

	1,3,9-decatriene		1,3,8-nonatriene	
basis set	endo (cis)	exo (trans)	endo (cis)	exo (trans)
QUEST	0.0	0.18	0.0	1.07
STO-3G	0.24	0.0	0.0	0.17
3-21G	0.0	0.04	0.0	0.70
6-31G*//3-21G[b]	0.18	0.0	0.0	0.99
AM1//3-21G[c]	1.39	0.0	0.0	0.40
PM3//3-21G[d]	1.26	0.0	0.0	0.17
experimental	0.0	0.10	0.0	1.03

[a] The error limits associated with these relative energies for the QUEST, semiempirical, and ab initio calculations are ±0.5, ±0.1, and ±0.1 kcal/mol, respectively. [b] This calculation represents a single-point calculation at the 6-31G* level for the geometry found for the 3-21G TS. [c] This calculation represents an optimized stationary point calculation using AM1 fixing the forming bonds to that found for the 3-21G TS. [d] This calculation represents an optimized stationary point calculation using PM3 fixing the forming bonds to that found for the 3-21G TS.

isomer in the nonatriene system. These preferences can be alter dramatically based on the substitutions as indicated in Table I.

Semiempirical TS. The structures were optimized employing both AM1[12] and PM3[13] holding the forming bond lengths fixed to those found for the authentic ab initio structures for all cases. The resulting structures were nearly identical to those determined by the ab initio methods. However, these stationary points had two negative eigenvalues. A local transition structure search was carried out both by automated procedures found in MOPAC and by a systematic variation of the forming bonds. No transition structures resembling the ab initio structures were found. The systematic procedure indicated that a very unsymmetrical structure was favored. The ΔE for the IDA systems, constrained to the ab initio forming bond lengths, was quite inaccurate. This is reminiscent of semiempirical calculations on the intermolecular systems, where constrained symmetric geometries are reasonable but the energies are not.[4b]

Conclusion

These studies provide evidence that the QM/MM method correctly predicts structural features found in the ab initio TS. The good agreement between the full ab initio and QUEST structures demonstrates that a highly coupled and highly strained system can be qualitatively studied using the combined gradient method in QUEST.

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Supplementary Material Available: Internal and cartesian coordinates of the QUEST and ab inito 3-21G fulminic acid-ethylene intramolecular transition structures and internal and cartesian coordinates of the QUEST and ab initio STO-3G and 3-21G determined Diels–Alder intramolecular transition structures (34 pages). This material is contained in many libraries on microfiche, immediately following this article in the microfilm version the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Effect of Multiple Halide Substituents on the Acidity of Methanes and Methyl Radicals. Electron Affinities of Chloro- and Fluoromethyl Radicals

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Ab initio molecular orbital calculations are reported for methanes, methyl radicals, and methyl anions CH_mF_n and CH_mCl_n where n takes values from 0 to 3, and for mixed halides $CH_mF_nCl_p$ where $(p + n)$ takes values from 1 to 3. Structures were optimized at HF/6-31++G(d,p), and single-point calculations are reported at MP4SDTQ/6-31++G(d,p) and, for the smaller molecules, at MP4SDTQ/6-311++G(2df,p). For methyl anions containing chlorine atoms optimization at the Hartree–Fock level gave unrealistically long bond lengths, and more satisfactory structures were obtained by including correlation energy in the optimization calculations (MP2/6-31++G(d,p)). Stabilization energies for isodesmic reactions of the type $X_nCH_m + (n - 1)\ CH_{m+n} \rightarrow nXCH_{(m+n-1)}$ show geminal interactions to be largest between F atoms in methyl anions (in CF_3^-, 43.1 kcal/mol), somewhat smaller between F atoms in methanes and methyl radicals (in CHF_3, 26.7 kcal/mol; in CF_3, 16.6 kcal/mol), very small between Cl atoms in anions (in CCl_3^-, 5.3 kcal/mol) and negligible in chloromethanes (in $CHCl_3$, −0.7 kcal/mol). The acidity of methane increases by approximately 19 kcal/mol for every additional Cl substituent; i.e., the effect of multiple substitution is roughly additive. One F atom increases the acidity of methane by only 10.4 kcal/mol, two by an *additional* 14.9 kcal/mol, and three by a further 21.7 kcal/mol; i.e., in the fluoromethanes, F–F interactions have a synergistic effect. Electron affinities evaluated from isodesmic reactions using energies from MP4SDTQ/6-311++G(2df,p) molecular orbital calculations are within 0.03 eV of the experimental values for CH_3 and CH_2Cl. This same level of theory gives calculated electron affinities for CHF_2 of 0.79 eV and for CH_2F of 0.27 eV.

In organic molecules, halogens function as powerful σ-acceptors and somewhat weaker π-donors.[1,2] In carbanions, σ-withdrawal to the halogen assists in delocalizing the negative charge onto the more electronegative sub-

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