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# Transition Structures for Conjugate and Carbonyl Additions of Cyanide to *s-cis-* and *s-trans*-Acrolein. An ab Initio MO Study

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**Abstract:** Transition structures for the addition of cyanide anion to *s-cis-* and *s-trans*-acrolein and to ethylene and formaldehyde have been located with ab initio MO calculations with use of the 3-21G and 6-31+G* basis sets. Energies of all stationary points, including reactants, ion–dipole complexes, and products, were evaluated at the second-order Møller–Plesset correlation level with the 6-31+G* basis set. The relative reaction barriers for conjugate and carbonyl additions are discussed for gas-phase and solution-phase reactions. Calculations predict that, in the gas phase, the reaction barrier for conjugate addition to *s-cis*-acrolein is slightly higher than that for carbonyl addition, whereas the reverse situation is found for addition to *s-trans*-acrolein. The conjugate addition products are also more stable than the carbonyl addition products. The reaction barrier for carbonyl addition is expected to become smaller than that for conjugate addition in solution, under which conditions the difference in the stabilities of the conjugate and carbonyl products should become relatively small.

## Introduction

Nucleophilic additions to $\alpha,\beta$-unsaturated carbonyl compounds are valuable reactions in the synthetic repertoire of organic chemists and are mechanistically intriguing processes as well.[1,2] An $\alpha,\beta$-unsaturated carbonyl substrate is an ambident electrophile to which nucleophilic additions can take place either at the carbonyl carbon (carbonyl or 1,2-addition) or at the $\beta$-carbon (conjugate or 1,4-addition). There has been a wealth of studies made on the factors controlling the regiochemistry of attack in solution, and many hypotheses have been proposed to rationalize the modes of nucleophilic additions.[3-8] There is ample evidence suggesting that the use of different solvents and counterions can influence regioselectivity. Conjugate addition generally affords more stable products, although carbonyl addition is often faster. Highly resonance stabilized carbanionic nucleophiles tend to favor conjugate addition. It is believed that carbonyl addition is likely a reversible process and that the more stable product from conjugate addition will finally predominate under conditions of thermodynamic control.[5,6]

Anh and co-workers have proposed a theoretical interpretation based on frontier molecular orbital (FMO) theory.[7,8] The atomic orbital coefficient of the LUMO of an $\alpha,\beta$-unsaturated carbonyl substrate is larger at the $\beta$-carbon than at the carbonyl carbon.[8,9] Since the dominant stabilizing interaction is between the HOMO of the nucleophile and the LUMO of the $\alpha,\beta$-unsaturated compound, it follows that this interaction favors conjugate addition over carbonyl addition. For a highly resonance stabilized carbanion, this frontier orbital interaction is generally more important than electrostatic effects, and thus conjugate addition is faster than carbonyl addition. However, Coulombic interactions become predominant for localized carbanions, and carbonyl addition is then expected. Interestingly, calculations have shown that the carbonyl carbon can have a larger LUMO coefficient than the $\beta$-carbon when the $\alpha,\beta$-unsaturated carbonyl substrate is protonated or coordinated with a Lewis acid,[9] thereby indicating that frontier orbital interactions can favor carbonyl attack over conjugate attack under such conditions. This has raised some interesting questions concerning the effect of cations and the role of HOMO–LUMO interactions in controlling regioselectivity.[4]

Although reactions in which conjugate addition is faster than carbonyl addition have been observed in some cases,[7c,10,12,13] these reactions involved the addition of lithium reagents in solution. It is well-known that lithium reagents are aggregated in solution and that the extent of aggregation depends on the nature of solvent and temperature.[11] Ogura et al. have reported that some lithium reagents undergo faster conjugate addition at −78 °C, while carbonyl addition of the same reactants is faster at 0 °C in the same solvent.[12] Cohen et al. recently reported another example where faster conjugate addition occurs only at low temperature. They attribute these results to the tendency of contact and solvent-separated ion pairs to undergo respectively carbonyl and conjugate addition.[13a] Recent experimental studies have revealed, however, that certain enolate anions also undergo faster carbonyl addition at low temperatures.[13b]

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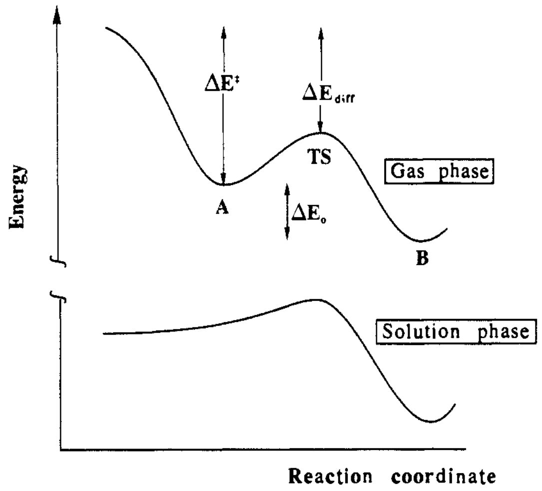

**Figure 1.** Schematic energy profiles of nucleophilic addition reactions in the gas phase (top) and in solution phase (bottom).

Gas-phase studies of these reactions offer the advantage of being able to probe the intrinsic reactivity and selectivity without complications due to solvation. Such studies will not only help to develop a better understanding of the nature of these reactions but should also shed light on the effects of solvent molecules on the reaction. Several attempts have been made to study gas-phase additions of various nucleophiles to $\alpha,\beta$-unsaturated carbonyl compounds.[14-17] In a flowing afterglow apparatus, cyclopentadienylidene anion radical and the cyclopentadienyl anion both add to acrylonitrile and methyl acrylate by conjugate Michael addition.[14] The helium buffer gas pressure used in these experiments was, presumably, sufficiently high (ca. 0.4–0.9 Torr) to remove excess energy from the conjugate addition adducts, thereby enabling them to be observed.

In contrast, the reaction of methoxide anion with acrylonitrile in a trapped ICR spectrometer leads only to proton transfer and not to conjugate addition.[15] The failure to detect any addition products is probably due to the very low pressure used in the experiment. Consequently, any formed adduct cannot rid itself of the excess energy sufficiently rapidly to prevent either back dissociation to reactants or fragmentation into other products.

However, Michael addition to acrylonitrile and nitroethylene could be observed with monosolvated methoxide anion [$MeO^-\cdots HOMe$] in place of methoxide anion as nucleophile.[15] In a related ICR study, Bowie and co-workers found the reactions of acrolein with fluoride ion donors $CF_3O^-$ and [$F\cdots HOMe$] to give observable [$M + F^-$] ions and with $MeO^-$ and [$MeO^-\cdots HOMe$] to yield [$M + MeO^-$] adducts. The structures of these adducts were not determined.[16] Unfortunately, no adducts were observed for the reaction of anionic nucleophiles with methyl vinyl ketone and acrylonitrile with ICR spectrometry, again possibly due to the low-pressure regimes used.[17]

Ab initio MO calculations provide additional means to study these problems quantitatively. Results from such studies can then be used to develop reliable parameters for carrying out molecular simulations for these reactions in solution.[18] Weinstein and co-workers have reported ab initio MO studies for the conjugate additions of $F^-$ to acrylic and methacrylic acids, but the issue of regiochemistry was not addressed in their studies.[19a,b] Theoretical studies have recently been reported on the reactions of methylcopper and methyllithium with acrolein.[19c]

The top curve in Figure 1 shows the potential energy diagram for a typical ion–molecule addition reaction involving a double-well potential in the gas phase.[20] For the nucleophilic addition of $Nu^-$ to an $\alpha,\beta$-unsaturated carbonyl substrate, the first local minimum, *A*, corresponds to an ion–molecule complex formed by attractive ion–dipole and ion–induced dipole forces. The second minimum, *B*, corresponds to the final addition product, separated from the ion–molecule complex by a central barrier. The overall rate of reaction depends, in part, on the collision rate of the reactants and the height of the barrier leading to the formation of the addition products.[20] RRKM theory can be employed to relate the potential energy surface to the gas-phase reaction rates, and important energetic parameters such as $\Delta E^{\ddagger}$ and $\Delta E_{diff}$ can be estimated experimentally.[20] Marcus theory has been successfully applied to a number of gas-phase reactions, such as methyl transfer ($S_N2$) reaction and other reactions.[21-23]

Simulation of the solution reaction is complicated, although qualitative information can be predicted from interactions of the reaction system with a few solvent molecules at each stationary point. Since the isolated reactants, ion–molecule complexes, and products in anionic addition reactions bear largely localized negative charges, solvation of these species is expected to be substantial.[18] On the other hand, the transition structure corresponding to the central barrier should exhibit substantial delocalization of the negative charge, and therefore, solvation of this species is relatively small, compared to reactants, complexes, and products. The potential surface for the corresponding reaction in solution phase should therefore resemble that shown at the bottom of Figure 1.

Our goal herein is to determine the gas-phase reaction potential surface for the reaction of cyanide anion with acrolein using ab initio MO theory and to locate structures and energies of various conformations of the ion–molecule complexes, transition structures, and products. For comparison, we have also located various stationary points for the reactions of cyanide anion with ethylene and formaldehyde. These calculations provide insights into the potential energy surface of these reactions, a first step toward the full understanding of reactions of this type in solution.

## Computational Methods

Ab initio MO calculations were performed with the GAUSSIAN 86 series of programs.[24] All the geometries of the reactants, complexes, transition structures, and products were fully optimized at the restricted Hartree–Fock (HF) level with the split-valence 3-21G basis set.[25] Transition structures were fully characterized through harmonic vibrational frequency analysis. Energies of the stationary points were further evaluated through inclusion of electron correlation with use of second-order Møller–Plesset (MP2) theory[26] and the 6-31+G* basis set,[27] which includes polarization and diffuse functions. These calculations, in which only valence orbitals were used in the correlation (frozen-core (FC) approximation), are designated as MP2/6-31+G*//3-21G. In order to check the reliability of the 3-21G optimized structures, all six transition structures for the addition reactions of cyanide anion to acrolein,

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**Table I.** Negatives of the Total Energies (hartrees) and Relative Energies (kcal/mol) of Stationary Points on the Cyanide Anion plus Acrolein Potential Energy Surface

| structure | HF/3-21G/ 3-21G | HF/3-21+G// 3-21G | HF/6-31G*// 3-21G | HF/6-31+G*// 3-21G | MP2(FC)[b]/ 6-31+G*// 3-21G | HF/6-31+G*// 6-31+G* | MP2(FC)[b]/ 6-31+G*// 6-31+G* |
|---|---|---|---|---|---|---|---|
| **1** | 281.45594 (21.9) | 281.53152 (19.3) | 283.05488 (17.6) | 283.08381 (14.6) | 283.92688 (25.2) | | |
| **2** | 281.46688 (15.0) | 281.54169 (12.9) | 283.06366 (11.8) | 283.09236 (9.2) | 283.93580 (19.6) | | |
| **3** | 281.46730 (14.7) | 281.54278 (12.3) | 283.06419 (11.5) | 283.09310 (8.7) | 283.93751 (18.5) | | |
| **4** | 281.46639 (15.3) | 281.54323 (12.0) | 283.06495 (11.0) | 283.09401 (8.2) | 283.93752 (18.5) | | |
| **5** | 281.47137 (12.2) | 281.54831 (8.8) | 283.07057 (7.5) | 283.09941 (4.8) | 283.94258 (15.3) | | |
| **6** | 281.46899 (13.7) | 281.54621 (10.1) | 283.06829 (8.9) | 283.09771 (5.8) | 283.94136 (16.1) | | |
| **7** | 281.46097 (18.7) | 281.53841 (15.0) | 283.06106 (13.4) | 283.09062 (10.3) | 283.93582 (19.6) | | |
| **8** | 281.45509 (22.4) | 281.53470 (17.3) | 283.05631 (16.4) | 283.08753 (12.2) | 283.92952 (23.5) | | |
| **9** | 281.46227 (17.9) | 281.54069 (13.6) | 283.06276 (12.4) | 283.09268 (9.0) | 283.93701 (18.8) | | |
| **10** | 281.44781 (27.0) | 281.52446 (23.8) | 283.04825 (21.5) | 283.07821 (18.1) | 283.92246 (28.0) | | |
| **11** | 281.45066 (25.2) | 281.52744 (21.9) | 283.05085 (19.8) | 283.08074 (16.5) | 283.92522 (26.2) | | |
| **12** | 281.45224 (24.2) | 281.52790 (21.6) | 283.05181 (19.2) | 283.08091 (16.4) | 283.92672 (25.3) | | |
| **13**[a] + CN⁻ | 281.43984 (32.0) | 281.52528 (23.2) | 283.04443 (23.9) | 283.08038 (16.7) | 283.92170 (28.4) | | |
| **14**[a] + CN⁻ | 281.43983 (32.0) | 281.52768 (21.7) | 283.04722 (22.1) | 283.08389 (14.5) | 283.92495 (26.4) | | |
| **15** + CN⁻ | 281.42569 (40.8) | 281.51330 (30.8) | 283.03392 (30.5) | 283.07087 (22.7) | 283.91265 (34.1) | | |
| **16** | 281.45297 (32.7) | 281.53328 (18.2) | 283.04827 (21.4) | 283.07420 (20.6) | 283.93500 (20.1) | | |
| **17** | 281.44599 (28.1) | 281.53268 (18.6) | 283.04679 (22.4) | 283.07451 (20.4) | 283.93350 (21.0) | | |
| **18** | 281.43809 (33.1) | 281.52454 (23.7) | 283.03900 (27.3) | 283.06701 (25.1) | 283.92812 (24.4) | | |
| **19** | 281.43869 (32.7) | 281.52543 (23.1) | 283.04007 (26.6) | 283.06838 (24.2) | 283.92826 (24.3) | | |
| **20** | 281.45140 (24.7) | 281.52556 (23.1) | 283.04727 (22.1) | 283.07369 (20.9) | 283.92836 (24.3) | 283.07277 (0.0) | 283.92774 (0.0) |
| **21** | 281.44921 (26.1) | 281.52265 (24.9) | 283.04392 (24.2) | 283.07072 (22.8) | 283.92305 (27.6) | 283.06976 (1.9) | 283.92314 (2.9) |
| **22** | 281.44323 (29.8) | 281.52207 (25.3) | 283.04175 (25.5) | 283.06764 (24.7) | 283.92575 (25.9) | 283.06870 (2.6) | 283.92437 (2.1) |
| **23** | 281.44898 (26.2) | 281.52280 (24.8) | 283.04331 (24.6) | 283.06785 (24.6) | 283.92652 (25.4) | 283.06956 (2.0) | 283.92567 (1.3) |
| **24** | 281.49078 (0.0) | 281.56232 (0.0) | 283.08245 (0.0) | 283.10700 (0.0) | 283.96701 (0.0) | | |
| **25** | 281.48402 (4.2) | 281.55636 (3.7) | 283.07851 (2.5) | 283.10267 (2.7) | 283.96199 (3.2) | | |

[a] Energy of acrolein from ref 31. [b] FC = frozen core.

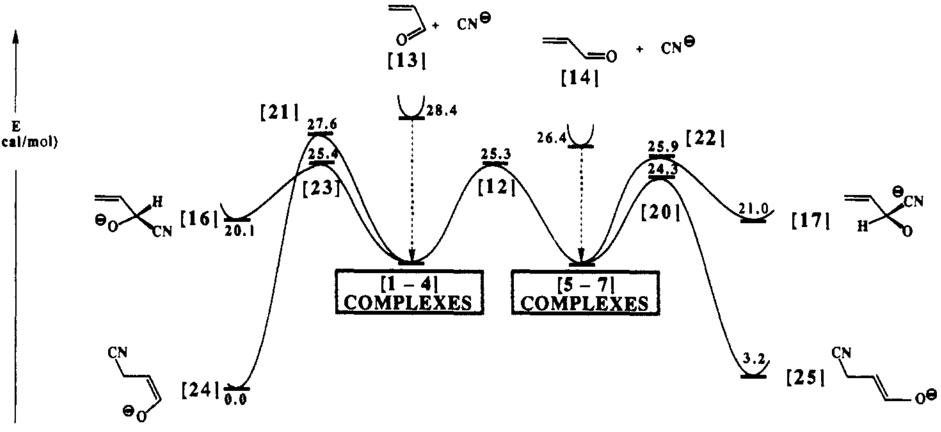
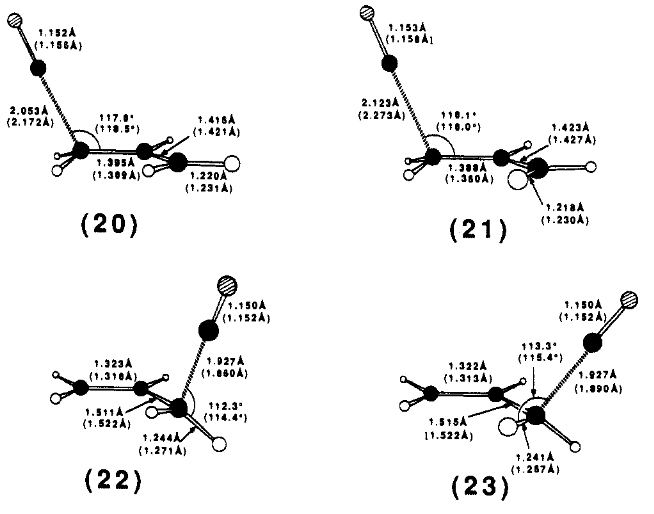


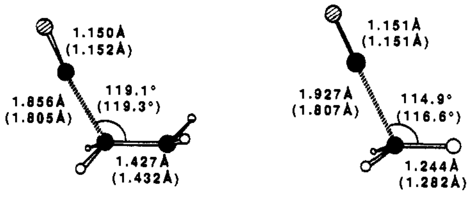
**Figure 2.** The MP2(FC)/6-31+G*//HF/3-21G energetics (kcal/mol) for the addition of cyanide anion to *s-cis*- and *s-trans*-acrolein.



(20) (21) (22) (23)

**Figure 3.** The 6-31+G* optimized transition structures for the addition of cyanide anion to s-cis and s-trans acrolein. The 3-21G values are shown in parentheses. o hydrogen; ○ oxygen; ▨ nitrogen; ● carbon.

ethylene, and formaldehyde were further optimized with the 6-31+G* basis set, and the energies were evaluated at the MP2/6-31+G*//6-31+G* level. Calculations of charge densities were carried out with use of the Weinhold Natural Population analysis method at the HF/3-21G level.[28]



(26) (27)

**Figure 4.** The 6-31+G* optimized transition structures for the addition of cyanide anion to ethylene and formaldehyde. The 3-21G values are shown in parentheses. o hydrogen; ○ oxygen; ▨ nitrogen; ● carbon.

## Results and Discussion

Absolute and relative energies of the stationary points on the cyanide plus acrolein potential energy surface are given in Table

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**Table II**. Cyanide Anion Addition to Ethylene and Formaldehyde, Negatives of the Total Energies (hartrees) and Relative Energies (kcal/mol)

(a) Ethylene

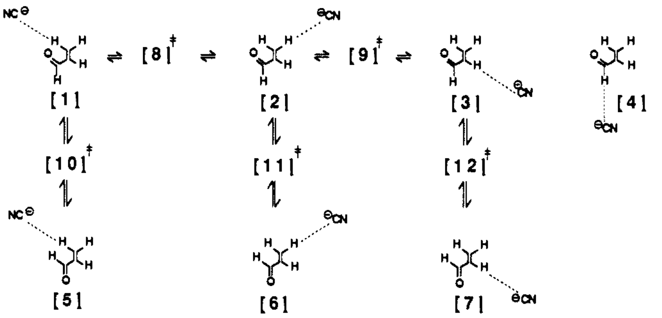
| level | $CN^- + C_2H_4$ | complex | **26** | product |
|---|---|---|---|---|
| 3-21G//3-21G | 169.350 94[a] (−19.9) | 169.366 33 (−29.6) | 169.310 63 (5.4) | 169.319 22 (0.0) |
| 3-21+G//3-21G | 169.415 83 (−30.6) | 169.421 30 (−34.0) | 169.358 79 (5.2) | 169.367 14 (0.0) |
| 6-31G*//3-21G | 170.317 37 (−24.7) | 170.326 28 (−30.3) | 170.267 10 (6.9) | 170.278 06 (0.0) |
| 6-31+G*//3-21G | 170.350 56 (−29.4) | 170.353 20 (−31.1) | 170.292 66 (6.9) | 170.303 68 (0.0) |
| 6-31+G*//6-31+G* | | | 170.292 38 | |
| MP(FC[c])2/6-31+G*//3-21G | 170.891 05 (−21.0) | 170.896 01 (−24.1) | 170.849 09 (5.4) | 170.857 66 (0.0) |
| MP2(FC[c])/6-31+G*//6-31+G* | | | 170.848 19 | |

(b) Formaldehyde

| level | $CN^- + CH_2O$ | complex | **27** | product |
|---|---|---|---|---|
| 3-21G//3-21G | 204.971 77[a] (8.6) | 204.997 64 (−7.7) | 204.984 17 (0.8) | 204.985 44 (0.0) |
| 3-21+G//3-21G | 205.052 37 (9.0) | 205.070 01 (−2.1) | 205.058 82 (5.0) | 205.066 71 (0.0) |
| 6-31G*//3-21G | 206.150 97 (6.6) | 206.170 21 (−5.5) | 206.157 12 (2.8) | 206.161 52 (0.0) |
| 6-31+G*//3-21G | 206.185 01 (1.2) | 206.198 08 (−7.0) | 206.181 00 (3.8) | 206.186 98 (0.0) |
| 6-31+G*//6-31+G* | | | 206.180 64 | |
| MP2(FC[c])/6-31+G*//3-21G | 206.777 04 (9.2) | 206.791 32 (0.3) | 206.784 92 (4.3) | 206.791 76 (0.0) |
| MP2(FC[c])/6-31+G*//6-31+G* | | | 206.781 65 | |

[a] From thc Carnegie-Mellon Quantum Chemistry Archive, 3rd ed.; Whiteside, R. A., Frisch, M. J., Pople, J. A., Eds.; Carnegie-Mellon University, 1983. [b] $CN^-$ energies: −91.749 95[a] (3-21G); −91.807 96 (3-21+G//3-21G); −92.285 68 (6-31G*//3-21G); −92.314 82 (6-31+G*//3-21G); −92.601 05 (MP2(FC)/6-31+G*//3-21G). [c] FC = frozen core.

**Scheme I**



I, and the salient features of the MP2/6-31+G*//3-21G energy surface are sketched in Figure 2. Structural features of the transition structures for conjugate addition to *s-trans-* and *s-cis*-acrolein, **20** and **21**, respectively, and for carbonyl addition to *s-trans-* and *s-cis*-acrolein, **22** and **23**, respectively, are shown in Figure 3. Absolute and relative energies of the reactants, complexes, transition structures, and products for the addition of cyanide anion to ethylene and formaldehyde are given in Table II, a and b, respectively, and the two transition structures, **26** and **27**, respectively, are shown in Figure 4. **Z** matrices for all optimized structures are available as supplementary material. Unless stated otherwise, all energies in the ensuing discussion refer to the MP2/6-31+G*//3-21G level.

Addition of cyanide anino to acrolein proceeds first by the exothermic formation of one of several possible ion–molecule complexes, **1–7**, shown in Scheme I. These complexes are formed with no apparent reaction barriers.[29] The complexation energies are ca. 15–25 kcal/mol, which are typical for ion–molecule interactions.[30] Four stable ion–dipole complexes, **1–4**, were found for the s-cis conformation of acrolein and three, **5–7**, were found for the s-trans conformation. The s-trans analogue corresponding to **4** was unstable and spontaneously rearranged to form **5** without activation. The most stable conformation, **5**, is predicted to have the cyanide group associated with the vinylic proton of *s-trans*-acrolein. Previous calculations have shown that the s-trans conformation of acrolein is more stable than the s-cis conformation by 1.7 kcal/mol at the HF/6-31G*//3-21G level[31a] and by 2.0 kcal/mol at the MP2/6-31+G*//3-21G level.

Our calculations indicate that this inherent tendency for acrolein to adopt the s-trans conformation is significantly affected by electrostatic interactions between the carbonyl group dipole and the negative charge on the cyanide group in the ion–molecule complexes **1–7**. These interactions are destabilizing in **1** (the dipole is pointing toward the negative charge) but stabilizing in **5** (the dipole is pointing away from the negative charge). Consequently, the s-trans conformation of acrolein should be even more preferred in the complexed form, **5**, compared to the uncomplexed state. This prediction is substantiated by the finding that **5** is ca. 10 kcal/mol more stable than **1** and that the 8 kcal/mol excess stabilization energy, relative to the uncomplexed acrolein, can be attributed to the aforementioned electrostatic effects. These interactions should be weaker in **2** and **6**, compared to **1** and **5**, respectively, owing to the more remote location of the cyanide anion. Indeed, the energetic preference of 3.5 kcal/mol for the s-trans complex **2** over the s-cis conformer **6** is found to be only 1.5 kcal/mol greater than that for uncomplexed acrolein.

In marked contrast to the preceding complexes, these electrostatic effects stabilize the s-cis complex, **3**, and destabilize the corresponding s-trans conformer, **7**. Apparently, they are sufficiently strong to overcome the natural tendency for free acrolein to adopt the s-trans conformation, since we find that the s-cis conformer is more stable than the s-trans conformer by 1 kcal/mol.

The energies of the *s-cis-* and *s-trans*-acrolein complexes are quite insensitive to the position of the cyanide anion around the respective acrolein moiety, with the exception of **1**, which is 6–7 kcal/mol less stable than the other s-cis complexes, and **7**, which is 3–4 kcal/mol less stable than the other s-trans complexes. These two exceptions also bear testimony to the presence of the aforementioned destabilizing dipolar interactions in **1** and **7**.

Since interconversions of the intermediate complexes, **1–7**, could be important to the regioselectivity of reactions in solution, several transition structures, **8–12**, for some of these interconversions were located. Our calculations predict quite small activation barriers (less than 4 kcal/mol) for migration of cyanide anion among the s-cis complexes **1–3**. Such facile migration is expected because the interactions between the negatively charged cyanide group and the acrolein moiety are electrostatic in nature, involving both ion–dipole and ion–induced dipole forces, which have less angular dependence than for a covalent chemical bond. Equally low barriers to cyanide migration among the s-trans complexes, **5–7**,

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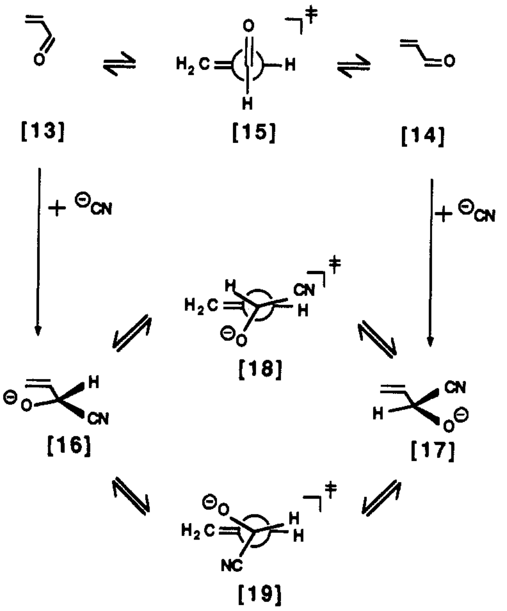
**Scheme II**



are expected, although the corresponding transition structures were not located.

The rotational barriers for the conversion of the s-cis complexes, **1**–**3**, into the respective s-trans conformers, **5**–**7**, obtained from the energies of the transition structures **10**–**12**, are 3–7 kcal/mol. These barriers are comparable to the value of 5–7 kcal/mol for free acrolein, proceeding via **15** (see the top part of Scheme II).

The products resulting from carbonyl and conjugate addition to *s-cis*- and *s-trans*-acrolein are **16**, **17**, **24**, and **25**. The carbonyl addition products, **16** and **17**, are interconverted by rotation about a C–C single bond, as shown in Scheme II. Transition structures, **18** and **19**, have been located for this process, and the barriers for the conversion of **17** into **16** are 3.4 (via **18**) and 3.2 kcal/mol (via **19**). As expected the conjugate addition products, **24** and **25**, are considerably more stable (by $>$17 kcal/mol) than the respective carbonyl addition products, **16** and **17**. This must be largely due to resonance stabilization of the enolate anions in **24** and **25**. This conclusion is supported by the observation that the C=C "double" bond length (ca. 1.51 Å) and the C—O "single" bond length (ca. 1.26 Å) in these species are respectively 0.2 Å longer and 0.1 Å shorter than the corresponding C=C and C—O bond lengths in methyl vinyl ether.[32a]

The transition structures **20**–**23** for conjugate and carbonyl addition of cyanide anion to *s-cis*- and *s-trans*-acrolein were optimized by using both 3-21G and 6-31+G* basis sets (Figure 3), as were the transition structures for addition of cyanide anion to ethylene and formaldehyde, **26** and **27**, respectively (Figure 4). The 3-21G and 6-31+G* optimized geometries of the transition structures are expected to be slightly different, but similar trends are found when comparisons are made between the two transition structures for conjugate addition and between the two transition structures for carbonyl addition. The forming CC bond for conjugate addition is 0.12–0.15 Å shorter with use of the 6-31+G* basis set than with use of the 3-21G basis set, but for carbonyl addition it is 0.04–0.07 Å longer with use of the 6-31+G* basis set than with use of the 3-21G basis set. The partially formed CC bond for cyanide addition to ethylene and formaldehyde is respectively 0.05 and 0.12 Å longer at the 6-31+G* level, compared to the 3-21G level.

For conjugate additions, both basis sets predict that the forming CC bond is longer for conjugate addition to *s-cis*-acrolein than to *s-trans*-acrolein. This is consistent with the finding that the C=C, C—C and C=O bond lengths in the s-cis transition structure, **21**, are respectively shorter, longer, and shorter than in the s-trans transition structure, **20**, although this is more marked with the 6-31+G* basis set. For carbonyl addition, both basis sets give a C=O bond length that is 0.003 Å longer in the s-trans transition structure, **22**, than in the s-cis transition structure, **23**.

It is noteworthy that the HF/3-21G attack angles for nucleophilic addition are larger for conjugate addition reactions (116–118°) than for carbonyl addition reactions (Figure 3), and this is also found with use of the 6-31+G* basis set, although the absolute values of the attack angles are systematically 1–2° smaller than those obtained with the 3-21G basis set. A similar HF/3-21G value for the attack angle for carbonyl addition was found for the addition of cyanide anion to propanal.[32b] The 3-21G (6-31+G*) attack angles for the addition of cyanide to ethylene and formaldehyde (Figure 4) are 119° (119°) and 117° (115°), respectively, and these are consistent with previous conclusions concerning the attack angles for nucleophilic additions in general.[33]

Summarizing, the optimized geometries of the transition structures **20**–**23**, **26**, and **27**, obtained with the 3-21G basis set are similar to those obtained with the 6-31+G* basis set. Importantly, perusal of Table I leads one to conclude that identical trends in the relative energies of the transition structures, **20**–**23**, are obtained, regardless of the basis set used for geometry optimization. This means that the MP2/6-31+G*//3-21G potential energy surface, shown in Figure 2, is a satisfactory approximation to the much more expensive MP2/6-31+G*//6-31+G* potential energy surface.

The transition structures **21** and **23** for conjugate addition and carbonyl addition to *s-cis*-acrolein, respectively, are, for all intents and purposes, isoenergetic at every level of HF theory used, the only exception being the HF/6-31+G*//3-21G single-point calculation which places the conjugate addition transition structure, **21**, 1.8 kcal/mol below the carbonyl addition transition structure, **23**. However, introduction of electron correlation to second order (MP2) stabilizes the carbonyl addition transition structure, **23** over **21**, by 2.2 (MP2/6-31+G*//3-21G) and 1.6 kcal/mol (MP2/6-31+G*//6-31+G*). Our calculations therefore indicate that the reaction barrier for carbonyl addition to *s-cis*-acrolein is lower than that for conjugate addition, in spite of the fact that the conjugate addition adduct, **24**, is 20 kcal/mol more stable than the carbonyl addition adduct, **16**.

In contrast, the activation barrier for conjugate addition to *s-trans*-acrolein is lower than that for the corresponding carbonyl addition at all levels of theory employed. The transition structure, **20**, for conjugate addition is more stable than the transition structure, **22**, for carbonyl addition by 1.6 (MP2/6-31+G*//3-21G) and 2.1 kcal/mol (MP2/6-31+G*//6-31+G*).

Our results suggest, therefore, that regioselectivities for nucleophilic addition reactions may be different for conformationally rigid s-cis and s-trans $\alpha,\beta$-unsaturated carbonyl compounds: carbonyl addition is preferred for s-cis structures, whereas the s-trans systems should show a preference for conjugate addition in the gas phase. This prediction should be tempered by the realization that gas-phase ion–molecule reactions generally occur under adiabatic conditions, at least under conditions of very low pressures. Consequently, the dynamics of the reactions are governed more by the number and the density of states associated with the potential energy surface for the reactions rather than merely by the energy difference between the transition structure and the reactants.[20]

The preference for acrolein to adopt the s-trans conformation, rather than the s-cis conformation, in the transition structures for conjugate addition (cf. **20** vs **21**) becomes stronger, by ca. 1 kcal/mol (MP2/6-31+G*//6-31+G*), relative to the same preference in free acrolein. However, this preference is actually reversed in the transition structures for carbonyl addition, where the s-cis transition structure **23** is now 0.8 kcal/mol (MP2/6-31+G*//6-31+G*) more stable than the corresponding s-trans

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transition structure **22**. The enhanced s-trans preference for the conjugate addition transition structure, relative to free acrolein, is probably due to the presence of repulsive electrostatic interactions in these species, between the carbon atom of the cyanide anion and the carbonyl oxygen atom, which should be stronger in the s-cis transition structure **21** than in the s-trans transition structure **20** (the HF/6-31+G* NC···O distances in **20** and **21** are 4.86 and 4.12 Å, respectively). It is most likely that these repulsive interactions in **21** are also responsible for destabilizing it, relative to the transition structure, **23**, for carbonyl addition.

Of the carbonyl addition transition structures, **22** and **23**, the s-cis conformer, **23**, is energetically preferred over the s-trans conformer, **22**. This is possibly due not to electrostatic interactions of the type discussed above (these should be similar for both **22** and **23**) but to the presence of an unfavorable orbital interaction in the s-trans transition structure. Since the terminal carbon and the carbonyl carbon atoms have opposite LUMO coefficient signs, orbital interactions between the HOMO of the cyanide anion and the LUMO component at the terminal carbon of acrolein are unfavorable. This destabilization is smaller in the s-cis transition structure, **23**, than in the s-trans transition structure, **22**, because the distance between the cyanide carbon and the terminal carbon in the acrolein moeity is 0.2 Å greater in the former structure. Similar destabilizing interactions, but now between the $CN^-$ carbon and the carbonyl carbon, are also present in the conjugate addition transition structures, **20** and **21**, but they are energetically less discriminating between these structures than between **22** and **23**, since the NC···C=O distance is now only 0.1 Å greater in **21** and in **20**. This effect, which weakly favors **21** over **20**, is presumably outweighed by the aforementioned electrostatic repulsions. It is also noteworthy that the LUMO of acrolein is lower in energy in the s-cis conformation than in the s-trans conformation. This probably causes the s-cis conformation to be favored in Diels–Alder transition states.[31b] Such an effect should also operate here as well, but it is, presumably, outweighed by electrostatic repulsions in the transition structures for conjugate addition.

At the HF/3-21G level, the length of the central CC bond of the acrolein moiety in the transition structures for conjugate addition is 0.05 Å shorter than that in isolated acrolein, whereas it is 0.05 Å longer in the transition structures for carbonyl addition, compared to isolated acrolein. These observations indicate that resonance interactions are maintained and developed even more strongly in the transition structures for conjugate addition, whereas such interactions are becoming weaker in the transition structures for carbonyl addition. The gain in resonance energy accompanying conjugate addition and the loss in resonance energy accompanying carbonyl addition largely account for the significantly greater (ca. 19 kcal/mol) stabilities of the conjugate addition products, **24** and **25**, relative to the carbonyl addition products, **16** and **17**. An idea of the degree of resonance stabilization enjoyed by the conjugate addition products, **24** and **25**, can be obtained by noting that the addition product of cyanide anion to ethylene is 24 kcal/mol *less stable* relative to the cyanide/ethylene ion–dipole complex, whereas **24** and **25** are ca. 18 kcal/mol *more stable* than their respective complexes.

Since the transition structures for conjugate addition are quite different from those for carbonyl addition, it is of interest to compare the evolution of various bonds in transition structures **20**–**23**. This may be conveniently explored by using Pauling bond orders $n_p$.[34a] These bond orders provide a useful measure of the extent of bond making and bond breaking in the transition structures, and they have been applied successfully to the analysis of transition structures for nucleophilic addition to various carbonyl compounds.[34b] The $n_p$ values are calculated from eq 1

$$\ln (n_p/n_0) = (R_0 - R)/0.3 \qquad (1)$$

where $R_0$ is the length (Å) of the fully formed bond either in the reactant (for $O_1{=}C_2$, $C_2{-}C_3$, $C_3{=}C_4$, and C≡N) or in the product (for the forming C···CN bond). $n_0$ is equal to 1, 2, and 3 for single, double, and triple bonds, respectively. $R$ is the length (Å) of the forming or breaking bond in the transition structure.[34] The $n_p$ values are given in Table III.

**Table III.** The HF/3-21G Pauling Bond Orders in the Transition Structures for the Reaction of $CN^-$ with Acrolein, Ethylene, and Formaldehyde

| bonds | **20** | **21** | **22** | **23** | **26** | **27** |
|---|---|---|---|---|---|---|
| $O_1{=}C_2$ | 1.86 | 1.89 | 1.63 | 1.67 | | 1.56 |
| $C_2{-}C_3$ | 1.19 | 1.19 | 0.85 | 0.86 | | |
| $C_3{=}C_4$ | 1.68 | 1.74 | 2.01 | 2.03 | 1.35 | |
| C···CN | 0.10 | 0.07 | 0.38 | 0.33 | 0.35 | 0.48 |
| C≡N | 3.1 | 3.09 | 3.15 | 3.15 | 3.15 | 3.16 |

The Pauling bond orders for a given type of addition (i.e. conjugate or carbonyl addition) are similar for both *s-cis-* and *s-trans*-acrolein conformations, except that the $n_p$ value for C···C bond formation for conjugate addition is slightly larger for *s-cis-* ($n_p$ = 0.10) than for *s-trans*-acrolein ($n_p$ = 0.07). This larger $n_p$ value for the s-trans addition, compared to that for s-cis addition, is a result of the shorter forming C···C bond length (by 0.1 Å) in the transition structure, **20**, compared to **21**. The $n_p$ values indicate bond weakening in the $C_3C_4$ and $O_1C_2$ bonds, with concomitant strengthening of the $C_2C_3$ bond in the transition structures **20** and **21** for conjugate addition. However, in contrast, the $C_2C_3$ bond is weakened in transition structures **22** and **23** for carbonyl addition. These results are in accord with expectations based on classical resonance theory (vide supra).

The reaction progress, indicated either by the forming CC bond lengths or, better, by the corresponding $n_p$ values, follows the Hammond postulate,[35] as the following comparisons demonstrate. The formation of conjugate addition products, **24** and **25**, from the ion–molecule complexes is strongly exothermic by 16–20 kcal/mol, whereas formation of the product arising from addition of cyanide anion to ethylene is strongly endothermic by a comparable amount (relative to the cyanide/ethylene complex). The transition structure, **26**, for the addition of cyanide anion to ethylene should therefore be much more product-like than the transition structures for conjugate addition, via **20** and **21**. This is nicely confirmed by the $n_p$ values for the forming C···CN bond, which are substantially smaller for **20** (0.1) and **21** (0.07), compared to **26** (0.35), and the $n_p$ values for the C=C double bond, which are larger for **20** (1.68) and **21** (1.74) than for **26** (1.35). On the other hand, carbonyl additions to both acrolein conformers and to formaldehyde are mildly endothermic, relative to their complexes, and by comparable amounts. Consequently, the $n_p$ values for the forming C···CN bond are only slightly smaller for **22** (0.38) and **23** (0.33) than for **27** (0.48), and those for the C=O bond are marginally larger for **22** (1.63) and **23** (1.67) than for **27** (1.56).

Finally, the $n_p$ values for the forming CC bonds for carbonyl addition (0.33–0.38) are larger than those for conjugate addition (0.07–0.10), which reflects the late character expected for the transition states for carbonyl addition, relative to those for conjugate addition.

The forming bond lengths calculated for conjugate addition lie within the range of HF/3-21G forming CC bond lengths observed in most of the transition structures involving CC bond formation such as Diels–Alder reactions,[36] aldol reactions,[37] the Cope and Claisen rearrangements,[38] cyclobutene electrocyclic ring openings,[39] and $CH_3Li$ additions to ethylene[40] and formaldehyde.[41]

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**Table IV.** The MP2(FC)/6-31+G*//HF/3-21G Intrinsic Barriers ($\Delta E_0^*$), Activation Energies ($\Delta E^*$), and Driving Forces ($\Delta E_0$) (kcal/mol) for the Various Reactions (the Reactions Are Identified by the Products That Are Formed)

| | **16** | **17** | **24** | **25** | ethylene + $CN^-$ | formaldehyde + $CN^-$ |
|---|---|---|---|---|---|---|
| $\Delta E_0^\ddagger$ | 6.08 | 7.44 | 16.32 | 14.36 | 14.99 | 4.16 |
| $\Delta E^*$ | 6.90 | 10.56 | 8.00 | 8.92 | 29.44 | 4.02 |
| $\Delta E_0$ | 1.58 | 5.70 | −19.58 | −12.18 | 24.07 | −0.28 |

The shorter forming CC bond lengths found in the transition structures, **22** and **23**, for carbonyl addition have extended the range of partially formed CC bond lengths that can be expected to occur in addition reactions.

The enthalpy change accompanying a reaction has long been viewed as the driving force for that reaction, and it plays an important role in determining the rate of reaction. Our results demonstrate that conjugate additions from the ion–molecule complexes are exothermic by ca. 12–20 kcal/mol, while the carbonyl addition reactions are slightly endothermic by ca. 2–7 kcal/mol. Thus, there is a substantial energetic advantage in favor of conjugate addition that may affect the barrier of reaction. A useful way of exploring the relationships between activation barriers and overall reaction energies is to use Marcus theory, in which the activation energy, $\Delta E^*$, can be expressed in terms of the driving force of the reaction, $\Delta E_0$, and the intrinsic barrier, $\Delta E_0^*$, by means of eq 2.[21]

$$\Delta E^* = \Delta E_0^*(1 + \Delta E_0/4\Delta E_0^*)^2 \qquad (2)$$

The intrinsic activation barrier is the activation barrier for the reaction were it to proceed with no driving force, that is when $\Delta E_0 = 0$. $\Delta E_0^*$ is assumed to be a constant for a series of structurally related substances.

In the present context, eq 2 applies to the conversion of the cyanide–substrate complex into addition products, as schematized in Figure 1. The intrinsic barriers for the conversion of various cyanide–substrate complexes into the respective products are given in Table IV, together with the corresponding driving forces and activation energies. The intrinsic barrier for the addition of cyanide anion to ethylene is about 11 kcal/mol larger than that for the addition to formaldehyde. This difference presumably reflects the more favorable electrostatic interactions obtaining in the latter reaction. A similar difference in the values of the intrinsic barriers (6.9–10.2 kcal/mol) is also found in the conjugate versus carbonyl additions of cyanide anion to *s-cis-* and *s-trans*-acrolein. Addition of cyanide to ethylene is strongly endothermic, and this leads to an activation energy for this process that is 14 kcal/mol greater than the intrinsic barrier. This is consistent with previous studies that have predicted high activation energies for nucleophilic addition reactions to the ethylene double bond.[40]

In marked contrast, the conjugate addition reactions of cyanide to *s-cis-* and *s-trans*-acrolein are quite exothermic, and this results in a substantial lowering (by 5–8 kcal/mol) of the activation energies for these processes, relative to the intrinsic barriers. This lowering is a measure of the importance of resonance stabilization obtaining in the transition structures for conjugate addition of cyanide to acrolein.

The driving force for carbonyl addition shows much less variation with the nature of the substrate than that for addition to the C=C double bond, ranging from essentially thermoneutral for formaldehyde substrate to weakly endothermic (by 5.7 kcal/mol) for the *s-trans*-acrolein substrate. Consequently, the activation energies for carbonyl addition are not much larger than the corresponding intrinsic barriers and, therefore, are fairly small (<11 kcal/mol). Such small reaction barriers are consistent with other studies on nucleophilic additions to the carbonyl group.[42]

**Table V.** Calculated Weinhold Natural Orbital Populations at the 3-21G Level for the Transition Structures for the Reaction of $CN^-$ with Acrolein with Charges of Attached Hydrogens Added to Those of Attached Heavy Atoms[a]

| bonds | **20** | **21** | **22** | **23** |
|---|---|---|---|---|
| $O_l$ | −0.670 | −0.657 | −0.819 | −0.814 |
| $C_2$ | 0.514 | 0.515 | 0.407 | 0.428 |
| $C_3$ | −0.380 | −0.392 | 0.011 | −0.047 |
| $C_4$ | 0.245 | 0.299 | −0.111 | −0.055 |
| $C_N$ | −0.124 | −0.158 | 0.042 | 0.024 |
| N | −0.584 | −0.608 | −0.531 | −0.536 |

[a] The calculated charge populations for free cyanide anion are C, −0.276e and N, −0.724e.

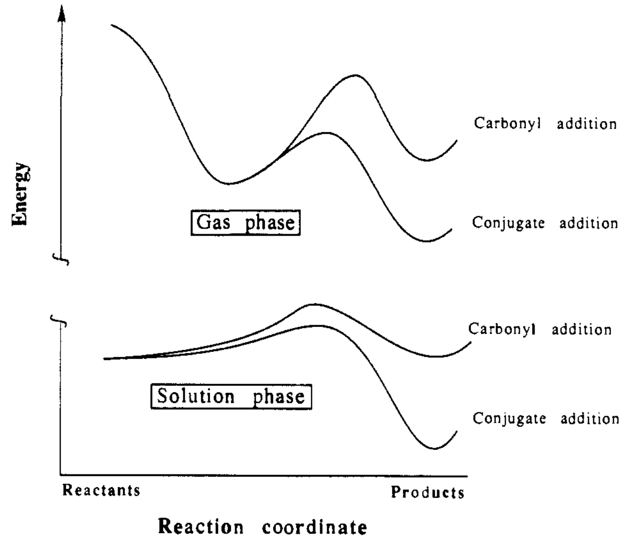

Figure 5. Schematic reaction profiles for the nucleophilic additions to s-trans acrolein in the gas phase and in solution phase.

Transfer of a reaction from the gas phase to the solution phase can, in principle, be quantitatively carried out with molecular simulation techniques.[18] We will only discuss qualitatively how solvation of various stationary points will change the potential energy surface using, as a guide, the maxim that solvation energies increase with increasing charge localization. Solvation of the charge-localized cyanide anion will lower the energies of isolated reactants considerably, and therefore, the initial step of the formation of a contact complex is likely to be thermoneutral. Solvation of the transition structures is expected to be less exothermic than that for the reactants, but subtle differential solvation effects on each transition structure should still be observed since the charge distributions vary from structure to structure. Furthermore, solvation may shift the transition structure along the reaction pathway, and even qualitative predictions are difficult to make without carrying out solution simulations.

Because the transition structures for carbonyl additions are more advanced than those for conjugated additions (vide supra) the oxygen should bear more negative charge in the former transition structures than in the latter. The 3-21G Weinhold Natural Orbital Population[28] analyses of the transition structures confirm this view. As shown in Table V, the charges are indeed more localized on oxygen in the transition structures for carbonyl addition, whereas the charges are more evenly distributed over all the transition structures for conjugate addition. Consequently, the transition structures for carbonyl addition should enjoy greater stabilization through solvation than the transition structures for conjugate addition.

The addition products should be strongly stabilized through solvation. Since the products arising from conjugate addition are delocalized anions, solvation of the species is expected to be less effective than that of the charge-localized anion products resulting from carbonyl additions. Indeed, ab initio MO calculations show that the solvation of delocalized anions such as the enolate anion of acetaldehyde and the carboxylic acid anion with one water

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molecule is about 4-10 kcal/mol less than that of the corresponding alkoxide anions,[30b,c] although solvation of ions involves much more than just one solvent molecule. The solvation energy for the carbonyl addition products, **16** and **17**, should, therefore, be greater than that for the conjugate addition products, **24** and **25**, although the latter should still be more stable than the former.

The above analysis suggests that the reaction barrier for carbonyl addition may become lower than that for conjugate addition for both *s-cis-* and *s-trans*-acrolein in the solution phase (shown schematically in Figure 5), as has been commonly proposed for solution-phase reactions.[13b,c]

Indeed, it has been found experimentally that base-catalyzed additions of HCN to $\alpha,\beta$-unsaturated aldehydes generally afford the carbonyl addition products.[1c] However, the conjugate addition product seems to be preferred in reactions with $\alpha,\beta$-unsaturated ketones carrying carbonyl substituents (e.g. esters).[1c] The reaction of acrolein itself with HCN in refluxing ethanol with EtONa as a catalyst is reported in a patent to give the conjugate addition product,[43] although the reaction conditions might be favoring thermodynamic control of the products rather than kinetic control. Lithium and sodium acetylidene undergo carbonyl addition to acrolein, presumably under conditions of kinetic control.[44] Most other nucleophiles are generally observed to undergo preferential carbonyl addition to $\alpha,\beta$-unsaturated aldehydes.[45]

## Concluding Remarks

In summary, ab initio MO calculations have been employed to locate stationary points on the potential energy surfaces for the addition reactions of cyanide anion with ethylene, formaldehyde, and acrolein. In the gas phase, the barrier for conjugate addition of cyanide anion to *s-trans*-acrolein is predicted to be lower than that for carbonyl addition by 1.6 kcal/mol, while the barrier for carbonyl addition to *s-cis*-acrolein is 2.2 kcal/mol lower than that for conjugate addition (MP2(FC)/6-31+G*//3-21G level). Conjugate addition is an exothermic process, whereas carbonyl addition is predicted to be endothermic, relative to the intermediate complexes. Both are exothermic relative to isolated reactants.

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**Supplementary Material Available:** Tables of Z matrices of the optimized structures (20 pages). Ordering information is given on any current masthead page.

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# Theoretical Investigations of Terminal Alkenes as Putative Suicide Substrates of Cytochrome P-450

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**Abstract:** In this study, we have applied ab initio quantum mechanics together with molecular mechanics and the known crystal structure of cytochrome P-450$_{\text{cam}}$ to assess the relative importance of electronic and steric factors in determining the suicide substrate activity of terminal alkenes. A current hypothesis focuses on competition between active oxygen addition to the terminal versus internal alkene carbon as the major determinant of N-alkylation of the heme. To test this hypothesis, we have calculated the preferential addition of small models for the active oxygen of P-450 to one or the other carbon atoms of the alkene bond in three prototypical terminal olefins, ethylene and propene, both of which are known suicide substrates, and 2-methylpropene, a model for a class of olefins known to be inactive as suicide substrates. In these studies four models for the active oxygen species in cytochrome P-450 with varying radical and anionic character, HO, LiO, O$^-$, and OH$^-$, were used. Ab initio studies were performed by optimization with a 3-21G basis set and MP2/6-31G* single-point calculations. To investigate the possible role of steric factors, empirical energy methods were used to calculate the interaction energy between an extended binding site, constructed from the crystal structure of P-450$_{\text{cam}}$, and the three alkenes in a geometry poised for covalent bond formation with each of the four pyrrole nitrogens. Taken together, the results suggest that steric rather than electronic factors determine suicide substrate activity for terminal alkenes. Specifically, the amino acids in the vicinity of the heme group, Gly 248 and Thr 252, play a major role in determining the regiospecificity of heme alkylation.

## Introduction

The cytochromes P-450 are a class of heme enzymes that have similar biological functions and spectral properties. Under normal aerobic conditions, they act as monooxygenases for a wide variety of nonpolar substrates in three general types of oxidative reactions: N- and C-hydroxylation,[1] aromatic and aliphatic epoxidation,[1-7] and addition of atomic oxygen to a heteroatom such as N and S containing nonbonded electrons.[1] During the normal enzymatic cycle of cytochromes P-450, a substrate binds to the ferric resting

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