

Compact Transition State and Asymmetric Induction: A Theoretical ab Initio SCF-CI Study of Enamine Addition to Carbonyl Compounds

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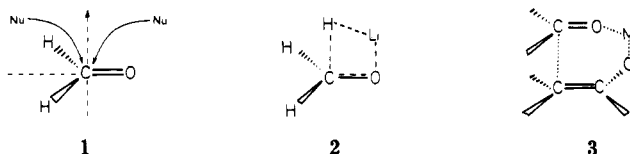
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An exploratory study of enamine addition to carbonyl compounds using ab initio SCF-CI calculations has been achieved. Simple model reaction paths have been investigated, by using vinylamine and formaldehyde as prototype substrates. It is shown that either anti or syn reaction paths are likely to yield zwitterionic species through endothermic processes. The latter moieties are not stable and no potential energy barrier prevents them from spontaneous decomposition, regenerating the starting reagents. It is shown that an irreversible concerted reaction, avoiding the formation of a zwitterion through concerted proton transfer, yields a stable neutral imino alcohol. The transition state corresponding to this process lies at lower energy than the zwitterions. The role of internal or external protonation on overall reactivity is emphasized. The results are in good agreement with the experimental results that are discussed throughout.

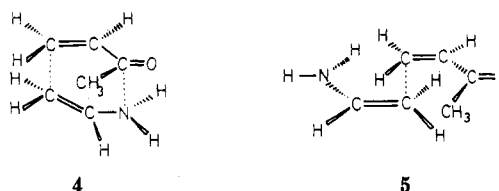
Introduction

The enantioselectivity observed in nucleophilic addition of chiral substrates to ketones still constitutes a fundamental field of investigation, for both experimentalists and theoreticians. For simplicity, let us consider the simple prototype displayed in structure 1. The actual nature of



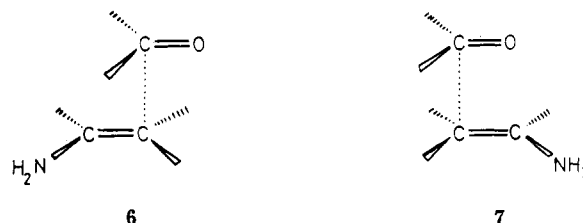
the π^* MO of the carbonyl whose central role has already been emphasized rules the directionality of the incoming nucleophile.¹ Model theoretical studies of the addition of H^- to formaldehyde have shown that the anionic species attacks the carbon atom with an O-C-Nu obtuse angle.² The situation is quite different when the nucleophile counterion is taken into account. A recent study of the addition of LiH to CH_2O has shown that the transition state has a four-center geometry, as in 2.³ The addition of a neutral moiety such as NH_3 also proceeds through a four-center transition state.⁴ We thus see that the directionality of the nucleophile approach merits further attention. A strong dependence on the nature of the nucleophile is expected. When dealing with ambident ionic nucleophiles, such as enolates, the situation is more complex. In an early study, Toromanoff⁵ emphasized the role of cationic complexation in aldol condensation, leading to compact reactive complex 3. A recent theoretical study by Anh et al.⁶ rationalizes the previous assumptions on the

grounds of an MO analysis and ab initio SCF calculations. Such a complexation cannot be postulated in the case of neutral ambident nucleophiles, among which enamines constitute a fundamental class of reagents. It has been shown that the addition of enamines to conjugated ketones proceeds through the competition of chair-like (or syn) reaction, as in 4, and tail-to-tail (or anti) reaction, as in



5.⁷ In neutral media, both processes are largely endothermic and it has been suggested that proton transfer, which can easily take place through an intramolecular process in 4, in fact controls the whole reaction profile. The experimentally observed enantioselectivity is in good agreement with these proposals.⁸

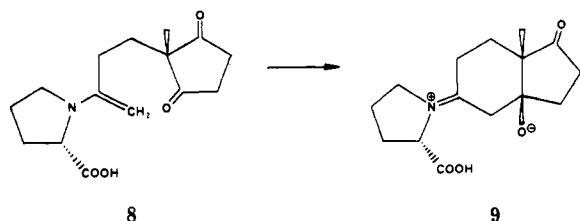
Similar questions arise upon considering the addition of enamines to carbonyl compounds,⁹ as, again, two limiting types of reactive complexes might be considered. In 6 (anti attack), the incoming nucleophilic carbon of the



enamine approaches from the side opposite to the oxygen, while the syn attack, in 7, involves a more compact structure. The difference between these structures could explain the stereoselectivity observed in cyclic systems. An example of this dichotomy is found in the addition of the

(1) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* 1977, 1, 61.
 (2) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* 1974, 30, 1563.
 (3) Bachrach, S. M.; Streitwieser, A. *J. Am. Chem. Soc.* 1986, 108, 3946.
 (4) Yamataka, H.; Nagase, S.; Ando, T.; Hanafusa, T. *J. Am. Chem. Soc.* 1986, 108, 601.
 (5) Toromanoff, E. *Bull. Soc. Chim. Fr.* 1962, 1190. Recent studies are found in: Yamataka, H.; Hanafusa, T. *J. Am. Chem. Soc.* 1986, 108, 6643.
 (6) Anh, N. T.; Thanh, B. T. *Nouv. J. Chim.*, submitted for publication.

(7) Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* 1986, 51, 2671.
 (8) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* 1985, 107, 273.
 (9) Hickmott, P. W. *Tetrahedron* 1987, 38, 1975.



proline enamine derivative **8** leading to **9**.^{10,11} Only a syn addition, as in **10**, is compatible with the control of the enantioselectivity through an intramolecular hydrogen bond, as already suggested.^{10b} In those conditions, cyclization would occur through a pre-chair transition state which exhibits a syn relationship between the enamine double bond and the ring carbonyl group (**10**, Figure 1). However an alternative anti relationship **11**, leading to a pre-boat transition state, might a priori be taken into account as, at first sight, this structural arrangement would agree with the Bürgi–Dunitz nonperpendicular trajectory. Analogous stereochemical dichotomies have already been pointed out by Seebach et al.¹² who, on the basis of chemical reasoning, concluded in favor of a syn approach of the prochiral centers. In this example, it is worth noting that the anti approach suffers from the peculiar and severe drawback that it would lead exclusively to a cis ring junction in the ketol produced. Yet, a trans ring junction was observed when starting from a substrate which is devoid of the angular methyl group.¹³ Keeping all these problems in mind, we propose in what follows a theoretical exploratory study of the addition of an enamine to a carbonyl compound.

Model Reaction Paths and Methodology

The reaction paths displayed in Figure 2 have been investigated by using the simplest prototype substrates: formaldehyde (**12**) and vinylamine (**13**). The various angular parameters used for describing the geometry are defined in Figure 3. The torsion angle α is of practical use for comparing limiting situations: syn path a corresponds to $0^\circ < \alpha < 90^\circ$ and anti path b corresponds to $\alpha = 180^\circ$. During the approach of the reactants, the formaldehyde and vinylamine units were kept into parallel planes ($\beta = 90^\circ$), up to an interplanar distance of 2.5 Å. Then, in going to shorter C_1 – C_2 distances, concomitant pyramidalization around C_1 and C_2 was achieved in order to progressively yield the zwitterionic geometry. Along path c, there is a reaction yielding the β -imino alcohol **15** through a concerted mechanism which couples C_1 – C_2 bond formation with the transfer of H from N to O. Finally, we also have investigated path d which consists of the proton transfer, occurring after the C_1 – C_2 bond is formed.

Ab initio SCF calculations were performed by using the minimal STO-3G basis, improved by a CI step involving all single and double excitations from the occupied orbitals displayed in Figure 4, to the π_3 and π^* empty MOs. A systematic search for optimal geometry was conducted throughout, keeping the CH and NH bonds at their initial values. The actual nature of the system, and the large number of degrees of freedom (30), imposed restrictions on the basis size. A total of 250 independently calculated

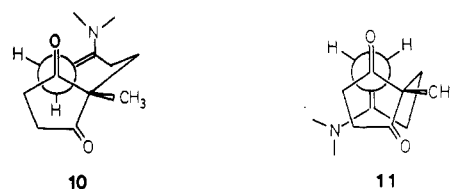


Figure 1. Pre-chair (**10**) and pre-boat (**11**) geometries corresponding to syn and anti geometries.

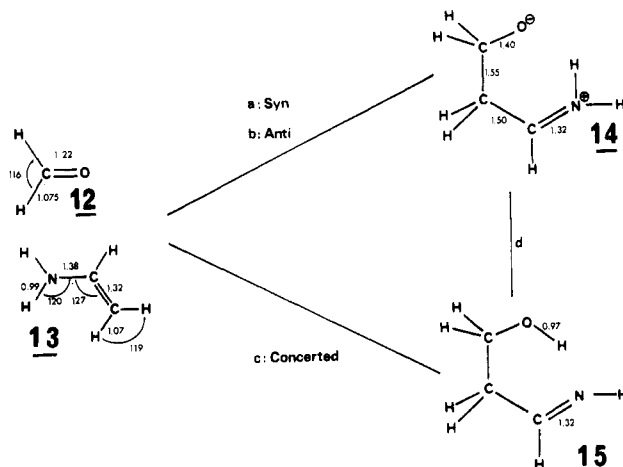


Figure 2. Chart of the reaction paths that have been theoretically explored in our study. Bond lengths and angles are reported for the various model molecules.

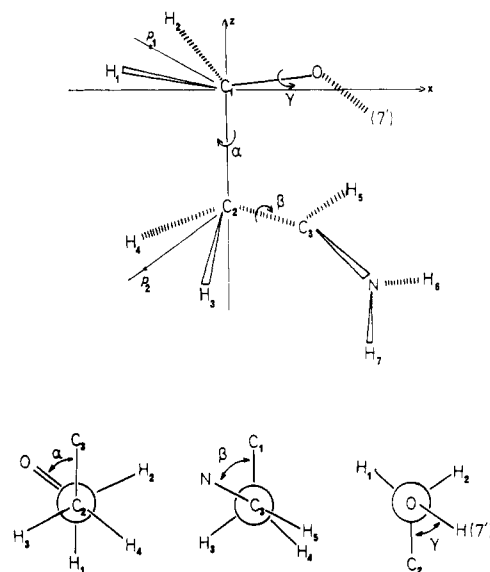


Figure 3. Definition of the various angular parameters. P_1 and P_2 are dummy points that have been used for defining the pyramidalization around C_1 and C_2 .

points were used for describing the ground-state behavior, in various geometries. Those calculations are time-consuming and imposed upon us the use of a limited basis set. This inconvenience is partly compensated by the CI step which takes into account the major part of the correlation of all the π and nonbonding electrons.

We are aware of the fact that these calculations only afford benchmarks for an exploratory study and that these are only semiquantitative results, the relative comparison of which remains of chemical significance. Our goal is essentially to emphasize the difference which exists between the formation of zwitterionic moieties (paths a and b) and a concerted or "proton-transfer-assisted" path avoiding charge separation (path c).

(10) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* 1974, 39, 1615. (b) Agami, C.; Puchot, C.; Sevestre, H. *Tetrahedron Lett.* 1986, 27, 1501.

(11) Our attention was called to this point thanks to a suggestion made by Professor D. Arigoni.

(12) Seebach, D.; Golinski, J. *Helv. Chim. Acta* 1981, 64, 1413.

(13) Agami, C.; Levisalles, J.; Sevestre, H. *J. Chem. Soc., Chem. Commun.* 1984, 418.

Table I. Relative Energies (kcal/mol)

| C1-C2, Å | α , deg | | | | | | |
|----------|----------------|------|------|-------|------|------|------|
| | 0 | 30 | 60 | 75 | 90 | 120 | 180 |
| 2.5 | 21.4 | 19.6 | 17.3 | | 17.1 | 16.8 | 16.1 |
| 2.1 | 68.5 | 57.8 | | 61.1 | | | 41.5 |
| 1.55 | 77.9 | 80.9 | | 71.9 | | | 73.8 |
| (14) | | | | | | | |
| 1.55 | | | | -17.3 | | | |
| (15) | | | | | | | |
| TS | | | | 62.1 | | | |
| (16) | | | | | | | |
| infinite | | | | | | | |

reference energy SCF-CI-6633.2506 eV (0.00)

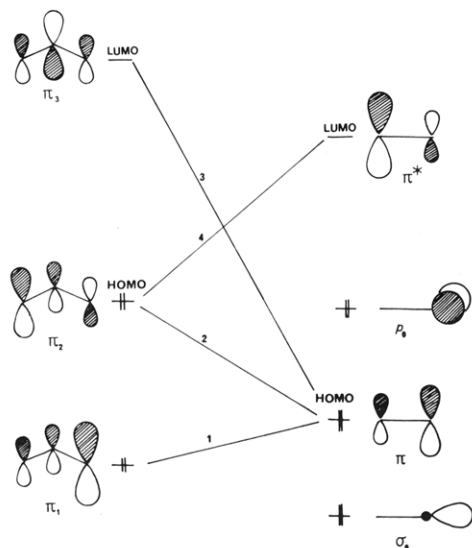


Figure 4. Schematic drawing of the frontier MOs of vinylamine (left) and formaldehyde (right). σ_0 and p_0 are the MOs corresponding to the lone pairs of the carbonyl group located in the molecular plane. These MOs are orthogonal to the π system and are not of concern for symmetry reason.

Approach of the Reactants

The approach of the reactants has been examined by assuming the following constraints: the C_1 - C_2 direction was taken constant in the motion, formaldehyde and vinylamine being fixed in parallel planes. At each C_1 - C_2 (i.e. interplane) distance, ranging from 10 to 2 Å, α was allowed to vary between 0 and 180°. Two points are worth noting: (i) between 10 and 2.5 Å, the approach is quite athermic and practically not α -dependent; (ii) going from 2.5 to 2.1 Å, we enter the strongly repulsive region of the potential energy surface. The resulting destabilization is now α -dependent, around 20 kcal·mol⁻¹ for 180° < α < 60° and larger for smaller α values, 0 and 30°, at 2.1 Å (Table I).

Looking at the energies of the close approach geometries, we see that a compact structure such as the one corresponding to $\alpha = 60^\circ$ and the less crowded one having $\alpha = 180^\circ$ are quite isoenergetic. This behavior can be qualitatively rationalized by using simple perturbation theory arguments. As shown in Figure 4, where the relative size of the MO coefficients are taken into account, the dominant four-electron repulsive interaction between the HOMOs, labeled 2, is maximum when α is small and dominates over all other types of interaction. The leading two-electron attractive interaction (labeled 4), arising between the HOMO of vinylamine and the LUMO of formaldehyde deserves attention. As displayed in Figure 5

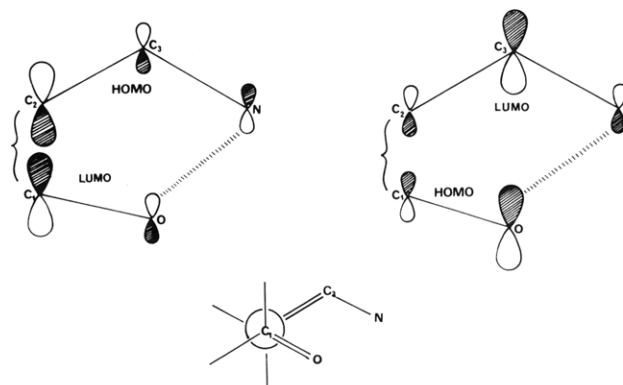


Figure 5. Schematic drawing of the couple of HOMO/LUMO interactions. Residual interaction between O and N is outlined by broken lines.

action and increases the attractive O-N interaction.¹⁶ The same kind of conclusion can be drawn regarding the second two-electron interaction arising between the π -type HOMO of formaldehyde and the LUMO of vinylamine. This interaction is less important than the latter one because the coefficients on C_1 and C_2 are small and the energetic gap between the levels is large. Nevertheless, here again, the balance between the repulsive O- C_3 interaction and the attractive O-N interaction favors the value $\alpha \approx 60^\circ$. At this point in our study, a problem arises: due to secondary MO interactions, a close syn approach of the reactants with 60° < α < 90° is only slightly destabilized with respect to the anti geometry. Obviously, one must be aware of the fact that our model does not take into account the role of the steric hindrance which is likely to be found in various systems with bulky substituents. We will examine in the next paragraph the changes brought about by the C_1 - C_2 bond formation.

Formation of a Zwitterion (Paths a and b)

As already seen, once the reagents have been brought together ($C_1 \cdots C_2 < 2.5$ Å), further approach becomes rapidly highly endothermic. In order to yield the zwitterionic species resulting from path a or b, the following strategy was adopted: starting from the geometry of the reactants at a $C_1 \cdots C_2$ distance of 2.1 Å, and keeping α and β constant, a preliminary scanning of the potential energy surface (PES) was first made, assuming a linear variation of all other geometrical parameters between the initial geometry and the final one. This motion involves synchronous bond length variations and pyramidalization around C_1 and C_2 . We thus obtain a first series of PESs. Then, in a second

(14) Brown, K. L.; Damm, J.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratki, C. *Helv. Chim. Acta* **1978**, *61*, 3108.

(15) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412.

(16) For $\alpha = 0^\circ$, the C_3 -O and N-O distances are respectively 2.003 and 2.466 Å; these values are 2.372 and 2.527 Å for $\alpha = 60^\circ$. We thus see that the C_3 -O distance increases more rapidly than the N-O distance.

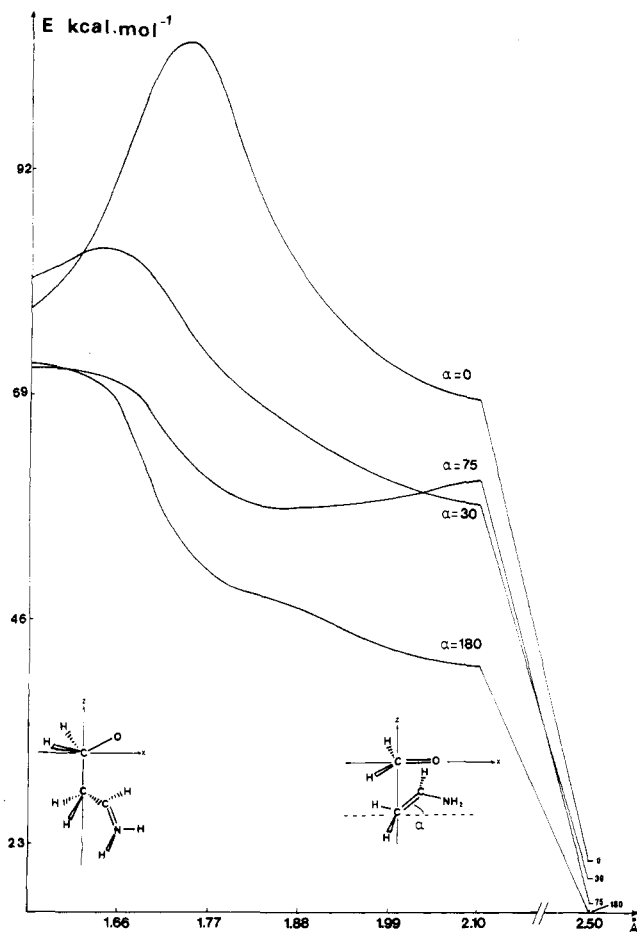


Figure 6. Calculated PES for four values of α . Reaction coordinate is defined in the text. Behavior of the system upon close approach between 2.5 and 2.1 Å is given on the right side of the figure.

step, for a series of fixed $C_1 \cdots C_2$ distances between 2.1 and 1.55 Å, an attempt to optimize the other parameters was made. This procedure was repeated for various α , thus yielding an optimal PES, for each value of this parameter. Four typical PESs, corresponding to $\alpha = 0^\circ$, 30° , 75° , and 180° are displayed in Figure 6.

The first important point to note is that all processes are endothermic by more than $70 \text{ kcal}\cdot\text{mol}^{-1}$. This largely reflects the unfavorable thermodynamic balance between the final species bearing two localized and separated charges and the neutral reagents. It might be argued that, as the reaction proceeds, the charge creation is compensated by the exothermicity of the C_1-C_2 bond formation and by electrostatic attraction. This is only true to some extent, and the latter arguments can be ruled out by comparing, in Table I, the various zwitterionic forms (14) to that of the neutral species 15 having the same number of bonds. The O-H and N-H bond energies are of comparable magnitude. The small difference in favor of the O-H bond (around $15 \text{ kcal}\cdot\text{mol}^{-1}$) is small compared to the gap separating the ionic and neutral species. This result clearly shows that in nonpolar solvents, and in the absence of protic solvation, the formation of a zwitterionic moiety is not likely to take place.

The latter conclusion is largely supported by an examination of the PES profiles (Figure 6). A striking difference is found when looking at the role of α . For $\alpha = 0^\circ$, a transition state is found along the PES; a much smaller one remains when $\alpha = 30^\circ$, but for larger values, there is no transition state and the reactants are linked to the products through a surface without an energy maximum.

In other words, for $\alpha \approx 45-50^\circ$, the reverse reaction, i.e. decomposition of the zwitterion, leading to separated reactants is spontaneous. The presence of an important PE barrier for $\alpha = 0^\circ$ is already anticipated in the high endothermicity of the approach in this geometry. Upon shortening of the C_1-C_2 distance, a maximum number of bonds are eclipsed, and it is conceivable that this repulsive energy is dominant, until the C_1-C_2 bond formation is achieved. The steric congestion sharply decreases when α increases and some memory remains at $\alpha = 30^\circ$. This barrier whose nature is essentially steric disappears at higher α values as those constraints are relieved. At the same level of optimization, we have found that the potential energy gradient is larger for $\alpha = 180^\circ$ than for $\alpha = 75^\circ$, the former geometry being favored by an easier approach. However, one must note that from a pure thermodynamical point of view, both reactions are of same feasibility. The same is true for the reverse process, or, in other words, both syn and anti processes of lowest energy, which lead to a zwitterion without PE barrier, are not likely to be efficient, the reverse reaction being spontaneous. *As an end result, it appears that the formation of a zwitterion is not feasible in weakly polar media.*

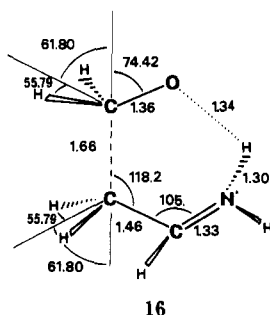
Proton Transfer from N to O (Path d)

Prior to a study of a concerted process, it is interesting to briefly depict the energy requirements found when an hydrogen atom (H_7) is moved from N to O (H_7). A realistic pathway is as follows: starting from the geometry with $\alpha = 75^\circ$, the imminium extremity rotates around C_3-C_2 , so as to decrease β . The shortest O-N distance would be found at $\beta = 0^\circ$, but this corresponds to a species of high energy, far above all these previously described. The obvious reason is that the repulsion between either the N- H_7 bond and the electron pair born by C_1-O^- becomes dramatically important for that geometry. A reasonable pathway was tested around $\beta = 40^\circ$, and we found that the zwitterion has to overcome a PE barrier of at least $25 \text{ kcal}\cdot\text{mol}^{-1}$ prior to reaching the stable neutral structure 15. If one recalls that, starting from the reagents, the formation of a zwitterionic species is endothermic and reversible, it is clear that proton transfer according to path d does not constitute a possible way of evolution along the PES of the zwitterion.

Concerted Reaction (Path c)

The preceding study has shown that the formation of a zwitterion is not possible. Of course, our model does not take into account the role of the solvent, but it is likely to remain valid for aprotic or weakly polar media, as usually used in experimental conditions for those reactions. In considering the relative stabilities of 14 and 15, it is therefore clear that protonation of the $C-O^-$ extremity might be determinant, and, moreover this protonation must occur as the reaction proceeds, in order to avoid charge separation. In this perspective, a strategy remains possible: it consists of assuming that the proton source is "external", as for example the COOH group in 8. The simplest model for testing this possibility is given by a reaction path which couples the C_1-C_2 bond formation and the proton transfer from N (H_7) to O (H_7) (Figure 3). One must remark that this model process is arbitrary and constitutes a limiting pathway whose activation energy is very likely to be above the actual one. For example, proton transfer from RCOOH is easier than from RNH_2 . Nevertheless, the latter process has been explored since it finally shows that concomitant proton transfer provides a reaction channel which is of lower energy than the zwitterion formation, the overall reaction being irreversible.

For realizing a synchronous reaction path, we have adopted the following strategy: (i) Starting from the approach distance of 2.1 Å, at $\alpha = 75^\circ$, regular variation of the C_1-C_2 distance was first assumed. At each point we made use of the pyramidalization parameters already found in the study depicted in Figure 6. (ii) In a second step, variations of β and/or $N-H_7$ $O-H_7$ distances were explored. We thus defined a series of points on the total hypersurface, the one of highest energy yielding a reasonable approximation of the transition state along path c. The complete determination of this grid has required the calculation of around 20 points in the transition region; however, our structural determination cannot pretend to be absolute. The complete optimization of 16, including



its 30 independent degrees of freedom, lies beyond the scope of this study. We can only describe a region which is very close to the actual saddle point. In structure 16, one sees that C-C bond-forming is assisted by hydrogen transfer, the latter migrating atom being at quite equal distances from N and O. The most important result is that this transition region lies at an energy which is below that of the corresponding zwitterion (see Table I).

This finding provides us with a new realistic reaction scheme, since it shows that protonation of the developing charge on the anionic C-O⁻ group drives the reaction on a PES which is of lower energy than that leading to the ionic species. The new transition state nevertheless corresponds to a geometry which is quite close to that of the optimal PES leading to the best syn zwitterion.

Proposition of an Overall Reaction Scheme

On the basis of the preceding finding, a qualitative description of the overall reaction process can be proposed: upon activation, the reactants are brought together through an endothermic approach. Two distinct PE channels are available. The anti channel, of lowest energy gradient, is monotonously endothermic and might lead to the reversible formation of a high energy unstable transient zwitterionic species, whose decomposition, regenerating the starting system, is very fast since all its possible evolution channels are even more endothermic. For example, rotation around C_1-C_2 , yielding a compact syn structure where proton transfer would occur, requires supplementary activation energy. The latter energy is not likely to be stored in the intermediate since spontaneous reverse reaction is possible for all geometries, ranging from 180° to 75° . The alternative consists of bringing the reagents together in a syn geometry, via an energy gradient which is slightly more pronounced than that in the anti case. From this situation, an irreversible concerted reaction path is available, the activation energy of which is less than that required to form a zwitterionic moiety. Several points emerge finally: (i) The reaction is not likely to be efficient since a low energy dead end channel, leading to an unstable transient zwitterion, is available from the anti approach. (ii) The irreversible competing reaction path has a syn transition

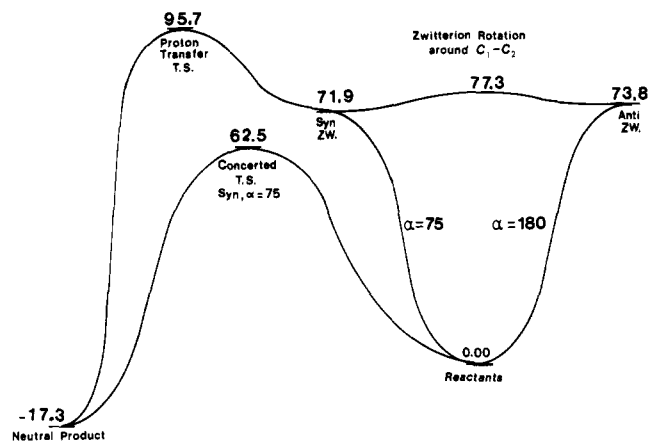


Figure 7. Summary of the various energetic aspects encountered in the discussion of overall reactivity. Energies are in $\text{kcal}\cdot\text{mol}^{-1}$.

state. The scheme displayed in Figure 7 summarizes the various possibilities.

A word of caution must be added, since in our model we have emphasized the role of internal proton transfer yielding irreversibly a stable final species. It is obvious that in the presence of an external proton source, our model would lose some validity. First, solvation of the reactants might change our considerations regarding the approach in a way which is not easy to predict. Concerning this aspect, contradictory arguments can be put forward while the increasing size of the "anionic" heads around O and N might favor an anti approach, strong solvation might also keep the O and N extremities in a syn complex, as in structure 3. In both cases, the reaction would be assisted by transfer, and now, anti and syn paths would compete. It follows that a careful examination of the nature of the reactants is necessary prior to using a mechanistic model that can only pretend to be valid in perfectly defined reaction conditions.

Comparison with Experiment

In the preceding theoretical study, the geometry of the reacting complex was deduced from the simplest model molecules, and obviously it is necessary to test the resulting conclusions in terms of experimental facts. In the case of 11 or 12, an enamine intermediate has been invoked so as to explain both the C-C bond formation and the enantioselectivity.^{10b,14,15} Our results show that the intramolecular condensation of the enamine moiety with a diastereotopic carbonyl group in 10 is feasible through a syn arrangement ($\alpha = 75^\circ$) of the reacting centers, provided that the C-C bond formation and proton transfer are more or less concerted (or assisted). It should be noted that in most usual cases, contrary to the model which supports the theoretical treatment, the syn approach is much less crowded than the anti one. Moreover, the anti arrangement leads to a boat-like transition state which is notoriously less favorable than a chair-like geometry such as the one resulting from a syn complex.⁷ These results are in good agreement with previous suggestions,^{10b} the proton transfer being mediated by a second proline molecule, within a reactive conformation which is stabilized by an intramolecular hydrogen bond linking the enamine moiety and the carbonyl group. This conclusion agrees with the unfavorable character of an intermolecular hydrogen bond, since it has been reported that changing the aprotic solvent by a protic one leads to a dramatic decrease of the enantioselectivity.^{10a}

Registry No. CH_2O , 50-00-0; $\text{H}_2\text{C}=\text{CHNH}_2$, 593-67-9.