56. A Theoretical Investigation of Enantioselectivity: *Michael* Reaction of Secondary Enamines with Enones

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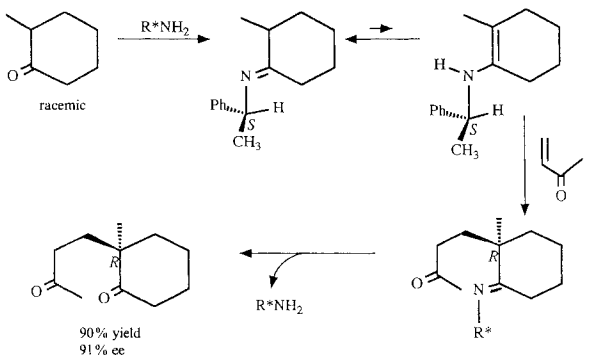
A theoretical study of the enantioselective *Michael*-type addition of chiral secondary enamines to enones has been achieved. In a first step, the structures of various free enamines have been investigated at the *ab initio* and MNDO levels. The results clearly show that upon substitution of the prototype vinylamine, the N-center is pyramidalized. The study of enamines with chiral N-substituents such as (*S*)-Ph(Me)CH or (*S*)-cyclohexyl(Me)CH reveals a very complex pattern, where up to 8 local energy minimums are characterized whose examination shows that *no prediction can be done* regarding the final enantioselectivity of their reaction with enones. These sets of conformers can be regarded as nearly energetically degenerate, at least for the three or four ones of lowest energy. The study of the compact complexes formed between the latter optimal conformers and acrylaldehyde shows that: *i*) *syn* complexation with respect to the N lone pair is the only one which remains possible for steric reason, *ii*) small geometrical rearrangements take place as the complexation proceeds, *iii*) no clear-cut correspondence exists between the relative sequence of the low-energy conformers of the free enamines and the sequence of the low-energy complexes, *iv*) the examination of the relative gradients of the complexation energies provides an index for predicting the relative facilities of the enantiometric pathways, in good agreement with the experimental facts. Our study emphasizes the great complexity of systems of realistic size and brings about critical conclusions regarding classical *ad hoc* models.

Introduction. – The problem of asymmetric induction is more than ever central in chemistry. However, despite of the vast number of experimental results, it still remains very difficult to rationalize the observed facts. Most of the proposals rely on the actual observed results and are based on the analysis of molecular models, with the help of chemical knowledge and intuition; they propose transition-state structures that are essentially derived from *ad hoc* considerations [1][1]). Quantum-mechanical calculations can play an important role. First of all, they provide independent numerical tests of the various hypotheses. Moreover, simple electronic schemes can be proposed which constitute new challenges for experimentation, with the hope that the process converges. Another general problem arises, regarding the transferability of the conclusions obtained with idealized models to real systems of much larger complexity. In this perspective, the well-documented 'deracemizing alkylation' of 2-substituted cycloalkanones, occurring through the *Michael*-type reaction of chiral secondary enamines and electrophilic olefins

[1]) See a critical discussion of *Hammond*'s postulate by *Dewar* [1d]; a survey of the *Curtin-Hammett* principle is found in [1e].

Scheme. *Enantioselective Alkylation of Chiral Secondary Enamines with Enones*



[2], with a very high enantioselectivity, according to the *Scheme*, provides an interesting field of investigation.

In a previous theoretical exploratory study [3] of this reaction, two of us have proposed a model: *i*) the reactive complex has a compact structure, stabilized by secondary orbital interaction between the N-atom and the C-atom of the carbonyl group; *ii*) this complex is, therefore, very sensitive to the steric environment of the N-atom. Those conclusions were reached with vinylamine and acrylaldehyde as model substrates in an *ab initio* SCF-CI study. The enantioselectivity was then *qualitatively* discussed. 'Reasonable assumptions' were made dealing with the conformation of the chiral group around the N–C* bond of the enamine, leading to the configuration displayed in the *Scheme*. Thus, two different faces would be seen by the incoming electrophile, the least hindered being the face containing the Me group. Moreover, an easy H-transfer can take place from N to the intermediate moiety, avoiding the formation of a zwitterionic species which is very unlikely in non-protic media [4]. Although the model was successful in explaining many experimental results, we see that, apart from the fact that 'compact complexes' are likely to play a dominant role, it remains mostly conjectural, since all the reasoning about enantioselectivity was inferred using classical arguments that were not tested by calculations. Since that time, our attention has been focused on several important facts: *i*) X-ray studies of a series of enamines show a substantial pyramidalization around the N-atom [5]; *ii*) new experimental results with different chiral substituents have become available [6]. We wish to propose here a complete re-examination of our previous model with substrates that are as close as possible to the real ones. In a first step, we have studied the actual structures of isolated secondary enamines bearing various substituents and chiral groups. Then, we have examined the changes brought about by the interaction of these substituted enamines with acrylaldehyde.

Methodology. – The first part of this work deals with the study of enamine structures derived from the general substitution pattern displayed in *Fig. 1*. In a first step, we have studied vinylamine and its methylated derivatives (*Fig. 1*, $R^1 = R^2 = R^3 = R^4 = Me$) at the *ab initio* SCF level using the 3-21G, 3-21G**, 6-31G, and 6-31G** basis sets [7]. For vinylamine itself, we have carried out a complete molecular geometry optimization using the Monstergauss program [8]. For the Me-substituted derivatives, owing to the size of the systems of concern, the optimization has been limited to the bond and dihedral angles

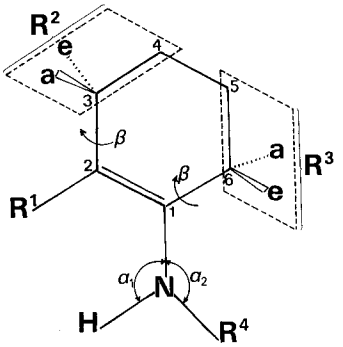


Fig. 1. *Angular parameters and substitution pattern used in text*

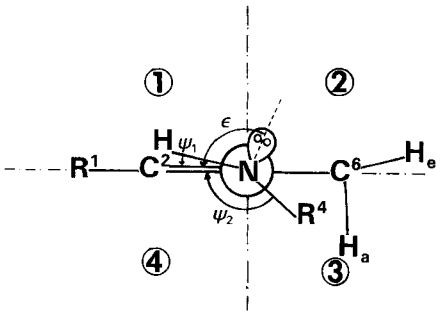


Fig. 2. *Dihedral parameters involved in pyramidalization of the N-atom.* H_a and H_e refer to the axial or equatorial position of the H-atoms on C(6) (R^3) of *Fig. 1.*

concerned by the pyramidalization of the N-atom, namely α_1, α_2, Ψ_1, and Ψ_2 (*Figs. 1* and *2*), and the rotation of the R^1 and R^4 Me groups. Then, these results were used in the MNDO [9] study of larger structures having $R^1 = R^2 = R^3 =$ Me and $R^4 =$ Ph(Me)CH and C_6H_{11}(Me)CH (C_6H_{11} = cyclohexyl), both in the (*S*)-configuration. These two examples were chosen because they experimentally lead to different enantioselective efficiencies when the reaction is achieved with methyl vinyl ketone as an electrophile [6]. In these cases, only the bond angles at the N-atom and all dihedral angles were optimized, the number of degrees of freedom of the systems considered prohibiting a complete optimization. Finally, we have studied the enamine plus acrylaldehyde complexes using the precedingly optimized compounds as starting points for a new optimization, again at the MNDO level. In both *ab initio* and MNDO calculations, the optimization runs were achieved using routine full gradient techniques that involve the simultaneous derivative of the energy with respect to all the geometrical parameters that are not frozen. Obviously, this technique becomes very much time-consuming dealing with our large molecules, hence the restrictions that we imposed upon the bondlengths and valence angles that were not of direct concern. The reliability of MNDO results can be questioned when dealing with a phenomenon such as asymmetric synthesis, where, at least, the observed ee (enantiomeric excess) depends on a very small energy difference. The same remark holds for the most elaborate *ab initio* calculations as well. Dealing with conformers, or enantiomeric complexes, we thus assume that *only relative energies make sense*, all things being equal, so the calculated values are only of qualitative grade and will be used as such in the coming discussion.

Prior to the detailed analysis of the calculated data, it is worth presenting our general strategy for optimizing the large number of conformational parameters involved in these molecules. In order to remain as close as possible to the real compounds, most of which having the amino group bound to a cyclohexane ring, we had to fix the geometry of R^2 and R^3 so as to reproduce the actual conformation of a half-chair cyclohexene[2]). Under these conditions, the relationship between pseudoaxial and pseudoequatorial H-atoms (a and e, resp.) is as shown in *Fig. 1*. For this purpose, the β angles can be considered as a set

[2]) See [10]; these authors propose a value of 15° for β; a value of 20° is better adapted to MNDO calculations.

of coupled parameters and the C-atoms labelled 4 and 5 in *Fig. 1* are only recalled for the sake of clarity while actually they were skipped and formally replaced by a H-atom without loss of generality. We are thus left with the independent angular parameters α_1, α_2 *(Fig. 1)*, Ψ_1, and Ψ_2 *(Fig. 2)*. Additional dihedral parameters appear, when R^4 is different from Me, and they will be discussed later on. This set of four primary parameters defines a complex topological space that has first to be described in a formal sense, *i.e.* independently of all calculated values.

Topological Aspects. – For convenience, let us first assume that C(2), C(1), N, H, and R^4 lie in a plane (N not pyramidalized). Two cases can be distinguished: looking at the C(1)–N bond, R^4 is either (*Z*) or (*E*) with respect to C(2) ((*E*) in *Fig. 1*). Once this requirement is satisfied, other parameters have to be determined: considering the most stable conformations of the cyclohexene ring, *i.e.* the half-chairs, the two pseudoaxial H-atoms on C(3) and C(6) lie on each side of the C(3)–C(2)–C(1)–C(6) plane and are interconverted with the two corresponding pseudoequatorial H-atoms upon ring inversion.

When N is pyramidalized, a new asymmetric center is created. With the drawing conventions of *Fig. 1*, and taking the N lone pair as the substituent of lowest priority in the classical rule, the N-atom has the (*R*)-configuration when R^4 and H come out of the plane aforementioned in the direction of the observer, and the (*S*)-configuration in the reverse case. We thus get a set of three independent possibilities, yielding eight different types of topological structures. They can be easily described with the help of *Fig. 2*. Taking the same plane and the perpendicular plane containing the C(1)–N bond, four quadrants are obtained. Three independent topological parameters can then be defined: *i*) the pyramidalized N-atom can be either (*R*) or (*S*); *ii*) the position of R^4 can be either (*Z*) (quadrants 1 or 4) or (*E*) (quadrants 2 or 3); *iii*) the H-atom on C(6), in quadrant 2, can be either axial (a) or equatorial (e). In fact the pyramidalization of N is characterized by the valence angles α_1 and α_2 *(Fig. 1)*, and the dihedral angles Ψ_1 and Ψ_2. The latter two are taken in the order H, N, C(1), C(2) and R^4, N, C(1), C(2) as drawn and are positive when clockwise; *e.g.*, Ψ_1 is negative and Ψ_2 positive in *Fig. 2* (we only use two angular parameters per H-atom, the bond length being fixed). Resulting from this set of three independent topological parameters, eight limiting geometries can be defined as displayed in *Fig. 3* where the topological labels a or e (pseudoaxial or -equatorial), *E* or *Z* ((*E*)- or (*Z*)-configuration), and *R* or *S* ((*R*)- or (*S*)-configuration) are given in this relative order.

On the apices of a cube are given the structures corresponding to the optimized geometries displayed in *Fig. 4*, labelled **1**–**8** in order of increasing energies *(Fig. 3)*. Each edge corresponds to one change of the aforementioned independent conformational parameters. The four horizontal edges represent a 180° rotation of the NHR^4 group around the C(1)–N axis (*E*↔*Z*), the oblique edges represent a ring inversion (a↔e for the H-atom in quadrant 2) and the vertical edges represent an N inversion (*R*↔*S*). We thus see how the various structures can be linked by elementary motions, one at a time. *E.g.*, we can go from **1** to **4** by one motion (N inversion), but going from **1** to **5** involves the possible ways **1** → **8** → **5**, **1** → **4** → **5**, **1** → **3** → **2** → **6** → **5**, *etc.* The **1** → **5** or **1** → **2** → **5** paths correspond to non-elementary motions, *e.g.* a coupled C(1)–N rotation and N inversion in the transformation **1** → **5**. This topological graph is useful in showing that the interconversion of any limiting structure into another depends on sizeable potential-energy

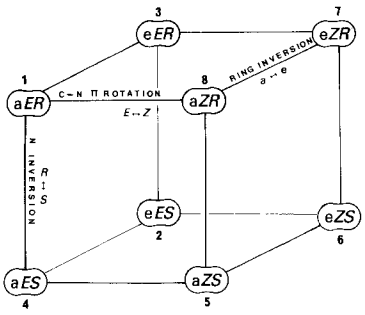


Fig. 3. *Relationship between the topological parameters used in the description of the chiral secondary enamines*

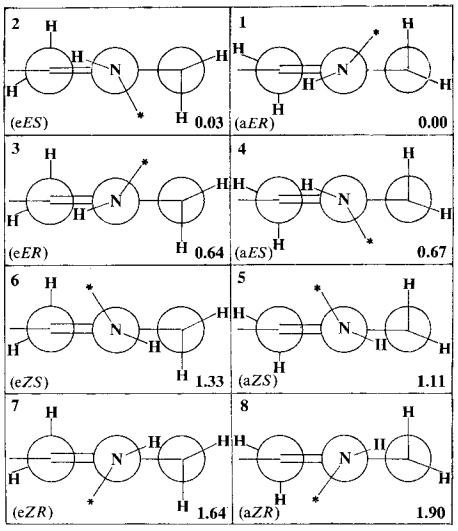


Fig. 4. *Calculated structures of the eight local optimal geometries* **1**–**8** *of the chiral enamine having* R^4 = *(S)-Ph(Me)CH.* The labels correspond to the topological definitions of *Figs. 2* and *3*. The relative energies are given in kcal/mol. Absolute energies are given in *Table 3*, along with geometrical parameters.

barriers that can be estimated in model runs. When bulky substituents are present, all those barriers range around 3 kcal/mol, as calculated in model runs. We thus conceive that various types of individualized local optimal structures may exist, as confirmed by the complete set of calculations *(vide infra)*. However, it must be clear that this description is only of topological use and does not presume of the actual existence of only eight distinct types of structures. The possibility of various local minima can be found in a given arrangement of the three labels, *i.e.* $(aER)_1, \ldots, (aER)_n$; in fact, a quasi-continuous set of conformers might be imagined. In this study, we just used the topological description in order to depict the local optima in a practical and pictorial fashion.

When R^4 bears no asymmetric center as in the case of Me, the eight conformers are reduced to four pairs of isoenergetic enantiomers (**1**/**2**, **3**/**4**, **5**/**7**, and **6**/**8**). This is no longer the case when R^4 is a chiral group of a given absolute configuration: for example (*S*)-C/(R)-N and (*S*)-C/(*S*)-N now define a couple of diastereoisomers. We will see in the coming sections that this description is of practical use for describing the various conformers as well as the corresponding complexes with acrylaldehyde.

The preceding considerations provide a coherent stategy for calculating the optimized geometries of large enamines and related complexes. In a first step, a planar geometry of the (*E*)- or (*Z*)-type was fixed, and all parameters were optimized. Then, systematic attempts were made starting from geometries having H, N, and R^4 in a plane at 45° and 90° with the C(2)–C(1)–N plane. In a second step, the minima thus obtained were refined: small deformations were made, and the system was reoptimized again in order to be sure that we had reached a true local minimum.

This procedure yielded eight structures; in each, the H-atom borne by N lies in a quadrant symmetrical to the one of R^4 with respect to N (*e.g.* quadrant 1 relative to 3 in *Fig. 2*). In all cases, the acute dihedral angle of N–H with the C(2)–C(1)–C(6) plane was found systematically smaller than the corresponding acute dihedral angle of N–R^4 with the same reference plane. Indeed these geometries allow a good conjugation of the lone

pair with the ethylenic system. So, the configuration at the N-atom is directly connected to the R^4 position: it is (*R*) when R^4 is located in quadrants 2 and 4 and (*S*) when in quadrants 1 and 3 *(Fig. 2)*. The final retained structures are the unique local minima which were actually reached from the different starting points. The fact that we, thus, obtained eight limiting structures is not fortuitous; it results from the already mentioned fact that they are separated by potential-energy barriers corresponding to weakly endothermic rearrangements of the whole system.

Conformational Study of Isolated Enamines. – We shall first deal with vinylamine, then with its various Me-substituted derivatives, and finally with more complex systems having a chiral group bound to N such as the one displayed in the *Scheme*.

Vinylamine ($R^1 = R^2 = R^3 = R^4 = H$, *Fig. 1*). Despite of its apparent simplicity, the actual structure of this molecule is not firmly established. On the basis of microwave spectra, *Lovas et al.* [11] attributed a slightly non-planar geometry to it. Other semiempirical calculations gave the same result [12]. However, they showed that the inversion state was only 65 ± 25 cm^{-1} above the ground state. The *ab initio* optimizations which have been performed (with the four basis sets) give in all cases a planar structure in agreement with our previous studies [3] as can be seen in *Table 1*. The role of allylic conjugation can be estimated by rotating the NH_2 group by 90°, keeping all the optimal parameters of the optimized planar form at their initial value. This motion corresponds to a destabilization of 0.015185–0.018628 a.u. (9.5–11.7 kcal/mol) depending on the basis set used (*Table 1*,

Table 1. Ab initio *Calculated Values* (in a.u.) *of Vinylamine Energy*. See *Figs. 1* and *2*, $R^1 = R^2 = R^3 = R^4 = H$.

Basis set	Molecular geometries[a])		
	A	**B**	**C**
3–21 G	– 132.326444	– 132.309858	– 132.317915
3–21 G**	– 132.402261	– 132.383633	
6–31 G	– 133.015746	– 133.000561	
6–31 G**	– 133.072989	– 133.056875	– 133.072202

[a]) **A**: values obtained after a complete optimization of the molecular geometry which in all cases gives $\Psi_1 = 0°$ and $\Psi_2 = 180°$. **B**: values obtained using the geometry **A** with $\Psi_1 = -\Psi_2 = 90°$. **C**: values obtained for the 'pyramidalized' conformation of vinylamine, geometry **A** with $\alpha_1 = \alpha_2 = 109.5°$, $\Psi_1 = 30°$ and $\Psi_2 = 150°$.

difference between **A** and **B** values). This rotational barrier which reflects conjugation is much more important than usual experimental and calculated inversion barriers in common amines [13]. In this whole series of compounds, rotation around the C(1)–N bond is always more difficult than N-inversion. The rotational barrier is, however, noticeably smaller than that of formamide which is 18–19 kcal/mol (experimental) and 15.3 kcal/mol (calculated) [14]. In the latter case, *Wiberg* and *Laidig* have noted that an ionic resonance scheme may contribute significantly to the phenomenon. Dealing with enamines, the same argument largely drops, for it would place a negative charge on the less electronegative C-atom.

The pyramidalization barrier was also investigated. With this aim, we started from the optimal planar geometry and imposed a tetrahedral geometry to the N-atom substituents, as a guess. Using this constraint, it is of practical use to define the N lone pair as

being directed along the fourth unsubstituted tetrahedral axis. More generally, it is convenient to give a geometrical definition of the lone-pair direction: in all cases concerning a pyramidalized N-atom, we can define a line passing through the center of the triangle corresponding to the three neighboring atoms and by N itself; the idealized N lone pair then points out along this line. In *Newman* projection, the N lone pair, therefore, lies in the plane which contains the C(1)–N bond and bisects the HNH angle as displayed in *Fig. 2* ($R^4 = H$). The corresponding dihedral angle with C(1)–C(2) is noted ε. When $\varepsilon = 90°$, the estimation of the pyramidalization energy is only 0.000787 a.u. (0.50 kcal/mol, 170 cm^{-1}) at the 6-31G** level (*Table 1*, difference between **A** and **C** values). This is close to the aforementioned experimental one [12] but in favor of the planar geometry. The corresponding 3-21G value of 5.35 kcal/mol clearly illustrates the fact that the basis-set quality is essential when dealing with absolute values of pyramidalization energies, small basis sets yielding values that are systematically larger than those resulting from bases having polarization functions. A similar trend will be found in the forthcoming study of substituted derivatives of vinylamine, but it is worth noting that if small basis sets overestimate the changes brought about by pyramidalization, no inversion of the relative energies is found in any type of calculation. Upon variation of the ε dihedral angle, we can estimate the role of conjugation in the pyramidalized forms. We see in *Table 1* (geometry **B**) that a net destabilization appears when the N lone pair moves aside from the 90° value. The results from different basis sets now behave in a parallel way, as previously found in the evaluation of conjugation. The order of magnitude of these data shows that, when strong steric interactions will be present, the N-substituents will quite easily adopt nonplanar geometries with $|\varepsilon|$ different from 90°. The latter point also justifies that, in the coming discussions, it might be of practical use to consider that the N lone pair is, to a large extent, located on the N-atom rather than delocalized in a pure allylic system. At any rate, this is only a question of language, since it does not appear in the calculation itself.

As in previous calculations using comparable methods [10] [11], MNDO calculations yield discrepancies since an optimal pyramidalized structure is obtained. We observed that it is also the case with the AM1 method [15]. Previous reports of this tendency have been published using comparable semi-empirical methods. An embarrassing point is raised, since obviously those methods emphasize the trend to move aside planarity in vinylamine. However, this inconsistency no longer persists, when vinylamine is substituted, as will be seen in the next paragraph.

Methyl-Substituted Vinylamines. In *Table 2*, the optimized values obtained by *ab initio* (3-21G) and MNDO methods show that, with the exception of the first two compounds *(ab initio)*, all structures have a pyramidalized N-atom. Of special interest are the last four compounds, all having $R^2 = R^3 = Me$, fixed so as to reproduce the cyclohexene geometry corresponding to *Fig. 1*. Upon N-distortion from planarity, the R^4 substituent ((*E*)-geometry), tends to remain in the same quadrant *(Fig. 2)* as the pseudoaxial H-atom of R_3 (at C(6) in *Fig. 1*), while the H-substituent on N lies in the quadrant that is symmetrical to that containing R^4 with respect to N. This important feature is found in both types of calculations, the corresponding angles being larger when obtained by MNDO. The *ab initio* barriers are rather small except for the last two entries; the MNDO barriers are larger, as already anticipated in the study of vinylamine. This study shows that upon substitution, pyramidalization around the N-atom takes place, its preferential

Table 2. *Values of the Bond* (see *Fig. 1*) *and Dihedral* (see *Fig. 2*) *Angles at the N-Atom of Vinylamine and Its Methylated Derivatives Obtained from* ab initio (3-21G) *and MNDO Computations*

R^1	R^{2a})	R^{3a})	R^{4b})	*ab initio*					MNDO				
				α_1	α_2	Ψ_1	Ψ_2	ΔE^c)	α_1	α_2	Ψ_1	Ψ_2	ΔE^c)
H	H	H	H	121	121	0	0	0.0	112	110	28	147	3.4
Me	H	H	H	122	121	0	0	0.0	116	113	30	154	2.5
H	H	H	Me	118	122	−7	167	0.4	115	121	12	150	1.8
Me	H	H	Me	119	122	2	167	0.1	121	124	0	179	0.3
H	Me	Me	H	121	121	4	174	0.02	114	113	10	133	3.7
Me	Me	Me	H	122	120	12	180	0.3	116	114	20	145	3.2
H	Me	Me	Me	115	122	−4	143	1.9	120	112	−25	104	7.3
Me	Me	Me	Me	117	122	−12	129	2.2	114	121	−26	107	6.5

a) Geometry as in *Fig. 1* (H pseudoaxial, pseudoequatorial).
b) R^4 is placed in an (*E*)-conformation.
c) Energy difference (in kcal·mol^{-1}) between the planar and pyramidalized conformations.

direction being related to the position of the axial H-atom at C(6) of the cyclohexene ring, R^4 being located in the same quadrant as the axial H-atom borne by C(6). These tendencies will be also observed in the study of larger enamine systems.

Chiral Enamines ($R^1 = R^2 = R^3 = Me$, R^4 = (*S*)-Ph(Me)CH or (*S*)-cyclohexyl(Me)CH, *Fig. 1*). As already indicated, two chiral centers located in R^4 have been investigated. In both cases, R^1, R^2, and R^3 were Me, R^2 and R^3 being fixed so as to reproduce the half-chair geometry of cyclohexene, while R^1 was free to rotate (see *Fig. 1*). The precedently described strategy for optimizing the geometries was followed. Eight local minima (*Figs. 4* (see above) and *9* (see below)), having the topological relationships of *Fig. 3*, were determined, the conformation of the substituents of the chiral C-atom being optimized at the same time. For all the minima obtained, the optimal arrangements of the R^4 group were very similar. So, for the sake of clarity, comprehensive results will not be given here[3]), and we will restrict ourselves to the salient geometrical trends.

In *Fig. 4* are displayed the schematic drawings and relative energies of the eight local optima **1**–**8** of the chiral enamine with R^4 = (*S*)Ph(Me)CH. Three *Newman* projections are given: those at the extremities concern the H-atoms at C(3) and C(6) and give the six-membered ring conformation, *i.e.* one of the two possible half-chairs, while the one in the middle reports the parameters describing the N-pyramidalization. The topological notation and the relative energies are given. Two sets of compounds can be distinguished. The first one, **1**–**4**, is composed of those of lowest energy, where general trends emerge: *i*) they all have the bulky chiral group in quadrants 2 or 3 *(Fig. 2)* and thus derive topologically from (*E*)-compounds; *ii*) the preferential pyramidalization tends to place the bulky group in the same quadrant as the pseudoaxial H-atom of R^3 (at C(6)); thus, **1** is more stable than **3**, and **2** more stable than **4**. This preference was already found in the above study of Me-substituted enamines *(Table 2)*. Moreover, we see that practically no energy difference is found between the (*R*)-N/(*S*)-C and the (*S*)-N/(*S*)-C diastereoisomers **1** and **2** on the one hand, and **3** and **4** on the other hand.

Let us now consider the set **5**–**8**. By comparison with the preceding criteria, we see that: *i*) they all have the bulky substituent in quadrants 1 or 4 and thus derive from (*Z*)-compounds; *ii*) here again, we observe a preferential position of the chiral group,

3) Material available upon request.

since it is located in the same half-space quadrants (1 + 2 or 3 + 4) as the pseudoaxial H-atom of R^3 (at C(6); **5** better than **6**, and **7** better than **8**); *iii*) now, the absolute configuration at the N-atom plays a role, the (*S*)-N/(*S*)-C and (*R*)-N/(*S*)-C couples of diastereoisomers **5** and **7** and **6** and **8**, respectively, having different energies, in favor of the (*S*)-configuration at N. Point *iii* results from the steric hindrance which is more pronounced in this set of compounds.

In comparing these two sets *(Table 3a)*, we see that a hierarchy of potential energies results. The most important feature deals with the (*E*) *vs.* (*Z*) preferential position of the chiral group. Once this feature is fixed, the preferential direction of pyramidalization places the chiral group in the same quadrant as the pseudoaxial H of R^3 (at C(6)), and this accounts for *ca.* 0.6 kcal/mol. The complete set **1**–**8** is spread only on a *ca.* 2 kcal/mol energetic range, but that does not mean that the corresponding compounds might easily

Table 3. *Angular and Dihedral Parameters* [°] *and Potential Energy for Various Geometries of Enamines* **1**–**16** *and Complexes* **1cp**–**16cp**

		α_1	α_2	Ψ_1	Ψ_2	Ψ_3[a])	*E* [kcal/mol]
a	**1** (a*ER*)	113.1	122.0	20.1	–117.0	8.2	–49293.45
	2 (e*ES*)	113.3	121.5	–25.9	113.6	4.9	–49293.42
	3 (e*ER*)	113.0	122.7	27.8	–113.1	7.6	–49292.81
	4 (a*ES*)	112.8	122.2	–35.5	103.9	1.7	–49292.78
	5 (a*ZS*)	112.0	121.6	136.6	–84.9	22.8	–49292.34
	6 (e*ZS*)	112.3	122.8	145.8	–75.0	24.9	–49292.12
	7 (e*ZR*)	112.6	123.2	–142.6	76.6	–13.8	–49291.81
	8 (a*ZR*)	112.2	124.1	–146.0	73.1	–11.4	–39291.55
b	**9** (a*ER*)	113.8	125.8	5.1	–136.5	–36.7	–51291.21
	10 (e*ES*)	116.1	130.6	–17.4	156.4	–1.9	–51289.20
	11 (e*ER*)	113.0	125.9	23.1	–18.2	–33.4	–51290.24
	12 (a*ES*)	115.7	131.5	–26.2	149.1	–8.3	–51287.69
	13 (a*ZS*)	111.9	137.8	155.2	–22.0	–3.3	–51284.32
	14 (e*ZS*)	113.6	133.1	149.7	–43.0	5.9	–51285.30
	15 (e*ZR*)	111.7	126.2	–155.9	65.9	–46.2	–51288.64
	16 (a*ZR*)	111.3	125.8	–154.3	67.2	–45.6	–51288.56
c	**1cp** (a*ER*)	111.9	119.7	22.1	–108.1	20.0	–66836.96
	2cp (e*ES*)	113.1	123.5	–10.5	126.9	39.1	–66837.86
	3cp (e*ER*)	112.1	119.6	25.7	–104.5	15.4	–66836.30
	4cp (a*ES*)	112.8	121.6	–20.7	113.7	7.1	–66837.30
	5cp (a*ZS*)	111.9	121.6	155.6	–70.8	32.2	–66837.13
	6cp (e*ZS*)	111.0	121.1	145.0	–73.4	27.0	–66837.29
	7cp (e*ZR*)	111.9	119.1	–150.8	78.8	–15.1	–66835.30
	8cp (a*ZR*)	111.0	120.1	–153.9	74.2	–17.7	–66835.54
d	**9cp** (a*ER*)	113.8	121.0	20.1	–113.2	–29.4	–66833.22
	10cp (e*ES*)	115.3	125.1	–11.5	135.2	–2.4	–68832.20
	11cp (e*ER*)	113.6	121.9	22.8	–111.0	–26.8	68832.80
	12cp (a*ES*)	114.7	126.1	–13.2	133.5	–8.3	–68831.37
	13cp (a*ZS*)	112.7	127.0	160.1	–57.1	7.9	–68829.27
	14cp (e*ZS*)	112.9	127.5	161.2	–55.6	13.3	–68829.27
	15cp (e*ZR*)	111.4	121.5	–153.1	76.3	–41.2	–68830.33
	16cp (a*ZR*)	111.3	121.7	–155.1	73.8	–43.2	–68830.40

[a]) Ψ_3: dihedral angle H–C*–N–C(1).

interconvert. Rotation around the C(1)–N bond not only is endothermic in non-substituted compounds *(vide supra)*, but in the presence of bulky groups, it becomes more difficult. The same remark holds for N-inversion: in the presence of a bulky group, planar geometries become hindered, so that the substituents have to change drastically their conformation in order to minimize the inversion barrier. These points will play a fundamental role in the general discussion of reactivity.

With respect to the conformation of the Me and Ph substituents of R^4, only minor changes around the situation displayed in *Figs. 5* and *6* are observed in the whole series **1**–**8**. The main trends are as follows: *i*) the C*–H bond roughly tends to be parallel to the bisector of the H–N–C* angle; *ii*) the Me substituent adopts the usual staggered conformation with respect to this H-atom; *iii*) the plane of the Ph group is almost parallel to the C*–H direction. On the one hand, the Ph conformation corresponds to a maximum overlap of its π system with the adjacent C*–N and C*–Me bonds, thus allowing for a better hyperconjugation, as observed in substituted alkenes and arenes [16a] (see also [16b] for the same kind of argument in circular dichroism). On the other hand, the π system of the Ph ring is roughly perpendicular to the bisector of the H–N–C* angle, along which one can visualize the maximum density of the more or less localized N lone pair. Due to this geometrical constraint, the overlap between the N lone pair and the Ph π orbital is nearly zero. Through-bond interaction between the Ph group and the C*–N bond would reach the nodal plane of the π-type orbital of the N lone pair and thus remains quite impossible. Another proposal, already pointed out by *Oppolzer et al.* [5b] and others [17], is that the H-atom borne by the N-atom might interact to some extent with the Ph group. Indeed, in the optimal geometry, this H-atom lies in regard of the Ph group, but there is no strong evidence that this effect plays an important role in stabilizing the pyramidalized geometry. In particular, we will see in the next section that when the Ph group is replaced by a cyclohexyl group, we also get optimal geometries that do not differ very much from those of *Fig. 4*. To summarize these facts, at least to a first qualitative glance, it seems that the conformational changes resulting from N-pyramidalization are mostly of steric nature and do not lead to evident electronic effects between the substituents at C* and the conjugated enamine system. The most important feature that results from this analysis is that well-defined local optima exist, having the general topology described in *Fig. 3*. The elementary motions along the edges defined in *Fig. 3* involve classical sizeable barriers, as recalled on the drawing. We have not attempted to calculate the magnitude of the actual barriers which possibly consist of a very complex mixture of all possible motions. The thing we can note is that the interconversion between the various conformers is not free since, otherwise, once the shape of the cycle is fixed, the 'blind' gradient technique would always yield the same pair of absolute *minimum minimorum*. Moreover, we will see in the final discussion of the overall reactivity that, at any rate, the preceding point does not bring about constraints, since the lowest-energy conformers are treated as being nearly degenerate in energy, with practically free interconversion. In the vicinity of a local optimum, smooth geometrical changes are possible, mostly dealing with small conformational changes of the substituents on the chiral center, but these changes do not modify the overall topology. However, these smooth secondary rearrangements will play a leading role in the study of complexation.

At this stage of the study, an important preliminary conclusion can be drawn regarding the predictive ability of a model, concerning the enantioselectivity of the reaction,

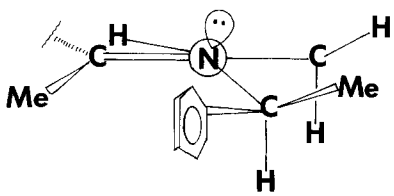


Fig. 5. *Perspective view of the optimal conformation of the (eES) conformer* **2** *of* Fig. 4

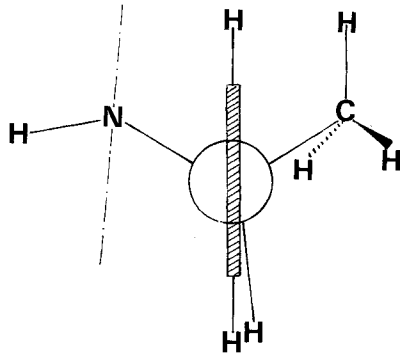


Fig. 6. *Conformation of the phenyl and methyl group borne by the chiral center, determined for the (eES) conformer* **2** *of* Fig. 4

which would be only based on the conformations of the free enamines [18]. By considering the lowest-energy conformers **1** and **2** of *Fig. 4*, an equal reactivity of (a*ER*) and (e*ES*) through a preferential reaction path, *syn* with respect to the N lone pair *(vide infra)*, could be predicted, thus *not* leading to any enantioselectivity. Even though the remaining of the conformer set might be regarded as nearly degenerate in energy, no clear-cut conclusion could be drawn. Other types of calculations might yield different orders for the various conformers, according to the method and/or parametrization: it remains that the same kind of conclusions will be brought about. This finding, in contradiction with experiment, clearly shows that a more refined approach is necessary, where, obviously, the role of the partner in the formation of a complex will have to be taken into account.

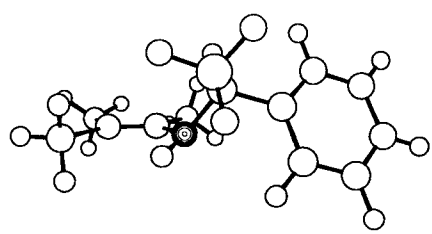


Fig. 7. *Perspective ball-and-stick drawing of the (aER) conformer* **1** *of* Fig. 4

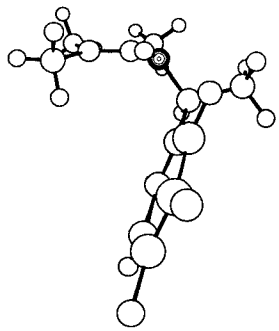


Fig. 8. *Perspective ball-and-stick drawing of the (eES) conformer* **2** *of* Fig. 4

Figs. 7 and *8* display perspective views of conformers **1** (a*ER*) and **2** (e*ES*), respectively, of *Fig. 4* which exhibit all the geometrical features precedently discussed.

In the study of the related chiral enamine with R^4 = (*S*)-cyclohexyl(Me)CH, we have followed the methodology already adopted in the preceding section. The results are displayed in *Fig. 9* and *Table 3b*, with the same topological conventions as those of *Fig. 4*. First of all, one has to note that the whole energetic scale for the series **9–16** is broader

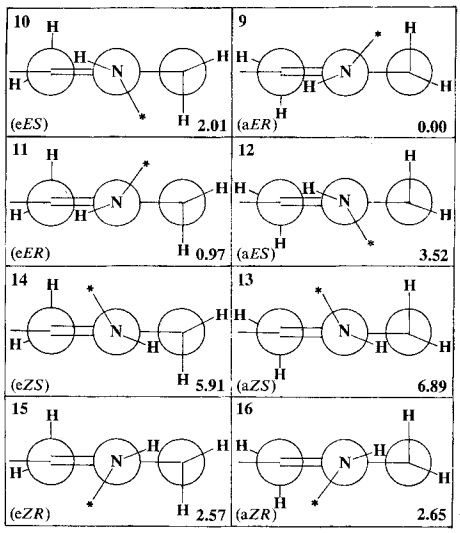


Fig. 9. *Calculated structures of the eight local optimal geometries* **9**–**16** *of the chiral enamine having* R^4 = (S)-*cyclohexyl (Me)CH*. The labels correspond to the topological definitions of *Figs. 2* and *3*. The relative energies are given in kcal/mol. Absolute energies are given in *Table 3*, along with geometrical parameters.

than in the preceding case (6.89 kcal/mol, compared to 1.90 for **1**–**8**). The (a*ER*)-compound **9** is again the most stable, but its (e*ES*)-partner **10** with respect to ring and N-inversions is now found at 2.01 kcal/mol. As previously, the (*E*)-compounds are at lower energy than the (*Z*)-compounds, at the exception of **12** (a*ES*) which is found at 3.52 kcal/mol (the corresponding energy difference of **4** (a*ES*) was only 0.67 kcal/mol when R^4 = (*S*)-Ph(Me)CH). It is, therefore, clear that the cyclohexyl ring brings about more severe steric constraints than the Ph ring. The conformation of the Me and cyclohexyl groups have also been determined. As in the case of Me and Ph (*Fig. 6*), the H-atom on C* is roughly parallel to the H–N–C* bisector and the Me group adopts a staggered conformation with respect to it. However, a striking difference arises dealing with the conformation of the cyclohexyl ring: in the (a*ER*)-compound **9**, the preferential conformation of the mean plane of the cycle can be deduced from that of the Ph ring in *Fig. 6* by a rotation of *ca.* 90°. Clearly, the six-membered saturated cycle interferes with the rest of the enamine framework much more strongly than the Ph group, thus yielding conformers that are separated by large energy differences. It is noteworthy that the most stable compound, apart from its cyclohexyl conformation, has the same topological characteristics as the most stable compound of the Ph series. The latter points comfort the idea that the observed conformational effects are of steric nature and do not involve important electronic effects arising from the phenyl π system, as already stated.

Complexation of Chiral Enamines with Acrylaldehyde. – Prior to the detailed study of complex structures, several important points have to be discussed. The first one deals with complexation itself. In our previous theoretical study [3], we pointed out the fact that although 'loose' complexation with the electrophile is the preferred one, it reversibly leads to a high-energy zwitterionic species. In the case of a 'compact' complex, early H-transfer

from NH to the developing zwitterion can take place, thus avoiding the formation of a high-energy species. This latter type of complex was, therefore, proposed as ruling the overall process. In our new approach of this reaction, we have examined both types of complexes in order to test the validity of these proposals. Another important point deals with N-pyramidalization: it creates an intrinsic anisotropy of the electron density with respect to the C(2)–C(1)–N plane and might, therefore, induce a preferred side for complexation and thus for reaction. The latter point constitutes a classical problem in itself and has to be treated first.

One can define a *syn*- and an *anti*-approach with respect to the N lone pair for complexation with an electrophile, provided that the C(2)–C(1)–N linkage defines a reference plane, and that the N lone pair direction can always be defined by considering the H–N–C* bisector (see *Fig. 2*). We find here a situation analogous to the classical geometry proposed in the studies of the S_N2' reactions [19], and the same kind of analysis can be attempted. Unfortunately, in the latter series of studies, despite the vast number of experimental and theoretical works, no clear-cut rationalization has been found for the observed results. *Bach* and *Wolber* [20] claimed recently that 'the theoretical studies to date are far from conclusive and offer no clear preference for *syn vs. anti* stereochemistry in the S_N2' reaction'. It, nevertheless, remains that an effect does exist, and we had to test whether a similar one is found in our system. We have proceeded as follows: in a model study, we started from vinylamine, and we forced the N-atom to adopt a tetrahedral geometry. Then, formaldehyde, taken as a model electrophile, was approached to the terminal C-atom of vinylamine, at various distances, in quadrant 1 *(Fig. 2)*. The C=O axis was set parallel to the C=C bond, the O-atom pointing out of the C=C bond. We

Table 4. *Variation of the Energy of the Vinylamine-Formaldehyde*[a]) *Complex* (d = 3.0 Å between the two molecular planes) *with Pyramidalization and the Orientation of its Lone Pair*

Angles [°]					ΔE [kcal/mol]		Approach
ε	Ψ_1	Ψ_2	α_1	α_2	3–21G	6–31G**	
± 90	0	180	120.9	121.1	0[b])	0[c])	
− 90	30	150	109.5	109.5	4.6	−0.4	*syn*
90	−30	−150	109.5	109.5	6.5	1.2	*anti*
45	75	−165	109.5	109.5	9.1	3.7	*syn*
45	−75	165	109.5	109.5	10.9	5.4	*anti*
− 135	−15	105	109.5	109.5	7.2	2.2	*syn*
135	15	−105	109.5	109.5	8.3	3.2	*anti*

[a]) Formaldehyde 'loose' approach in quandrant 1 *(Fig. 2)*.
[b]) The complex total energy is −245.547710 a.u.
[c]) The complex total energy is −246.939215 a.u.

thus had the geometry of a loose complex. At 3 Å, three types of *syn*-approaches ($0° > \varepsilon > -180°$) and three types of *anti*-approaches ($0° < \varepsilon < 180°$) were investigated, with the 3-21G and 6-31G** basis sets. The results are given in *Table 4*.

We see that in all cases, the *syn*-complex is preferred (1.0–1.7 kcal/mol at 3 Å, 6-31G**). After careful examination of the calculated results, we finally reached the same conclusions as *Bach* and *Wolber* [20]: practically no changes appear in the energies of the

occupied orbitals, the energy difference between *syn*- and *anti*-structures essentially coming from small changes in inner σ orbitals. We are thus led to the trivial conclusion that the *syn* preference is an indubitable effect, the rationalization of which remaining beyond the scope of this study. Moreover, in our coming discussion of complexation, we will see that in reality, for purely steric reason, the *syn*-approach requirement is always fulfilled in enamines bearing a bulky chiral substituent on N.

Compact Complexes between Enamines and Acrylaldehyde. – *Enamine with R^4 = (S)-Ph(Me)CH.* The eight complexes corresponding to the optimal geometries of the free enamines *(Fig. 4)* were obtained in two steps. In the first step, planar acrylaldehyde was set at a given distance *d* of the C(2)–C(1)–N enamine plane so as to form a pseudo-chair arrangement, as schematically displayed in *Fig. 10,* according to our previous theoretical model which showed that pseudo-boat arrangements were of higher energy [3].

In this geometry, the carbonyl group of acrylaldehyde might be either pseudoequatorial (O^1, s-*trans*-acrylaldehyde) or pseudoaxial (O^2, s-*cis*-acrylaldehyde)[4]). We also see that the position of the chiral group is pseudoequatorial when the enamine has an (*E*)-structure and pseudoaxial for a (*Z*)-structure. The geometry at all centers of the enamine was then fixed at the optimal values of the isolated species. Calculations carried out for enamines interacting with s-*trans*- and s-*cis*-acrylaldehyde showed that the complexes containing the former conformation of the aldehyde are the more stable, while the reverse situation has been found for similar complexes with vinylamine itself [3]. This finding results from the fact that in heavily substituted compounds, the s-*cis*-conformation tends to place the carbonyl group in front of the most hindered region of the system (see *Fig. 10*). Looking at *Figs. 4* and *5*, we see that in all cases only an approach *syn* with respect to the N lone pair should be possible. In an *anti*-approach, very severe steric hindrance would occur between the substituents of the chiral C-atom, especially the Ph group, and acrylaldehyde. Obviously, the energy of *anti*-complexes cannot be reached *via* optimization, for N-inversion and other motions would restore a *syn*-type geometry.

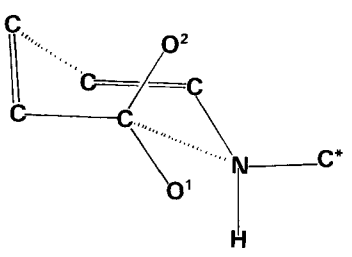


Fig. 10. *Chair-like geometry of the chiral enamines compact complexes with acrylaldehyde.* The O^1 and O^2 positions refer to the s-*trans*- and s-*cis*-conformations, respectively, of acrylaldehyde.

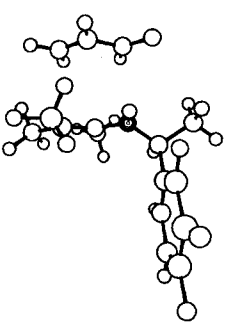


Fig. 11. *Perspective view of the* (e*ES*) *complex* **2cp**

[4]) Similar models, sometimes referred to as '*Zimmerman-Traxler*-like transition-state model', have been proposed for aldol reactions [21].

Upon examination of *Fig. 11* (see also below), it is clear that setting the acrylaldehyde moiety in the bottom half-space leads to unrealistic short distances between nonbonded atoms.

Thus, a very important point is raised: dealing with mobile systems such as ours, it is misleading to treat enantioselectivity as resulting from competitive attacks on one 'free' face and one 'hindered' face. Obviously, strained complexes will *never* be formed. Were an incoming electrophile to approach, the system should evolve so as to always present a global arrangement of low energy.

In the second step, the conformation of the Me group R^1, the bond angles at the N-atom and all the dihedral angles of the H–N–C* part of the system were allowed to relax. This procedure preserves the initial pseudo-chair conformation at C(3) and C(6) so that the topological definitions of *Figs. 2* and *3* remain valid. We, thus, get an univocal correspondences between the conformers of the isolated compounds and the related complexes. Once the approach distance is fixed at *ca.* 3 Å, only very small geometrical rectifications are possible: neither N-inversion nor rotation around C(1)–N are possible, and in reality, only minor changes in the pyramidalization angles, inducing small confor-

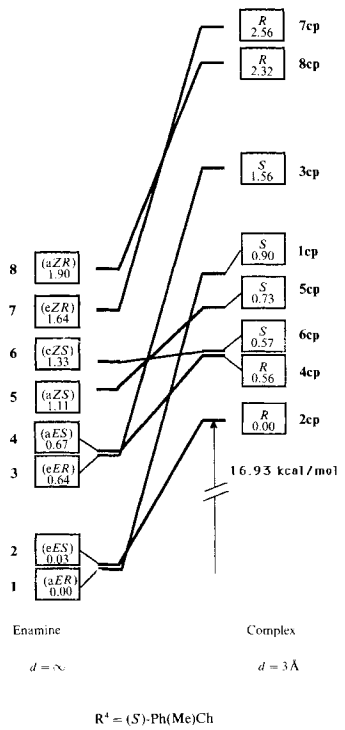


Fig. 12. *Correlations between the eight optimal conformers* **1–8** *described in* Fig. 4 *and the optimized compact complexes* **1cp–8cp** *with acrylaldehyde, at a distance of 3 Å.* The 16.93 kcal/mol energy shift (right) corresponds to the endothermic approach of the partners. On both sides, the relative energies are recalled.

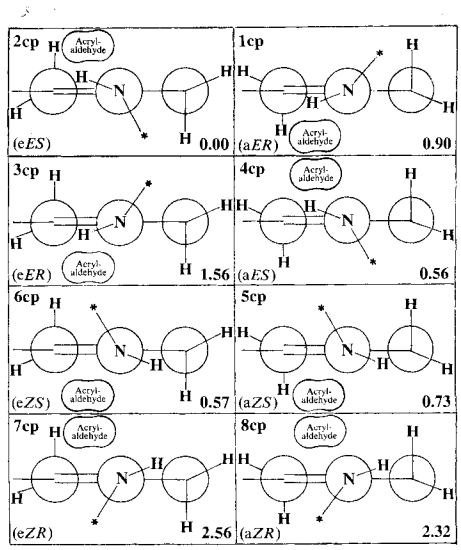


Fig. 13. *Relative energies of the eight optimal structures* **1cp–8cp** *of compact complexes formed between acrylaldehyde and the enamine having* R^4 = (S)-*Ph(Me)CH, at a distance of 3 Å.* Absolute energies are given in *Table 3*, along with geometrical parameters.

mational changes in the substituents of C*, take place. As a main result, these complexes *can not* change their overall topology once they are formed: they can evolve towards a unique product or dissociate, since complexation is endothermic. A practical point results from the analysis of the complex formation: when the terminal C-atom of acrylaldehyde is located in quadrant 1 of *Fig. 2*, the resulting alkylated compound will have a quaternary C-atom C(2) of (*R*)-configuration (see *Scheme*), while an (*S*)-configuration will be obtained when the same C-atom is in quadrant 4.

In *Fig. 12* are reported the one-to-one correlations between free enamine conformers **1**–**8** and the related *syn*-complexes **1cp**–**8cp** at a 3-Å distance of acrylaldehyde. The corresponding schematic geometries and relative energies are displayed in *Figs. 4* and *13*, respectively. The 16.93 kcal/mol value indicated in *Fig. 12* corresponds to the endothermic energy difference between complex **2cp** and the sum of enamine **1** plus acrylaldehyde at infinite separation. A very important result comes to the fore: upon complexation, the correlations between left and right structures (*Fig. 12* and *Table 3c*) are not straightforward, and several crossings appear. The most striking feature concerns the lowest-energy free compounds **1** (a*ER*) and **2** (e*ES*) which yield a high-energy complex **1cp** and the most stable one **2cp**, respectively. The same finding holds with the next duo of quasi-isoenergetic free conformers **3** (e*ER*) and **4** (a*ES*). We see that among the four low-energy systems at infinite separation, two of them (**2** and **4**) yield the lowest-energy complexes leading to an (*R*)-configurated quaternary C-atom C(2) after addition, while the other two (**1** and **3**) yield high-energy complexes leading to (*S*)-configurated C(2). Moreover, the lowest-energy complex **6cp** leading to (*S*)-configurated C(2) is correlated with the high-energy conformer **6** at infinite separation.

These conclusions point out general criteria for the complexes: *i*) as dealing with free conformers, (*E*)-topology is preferred over (*Z*); *ii*) when the chiral group is in the quadrant 2 or 3, the preferred complex **2cp** has its pseudoaxial H-atom of R^3 (at C(6)) situated in the same quadrant as previously observed for the free enamine; *iii*) the only possible complexation places the acrylaldehyde molecule, *syn* with respect to the N lone pair; *iv*) it is noteworthy that in optimal complexes of (*E*)-geometry, the N–H bond somewhat points towards acrylaldehyde in a very favorable position for H-transfer. All those findings are clearly illustrated in *Fig. 11*, where a perspective view of the calculated structure of the (e*ES*)-complex **2cp** *(Fig. 13)* is displayed.

Enamine with R^4 = *(S)-Cyclohexyl(Me)CH.* The corresponding complexes **10cp**–**16cp** have been obtained using the procedure described in the preceding section. The results are displayed in *Fig. 14* and *Table 3d*. At a first glance, we see that the whole energetic range spans 3.95 kcal/mol which is larger than for complexes **1cp**–**8cp** with R^4 = (*S*)-Ph(Me)CH (2.56 kcal/mol, *Fig. 13*) on the one hand. On the other hand, by comparing complexes **10cp**–**16cp** to the conformers **10**–**16** of the free enamine *(Fig. 9)*, two features comes to the fore: *i*) the relative energies of the most stable complexes are lower than those of the related free enamines; *ii*) they appear in the same order for the first three, *i.e.* **9**, **11**, **10**, and **9cp**, **11cp**, **10cp**, so that correlations like those displayed in *Fig. 12* would bring about no crossings. Focusing our attention to the complexes of *Fig. 14*, some salient features emerge: *i*) as already noted, the (*E*)-complexes are of lower energy than the (Z)-complexes, *ii*) here again, the most stable complexes have the N–H bond placed in a geometry favorable for H-transfer, as the reaction proceeds. The selectivity will be discussed in the following section.

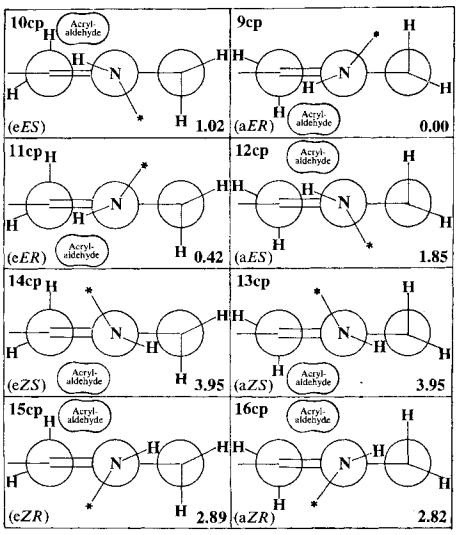


Fig. 14. *Relative energies of the eight optimal structures* **9cp**–**16cp** *of compact complexes formed between acrylaldehyde and the enamine having* R^4 *= (S)-cyclohexyl(Me)CH, at a distance of 3 Å.* Absolute energies are given in *Table 3*, along with geometrical parameters.

An Attempt towards a Model. – The elaboration of a general model that would be based on the preceding study of diastereoisomeric compact complexes remains problematic. Let us examine the results displayed in *Figs. 4, 9, 13,* and *14*. If one considers the (*E*)-conformers that are in a favorable geometry for forming complexes leading to an *easy H transfer from NH* to the forming enolate (*Figs. 4* and *9*), we are left with four quasi-isoenergetic conformers when R^4 = (*S*)-Ph(Me)CH and only three when R^4 = (*S*)-cyclohexyl(Me)CH. Let us assume that these conformers are in fast thermal equilibrium at room temperature, in such a way that an incoming electrophile, at large distance, would only 'see' a unique compound of global (*E*)-geometry. If one recalls that once a compact 'complex' is formed, the relative arrangement of the chiral atoms is fixed so that the absolute configuration of the future quaternary center is determined, a kinetic argument can be raised: *the easiest reaction paths will follow the smallest 'complexation' energy gradients.* In *Table 5* are reported the variations of the relative linear slopes

Table 5. *Relative Gradients in Going from Reactants to Complexes for Conformers (a*ER*), (e*ES*), (e*ER*), and (a*ES*)*

Chiral group R^4	Relative gradients[a])			
	(a*ER*)	(e*ES*)	(e*ER*)	(a*ES*)
(*S*)-Ph(Me)CH[b])	1.01	0.08	1.03	0.00
(*S*)-cyclohexyl(Me)CH[c])	0.99	0.00	0.44	–
Configuration of final quaternary center C(2)	*S*	*R*	*S*	*R*

[a]) The lowest gradient is taken as a reference.
[b]) These values are deduced from *Figs. 4* and *13*.
[c]) These values are deduced from *Figs. 9* and *14*.

obtained in going from reactants to complexes for each type of conformer, the smallest being taken as the reference (zero). We see that when R^4 = (*S*)-Ph(Me)CH, the lowest gradients yield preferentially complexes leading to (*R*)-configurated quaternary centers, while in the case of R^4 = (*S*)-cyclohexyl(Me)CH, this preference will be much less due to a competitive low-energy path yielding a (*S*)-configurated quaternary center. These findings are in good agreement with experimental results [6]. It is worth noting that this model is not free from hinted presupposition, since it relies on the principle that the gradient at the beginning of the reaction coordinate 'reflects' the actual positions of the transition states. This remains acceptable if we consider enantioselective reaction paths that are likely to be very close in character.

Loose Complexes. – The discussion will be restricted to the most stable complexes resulting from calculations with R^4 = (*S*)-Ph(Me)CH. For obtaining them, we have proceeded as in the case of compact complexes *(Fig. 10)* but now, the acrylaldehyde moiety still fixed in a plane parallel to C(2)–C(1)–N has its carbonyl end opposite to the N-atom, as displayed in *Fig. 15*. Two relative arrangements of the reactants.were tested: in the first one, *'endo'*, the carbonyl group of the s-*trans*-acrylaldehyde was set in the same half space as the amino group with respect to a plane perpendicular to the enamine and acrylaldehyde planes and containing the C(1)–C(2) bond *(Fig. 15)*. In the *'exo'* geometry, the carbonyl and the amino groups lied in both half spaces *(Fig. 15)*. At 3-Å distance, the *'endo'*-geometry is more stable by at least 1.7 kcal/mol than the *'exo'* one. From now on, we will only deal with the *'endo'*-geometry of the reactants. As in the preceding discussion of compact complexes, a *syn*- and *anti*-approach with respect to the direction of the N lone pair can be defined, and both were examined. In contrast with the case of compact structures where we have seen that only *syn*-complexes were likely to occur for steric reason, both types of complexes can exist with, however, a preference for the *syn* approach. The final optimized geometries of *'endo'*-complexes are given in *Fig. 16*.

Two quasi-isoenergetic complexes are first obtained, both having the *syn*-geometry. They derive from the low-energy conformers **1** (a*ER*) and **2** (e*ES*) of the free enamine. Then comes the related couple of *anti*-complexes at 0.32 and 1.12 kcal/mol, respectively. We see that the preferential *syn*-complexation is less pronounced than in the model study

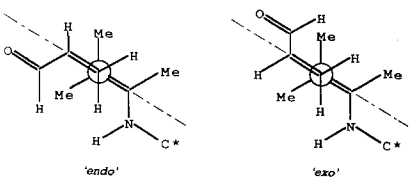
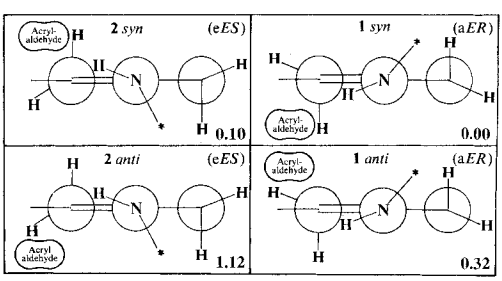


Fig. 15. *Geometries of the* 'endo' *and* 'exo' *loose complexes*



* = R^4 = (*S*)-Ph(Me)CH

Fig. 16. *Relative energies of the* 'endo' *loose complexes formed between acrylaldehyde and the chiral enamine having* R^4 = (S)-*Ph(Me)CH, at a distance of 3Å.*
The calculated energies are in kcal/mol; **1***syn* (a*ER*): −66839.55; **2***syn* (e*ES*): −66839.45; **1***anti* (a*ER*): −66839.23; **2***anti* (e*ES*): −66838.43.

of loose complexes of vinylamine and formaldehyde (*Table 4*). In the actually optimized structures, the direction of the N lone pair, as previously defined, is far from being optimal for strong conjugation. We have seen in *Table 4* that, in the absence of substituents, the *syn*-preference decreases rapidly upon rotation around the C(1)–N bond. In the substituted compounds, the latter electronic effect mixes with steric factors, and we just obtain some memory of the trends observed in unsubstituted compounds.

Comparison between Compact and Loose Complexes. – A crucial question arises concerning the competition between compact and loose complexes in order to account for the observed enantioselectivity. First of all, the main feature is that at all distances, loose complexes are more stable than the corresponding compact equivalents as already stated in our theoretical study of enamine addition to ketones [4]. *E.g.*, an energy difference of 1.6 kcal/mol is found between the loose *'endo'*-and compact *syn*-complexes of the (e*ES*) enamine conformer, at a distance *d* of 3 Å (see the energies in the captions of *Figs. 13* and *16*). It is, therefore, evident that no definitive argument in favor of compact reactive complexes can be found in the study of complexation alone. The fundamental point that we have already raised, based on both theoretical and experimental facts, is that in non-polar aprotic media, as for example in benzene which is frequently used, the formation of an intermediate zwitterionic species which would necessarily result from a loose complex, is very unlikely. Let us recall that it is the possibility of easy and concomitant H-transfer from N–H to the enolate in formation which avoids the formation of a high-energy, reversibly formed zwitterion. The assumption that these findings remain valid in the present case is of crucial importance. Due to the size of the system, it is practically impossible to optimize a complete reaction potential energy surface, so that we can only use arguments derived from the study of simpler systems. With this aim, let us consider the following reaction, calculated at 6–31 G** level with fully optimized structures:

$$\text{enolate} + NH_4^+ \rightarrow \text{enol} + NH_3 \qquad (\Delta E = -162 \text{ kcal/mol})$$

A potential energy excess of 162 kcal/mol in favor of the neutral system is found. Obviously, this value constitutes a qualitative benchmark. An energy of 80 kcal/mol was obtained for the endothermicity of vinylamine and formaldehyde aldolization, yielding a zwitterion [4]. In the latter case, a C–C bond was formed; if we substract its corresponding energy (*ca.* 80 kcal/mol) we get: 162 – 80 = 82 kcal/mol, which shows the qualitative convergence of both estimations. These data clearly show that, in aprotic and weakly solvating media, the simultaneous creation of two charged species, although compensated to some extent by a C–C bond formation, remains very unlikely and reveals the necessity of concomitant H-transfer in order to get an efficient reaction (many related reactions are fast at room temperature)[5]).

General Conclusion. – *1*) The study of several secondary enamines bearing various substituents has shown that, with the exception of the prototype vinylamine for which inversion is very easy, pyramidalized structures are generally found. This effect cannot be assigned to clearly separable electronic or steric effects. Indeed, electronic factors such as conjugation, interaction fo the N lone-pair electrons with the rest of the system, H-bonds,

[5]) A similar argument is proposed for the transition states of some *Michael* additions of lithium amide to acrylate in [22a]; see parent proposals in [22b–d].

hyperconjugation *etc.*, are obviously likely to play a role. Similarly, interactions between atoms and groups of atoms that are not directly bound are observed, but it is rather meaningless to try to separate them in order to devise a simple general rule. The actual calculated energy differences between the various free conformers appear to be very small (of the order of a few kcal/mol), much less than the effects that might be estimated in simple model compounds. As a matter of fact, in the calculation of these structures, no separation between σ and π electrons can be done, because both mix strongly upon geometry distorsion and although it remains very tempting to do so, any kind of reductionist description would be as arbitrary as artificial.

2) Another very important feature arises from the examination of the optimal structure geometries: the product distribution based on the lowest energy structures, *i.e.* (a*ER*) and (e*ES*) of *Fig. 4*, would lead to an erroneous conclusion, since the formation of (*R*)- or (*S*)-quaternary C-center could be predicted with equal facility. This finding shows that, at least in that case, predictions made from the examination of only one of the reactant structures are not justified. The latter point rules out our previous *ad hoc* model relying on a *a posteriori* assignment of the chiral-group conformation. We think that it should be the case for many other models built on the same premises.

Two important partial conclusions emerge from this part of our study: *i*) well-individualized local minima that can be interconverted through endothermic motions of the whole framework (C–N rotation N-inversion, cycle inversion, or combination of them) are found; *ii*) no reliable prediction of the enantioselectivity can be done upon examination of the free enamine conformers.

3) The study of the various types of complexes formed between a chiral enamine and acrylaldehyde has been achieved in several steps. First, with a pyramidalized vinylamine molecule and formaldehyde taken as an electrophile, we have shown that the preferential complexation tends to place the electrophile in a *syn*-geometry with respect to the N lone pair. In the investigated conformers of chiral enamines plus acrylaldehyde, *syn*-complexes were always the only realistic ones, their *anti*-counterparts being prohibited by very severe steric hindrance. This preference for *syn*-complexation was also found to a lesser extent in the study of loose complexes.

4) Dealing with the chiral group $R^4 = (S)$-Ph(Me)CH, we have shown that the energetic correlations between the conformers of the free enamine and those of the compact complexes are not straightforward, the energy order of the complexes being not the same as that of the free conformers. Upon formation of a complex, smooth relaxation of the system takes place so as to adapt itself to new overall requirements. The corresponding geometrical changes are not important in magnitude but they are sufficient to modify the energetic order found in the free substrates, hence the complicated correlation diagram of *Fig. 12*. An important feature is noteworthy: once the optimal geometry of a complex is reached through relaxation of the system, no further geometrical changes are possible because all the degrees of freedom are frozen: the complex can only evolve towards products passing through the remaining of the activation barrier or towards separation of the reactants (the complex formation is reversible).

5) Once the preceding considerations are taken into account, a simple and crude estimation of the overall reactivity can be proposed. It is based on the fact that, considering the low-energy conformers of the free enamine as nearly degenerate in energy, *i*) only those having a favorable geometry for further H-transfer are suited to yield reactive

complexes, *ii*) the relative energy gradients for reactive-complex formation is an index of the overall reaction competitive facilities since it might be assumed that the lowest-energy gradient – all things being equal – will lead to the lowest transition state, or, in other words to the fastest reaction. Upon examination of the relevant gradients, one is thus able to properly correlate the calculations with the experimental facts.

6) The preceding exploration, although far from being complete, shows that the problem of enantioselectivity depends on a large number of factors that cannot be examined independently on systems that are close to the real ones. The experimental (*R*)/(*S*) ratio is a number that hides a considerable complexity, and its easy measure tends to induce the elaboration of oversimplified models. As pointed out in the introduction, these models are nevertheless necessary, even with a simple dialectic perspective. They help in deriving new substrates and new experiments, and thus they must be improved. It appears that reasoning from the structure of one reactant, *e.g.* the chiral enamine alone, is misleading. The formation of a complex leading potentially to reaction involves secondary energetic factors of weak magnitude, such as small conformational changes (weak pyramidalization-angle variation, among others) that all lie in an energy range of *ca.* 1 kcal/mol which is the enthalpy difference ruling the final (*R*)/(*S*) ratio (apart from any entropic consideration). Therefore, it becomes aleatory to select the effect which looks determinant. At any rate, it is still more unrealistic to devise a general model which rely on one of these aspects, on the basis of the isolated reagent geometries. In the latter case, a number of additional more or less explicit assumptions are necessary so that the final model rather looks like a procrustean bed: all new data must fit and 'can fit' with some additional effort. The predictive power of these models is very poor; they only seem efficient in explaining the experiment which they derive from, and it is very difficult to escape from this tautology.

We are aware of the fact that our study, although partial, does not reach simple conclusions regarding the theoretical models of enantioselectivity. We wish to end by a provocative suggestion: the sophisticated systems that are experimentally used must rather be examined like something intermediate in complexity between simple well-defined molecules and enzyme-active sites. In this perspective, we have to change our usual approaches. Rigid models do not seem appropriate and to the classical 'lock-plus-key' image, we prefer that of a slug progressing on a soft wavy surface, at the least energetic cost, with smooth and progressive adaptation. We think that a considerable methodologic effort has to be done in that direction.

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