stable than the tetrahedral intermediates of acyl transfer reactions or, in other words, activation barriers for the breakdown of pentavalent intermediates are lower.

Experimental Section

Materials. The solid compound having either structure $R_{iv}OH$ or R_vOH was prepared as described by Granoth and Martin.[2] Reagents for the preparation of acid, base, or buffer solutions were analytical grade and were used directly as received. The ionic strength of all solutions was maintained constant at 0.1 M by the addition of sodium chloride. All experiments were carried out at 25.0 ± 0.1 °C. Conventional spectroscopic experiments were carried out with a Cary 2390 spectrophotometer interfaced with an Apple IIe microcomputer. A Durrum–Gibson spectrophotometer interfaced with a Tektronic 4051 microcomputer was employed for stopped-flow experiments.

Spectroscopic Acidity Constants. Curve I of Figure 2 was obtained by preparing a 4.8×10^{-4} M solution of $R_{iv}OH/R_vOH$ in 0.002 M HCl and placing this in one syringe of the stopped-flow apparatus. This was mixed with various sodium hydroxide or buffer solutions to give the desired final pH, and a wavelength of 275 nm was monitored. Absorbance readings are constant from 10 to 50 ms and were used to construct curve I.

Curve II of Figure 2 was obtained by mixing the stock 0.002 M HCl solution of $R_{iv}OH/R_vOH$ equally with various buffers and placing the resultant solution in a constant-temperature bath for 1 month. Full spectra were recorded on the Cary spectrophotometer. A wavelength of 267 nm was chosen for analysis.

Spectroscopic acidity constants were determined according to the formula $K_a = [H^+](A_{acid} - A)/(A - A_{base})$, where A_{acid}, A_{base}, and A are respectively the absorbance readings in acid, base, and the solution in question. Values of K_a were calculated for several solutions of intermediate pH, and the average was taken.

Kinetic Measurements. Kinetic measurements above pH 8 were carried out by addition of 2 μL of a stock acetonitrile solution of the substrate directly to a thermostated cuvette to give a solution of $2–5 \times 10^{-4}$ M. The decrease in absorbance at 267 nm was recorded as a function of time on the Cary spectrophotometer, first-order rate constants being calculated as the slope of plots of $\ln (A - A_\infty)$ vs. t.

The kinetic measurements below pH 7 were carried out by addition of the stock acetonitrile solution to 0.01 M NaOH. This solution was kept for at least 30 min to allow for completion of the transformation to B2. Measurements from pH 2.5 to 6 were carried out on the Cary by mixing the base solution with an appropriate acid or acidic buffer solution. Below pH 2.5, the stock base solution was placed in one syringe of the stopped-flow apparatus and mixed with the appropriate HCl solution. In both cases the increase in absorbance at 267 nm was recorded, and first-order rate constants were calculated as the slopes of plots of $\ln(A_\infty - A)$ vs. time.

Acknowledgment. Continued financial support of the National Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Registry No. $R_{iv}OH$, 67771-45-3; R_vOH, 67759-42-6.

Stereochemistry of the $R_1(X{=})C(sp^2){-}N(sp^3)R_2R_3$ Fragment. Mapping of the Cis–Trans Isomerization Path by Rotation Around the C–N Bond from Crystallographic Structural Data

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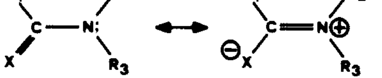
Contribution from the Centro di Strutturistica Diffrattometrica e Dipartimento di Chimica, Università di Ferrara, 44100 Ferrara, Italy. *Received July 30, 1985*

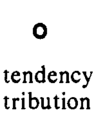
Abstract: The geometry of the $R_1(X{=})C(sp^2){-}N(sp^3)R_2R_3$ molecular fragment has been studied in 90 X-ray crystallographically determined molecules containing such a group (amides, thioamides, enamines, amidines, anilines, etc.). This tends to be planar owing to the partial double bond character of the C–N bond. In a crystal environment, however, it is often deformed from planarity, the deformation being described by the torsion angle τ around C–N ($0 \le |\tau| \le 90°$) and the out-of-plane bending of the amino nitrogen, χ_N, ranging from 0° for planar sp^2 to 60° for tetrahedral sp^3 nitrogen. It is shown that out-of-plane deformations are consistent with two different processes: (a) the simple out-of-plane bending of sp^2 nitrogen (a vibrational coordinate) and (b) a more complex motion combining the twisting around the C–N bond and the nitrogen bending (which, according to the structural correlation method, can be considered to map the geometrical changes of the group along the "reaction" path of cis,trans-isomerization of the group itself). An energetic model of the isomerization process, based on molecular mechanics considerations, has been proposed. Proper choice of the parameters in the force field gives rise to an energy map, $E(\tau,\chi_N)$, where the experimentally determined deformations are shown to be nicely located along the energy valley leading from the planar conformation to the rotated and pyramidalized transition state.

The $R_1(X{=})C(sp^2){-}N(sp^3)R_2R_3$ (hereafter shortly indicated as $C(sp^2){-}N(sp^3)$) molecular fragment **1** is found in a variety of



1 **1a**

organic molecules, such as amides and carbamates (O), thioamides and dithiocarbamates (S), amidines (N), enamines (D), anilines (A), and naphthylamines (B). The group displays a definite tendency to be planar, which can be accounted for by the contribution of the polar form **1a** to its fundamental state. A large number of dynamic NMR measurements have been carried out in an attempt to evaluating the barriers for rotation around the C–N bond. Typical values for *N*-dimethyl derivates are, on the average, 20.7, 18.1, 12.8, 9.0, and 5.1 kcal mol^{-1} for thioamides, amides, amidines, enamines and anilines, respectively.[1–5] This



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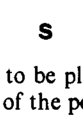

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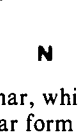

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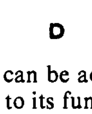

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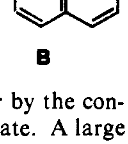

B

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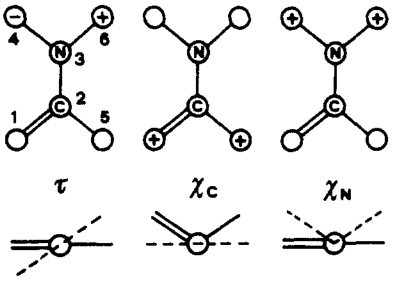
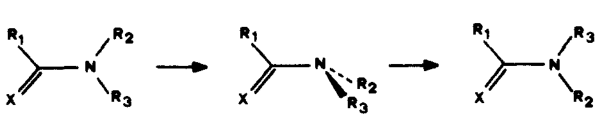


Figure 1. Internal coordinates system describing the out-of-plane deformation of the C(sp^2)–N(sp^3) group (0° ≤ $|\tau|$ ≤ 90°; 0° ≤ $|\chi_C|$, $|\chi_N|$ ≤ 60°).

suggests that the heights of the barriers can be directly related to the relative contribution of **1a**, which, on the other hand, is confirmed by the fact that the barrier increases to 7.0–8.6 kcal mol^{-1} in *N*-dimethylanilines para-substituted by various electron-withdrawing groups.[1]

In spite of this generic tendency of planarity, several crystal structures have been found where the group undergoes out-of-plane distorsions by rotation around the C–N bond and/or nitrogen pyramidalization. The basic idea of this paper is that of analyzing, using a suitable system of orthogonal coordinates, the out-of-plane distorsions in a large number of molecules containing the C(sp^2)–N(sp^3) fragment with the aim of finding the geometrical modifications along the path of what could be called the reaction of cis,trans-isomerization (**2** → **3** → **4**) of the group itself. This



2 **3** **4**

is an application of the so-called structure correlation method.[6] Partial applications of the method to the present fragment already have been reported. In particular, a study on the deformations of the amide group in medium-ring lactames[7] has defined most of the mathematical formalism to be used later, but the high rotation barrier in those compounds did not allow the finding of compounds deformed enough to map the entire reaction path; in subsequent studies[8,9] more severely distorted molecules, mainly amidines and enamines, were reported, and a generic interconnection between rotation around the C–N bond and nitrogen pyramidalization was observed but no general conclusion was drawn. Finally, preliminary accounts of this work have been given in scientific meetings.[10]

Coordinate System and Compounds' Selection. The out-of-plane deformation of the C(sp^2)–N(sp^3) group **1** can be more properly described[7,11,12] in terms of its internal orthogonal coordinates τ, the mean twisting angle around the C–N bond ranging from 0° (planar group) to 90° (when the two halves of the group are perpendicular), and χ_N and χ_C the out-of-plane bending angles of the N and C atoms, respectively, ranging from 0° (plane sp^2 atoms) to 60° (sp^3 atoms).

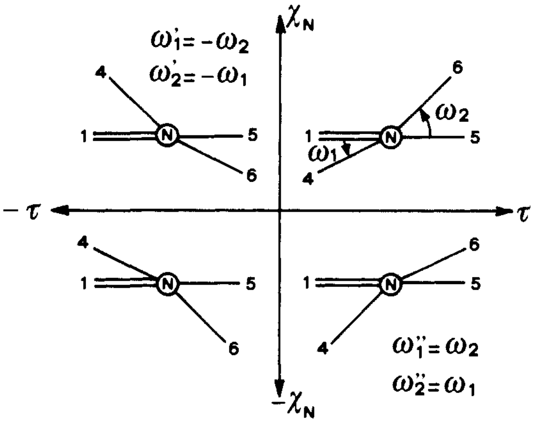


Figure 2. The four quadrants of the (τ, χ_N) space. Different molecular geometries corresponding to the four (+,+), (+,–), (–,+), and (–,–) combinations of the variables.

Defining the four torsion angles ω_1 = X–C–N–R$_3$, ω_2 = R$_1$–C–N–R$_2$, ω_3 = R$_1$–C–N–R$_3$, and ω_4 = X–C–N–R$_2$ it is easy to show by the methods of the group theory that $\tau = (\omega_1 + \omega_2)/2$, $\chi_C = \omega_1 - \omega_3 + \pi \pmod{2\pi} = -\omega_2 + \omega_4 + \pi \pmod{2\pi}$, and $\chi_N = \omega_2 - \omega_3 + \pi \pmod{2\pi} = -\omega_1 + \omega_4 + \pi \pmod{2\pi}$. The geometrical meaning of τ, χ_C, and χ_N is illustrated in Figure 1.

Experimental data for the present analysis were retrieved from the Cambridge Structural Database (1983 release).[13] A total number of 90 groups, found in 68 different references, have been taken into account.[14] Only crystal structures from diffractometer data without disorder problems were considered. For all compounds R$_2$ and R$_3$ N-substituents were alkyl groups (mostly methyl or ethyl) or were a part of six-membered piperidine, morpholine, and piperazine rings. Compounds where R$_2$ and R$_3$ were part of a five-membered ring were excluded as the free nitrogen pyramidalization appeared to be hindered[9] in such rings. The final list includes 23 anilines, 8 naphthalamines, 16 enamines, 14 amidines, 24 amides (including 4 carbamates), and 5 thioamides or dithioamides. Amides and thioamides represent a selection of structures displaying the highest out-of-plane deformations on a larger member of compounds retrieved.

Results

For each of the 90 C(sp^2)–N(sp^3) groups the corresponding values of the variables τ, χ_C, χ_N, $d_{C\text{-}N}$, and $\langle\alpha_N\rangle$ (i.e., the average value of the three C–N–C angles at the nitrogen) have been computed.[15] χ_C values are always very small (–6.0° ≤ χ_C ≤ 4.4°, average $|\chi_C|$ = 1.7°). This indicates that the sp^2 carbon has a stronger resistence to out-of-plane bending, and, therefore, this type of deformation can be neglected in the following discussion. Conversely χ_N values range from –54.4° to 53.9° attaining degrees of pyramidalization of the nitrogen not far from the sp^3 hybridization (χ_N = ±60°). In discussing the intercorrelation between χ_N and τ values, it has to be remarked that they are calculated with an algebraic sign; the (τ, χ_N) plane can be divided into four quadrants, ($+\tau$, $+\chi_N$), ($+\tau$, $-\chi_N$), ($-\tau$, $+\chi_N$), and ($-\tau$, $-\chi_N$),

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[14] The list of structural data references has been deposited as supplementary material (Table S1).

[15] The table of τ, χ_C, χ_N, $d_{C\text{-}N}$, and $\langle\alpha_N\rangle$ values together with their standard deviations and overall disagreement *R* factor has been deposited as supplementary material (Table S2).

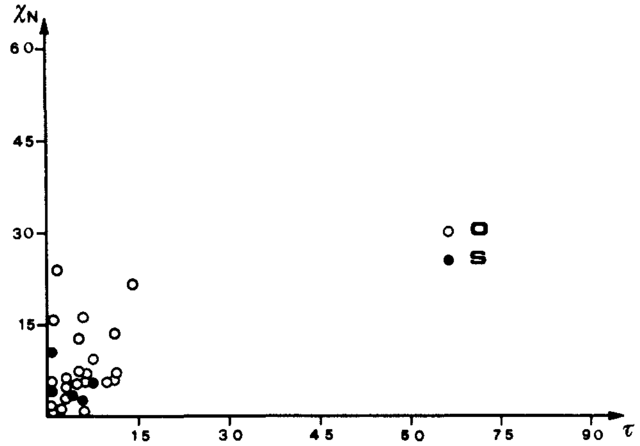

Figure 3. Correlation diagram τ vs. χ_N for the amides and thioamides investigated.

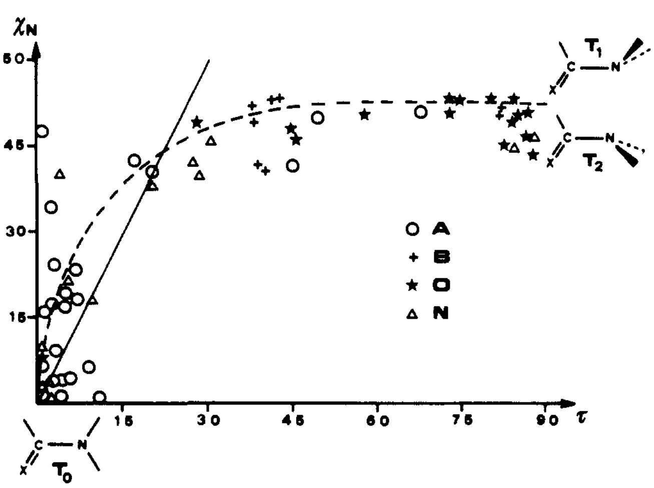

Figure 4. Correlation diagram τ vs. χ_N for all the other classes of compounds studied.

corresponding to the four out-of-plane deformations shown in Figure 2. Deformations in opposite quadrants (+,+) and (−,−) and, of course, (+,−) and (−,+) correspond to couples of enantiomeric conformations, which do not need to be distinguished as stereochemically and energetically identical if $\chi_C = 0°$ (as actually assumed in a first approximation). Conformations in adjacent quadrants are different only in the nonbonded interactions between third neighbors, $|\omega_1|$ being smaller than $|\omega_2|$ in (+,+) and (−,−) but wider in (−,+) and (+,−) quadrants. The distribution of the experimental data indicates that, while anilines do not show any quadrant preference, amides, thioamides, and amidines are mostly located in (+,+) and (−,−) quadrants and enamines in the (−,+) and (+,−) ones. This is in agreement with the observation that there is a smaller steric hindrance on the side of the double bond allowing $|\omega_1|$ to be smaller with the only exception of enamines. However, from the point of view of finding out the reaction path for the 2 → 3 → 4 isomerization the different distribution in the four quadrants seems to be a steric feature of minor importance, and, accordingly, all τ and χ_N values have been reduced to the first quadrant. The correlation diagrams τ vs. χ_N are shown in Figure 3 for amides and thioamides and are shown in Figure 4 for all the other classes of compounds.

The other parameter undergoing large variations is the d_{C-N} bond distance, which is found to be in the range of 1.314–1.461 Å. The d_{C-N} vs. χ_N correlation plot is reported in Figure 5; the linear correlation coefficient has been calculated to be 0.893. The d_{C-N} vs. τ plot is not reported here. It shows two distinct regions. In the first ($0° \leq \tau \leq 15°$), d_{C-N} distances are uncorrelated to τ values, being distributed almost uniformely in the range of 1.31–1.40 Å, the largest values corresponding to pyramidalized nitrogens. In the second one points are rather scattered associating an increase of d_{C-N} from 1.38 to 1.44 Å with τ changes from 15° to 90°. All these points correspond to increasingly pyramidalized nitrogens, and it must be concluded that d_{C-N} values are much more determined by χ_N than τ values.

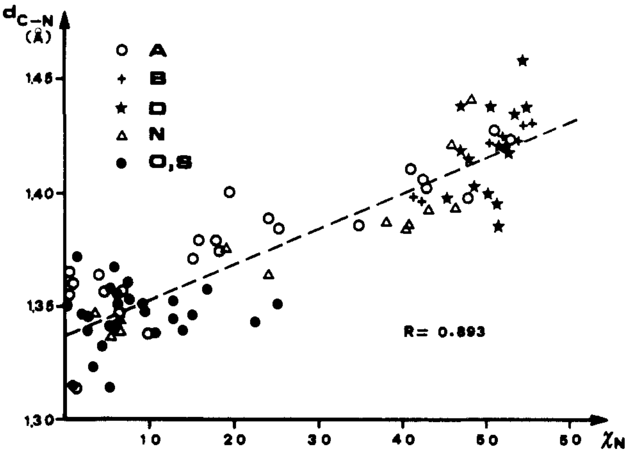

Figure 5. Correlation diagram between the d_{C-N} bond distances and the χ_N values for all the compounds studied.

Discussion

Data of Figure 3 for amides and thioamides show that both τ and χ_N values cluster near the origin, indicating a greater out-of-plane deformation resistance in such compounds, in agreement with what previously remarked on the effect of strong X electronegative substituents in **1**. This, however, is not the only reason for not having heavily deformed arrangements, the second one being probably related to the small steric hindrance of the C=O or C=S groups.

More severe distortions are more likely to be found in syn-amidines N, enamines D, ortho-substituted anilines A, and 8-substituted naphthylamines B both for steric hindrance and lower deformation energy. Figure 4 shows that this is the case. Here are clearly indentifiable two different deformation types. The first, causing simple nitrogen pyramidalization, is represented by the points at τ near zero and increasing χ_N and can be called "butterfly" deformation. The second, which could be called "combined", associates a rotation around the C–N bond (increasing τ) with nitrogen pyramidalization (increasing χ_N). The diagonal straight line of equation $\chi_N = 2\tau$ ideally separates mostly "butterfly" (on the left) from mostly "combined" conformations. The "combined" motion admits a simple VB interpretation; the rotation around C–N causes the decoupling of the π system, while nitrogen rehybridizes engaging its p_z AO into a sp^3 hybrid carrying the lone pair.

This point of view is supported by data of Figure 5, showing that the nitrogen $sp^2 \rightarrow sp^3$ rearrangement is associated with a remarkable lengthening of the d_{C-N} distance. Standard bond distance values for pure single $C(sp^2)–N(sp^3)$ and double $>C=N<$ bonds are usually reported to be 1.44 and 1.27 Å, respectively, and the presently observed range (1.314–1.461 Å) almost encompasses the full variation range.[16]

The main point about d_{C-N} variations is why they correlate reasonably well with χ_N but not with τ. This cannot be explained by changes of the S_π overlap integral between the p_z AO's on carbon and nitrogen. This overlap can be calculated to change with τ according to the expression

$$S_\pi \propto \cos(\tau) \qquad (1)$$

and decreases as 1, 0.97, 0.87, 0.71, 0.50, and 0 while τ assumes the values of 0, 15, 30, 45, 60, and 90°. The evaluation of the

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[16] Of course d_{C-N} is found to be inversely correlated with C=X variations. The scatter plot is not reported because of both the lack of relevance in the present discussion and the rather poor quality of the correlations. The two parameters are intercorrelated with correlation coefficients of 0.75 for amidines and 0.73 for anilines and naphtylamines together, while the variation ranges are too small for any intercorrelation to be established in the other classes of compounds.

overlap S_π of the nitrogen p_z AO with that on carbon as a function of the nitrogen pyramidalization angle χ_N can be reduced to the calculation of the p_z component of the nitrogen hybrid orbital carrying the lone pair vs. χ_N. A simple coordinate transformation on the formulas given in previous papers[17] shows that S_π can be expressed as

$$S_\pi \propto (1 - \mathrm{tg}^2(\chi_N/2))^{1/2} \qquad (2)$$

which decreases in the order 1, 0.98, 0.93, and 0.82 while χ_N assumes values of 0, 20, 40, and 60°. It can be seen that S_π decreases with τ much faster than with χ_N in complete disagreement with the observed fact that d_{C-N} changes according to χ_N and not τ variations. Yet the double bond formation can be considered as an effect of a second order perturbation of the p_z AO's on carbon and nitrogen. The energy of such a perturbation is of the form $E = \beta^2/\Delta E$,[18] where β is the exchange integral (roughly proportional to S_π) and ΔE is the energy difference between HOMO (p_z on nitrogen) and LUMO (antibonding π^* orbital on C═X). The energy of the former is, by itself, lower than that of the latter and is further lowered by the $sp^2 \rightarrow sp^3$ nitrogen rehybridization combining the s (nitrogen) AO whose energy is some 13 eV lower than that of the p (nitrogen) AO. So the overall effect of rehybridization is that of increasing the $|\Delta E|$ and decreasing $|E|$ with consequent decreasing of π-bond order and a lengthening of the d_{C-N} bond distance.

From the point of view of the structure correlation method[6] the "butterfly" motion corresponds to a single out-of-plane deformation not leading to any chemical reaction. Conversely, the "combined" motion can be considered representative of the geometrical changes undergone by the group along the reaction path of the cis–trans isomerization of the group itself, the point of (τ, χ_N) = (90, ≃50) in Figure 4 describing the plausible geometry of the transition state.

The data show that two different T1 and T2 transition states are conceivable, which are both sketched on Figure 4. Clearly they are not distinguishable if the C═X double bond is part of an aromatic system (e.g., anilines) and both are not attained for amides and thioamides. In the case of enamines and amidines they are both experimentally observed, but the former are mostly found to adopt the T1 form and the latter the T2 one. This second conformation can be imputed to a stereoelectronic effect causing the nitrogen lone pair to prefer the conformation trans to a polar bond (in this case the C═N bond).[19]

The reaction path for the rotation around the C–N bond in *N*,*N*-dimethylaniline, calculated by different MO approaches (EHT, CNDO/2, INDO, PCILO, and ab initio STO-3G),[20] has been reported. Such a path is completely different from that found from experimental geometries and illustrated by the dashed line in Figure 4. The latter seems to suggest the group inversion starts with the out-of-plane bending of the nitrogen (a simple molecular vibration), evolving in the rotation around the C–N bond only when the nitrogen is remarkably pyramidalized. This point of view is supported by the data of Figure 5 which show, through the lengthening of the d_{C-N} bond, that the weakening of the partial C–N double bond is mainly determined by the nitrogen pyramidalization.

An Energetic Model for the Cis–Trans Isomerization Process. The building up of a mathematical model for the energy hypersurface seems to be opportune at least for two reasons. The first comes from the already remarked discrepancy with the quantum mechanically calculated[20] isomerization path. The second one is of more general character, involving the central question whether the structure correlation method[6] actually maps the true reaction coordinate, that is if the determined path follows the valley connecting reagents and products on the energy hypersurface.

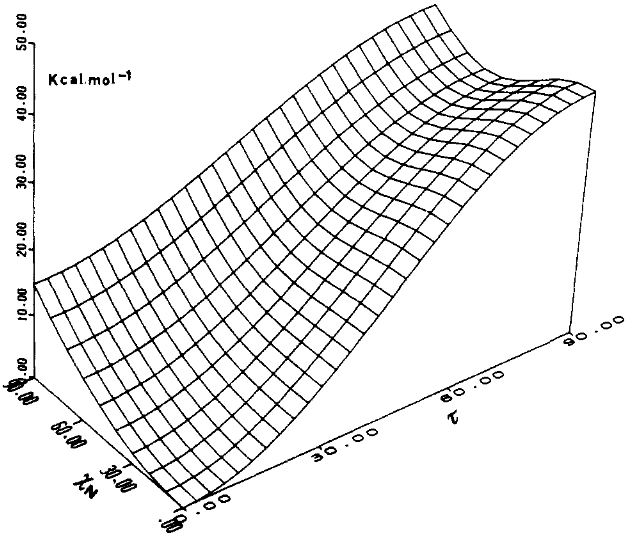

Figure 6. Potential energy surface as a function of $\tau = \tau'/2$ and χ_N calculated according to eq 3.

The energy model used here is based on rather simple molecular mechanics considerations. It has been originally proposed by Dunitz and Winkler[7,11] and substantially modified in this paper to make independent the three energy parameters. This model is summarized in the equation

$$V(\tau', \chi_N) = (\mathrm{CTIB} + \mathrm{IB})(1 - \cos\tau')/2 + \mathrm{QP}(1 + \cos\tau')\chi_N^2/2 + \mathrm{IB}(1 - \cos\tau')(\cos 3\chi_N - 1)/4 \qquad (3)$$

where the potential energy as a function of $\tau' = 2\tau$ and χ_N, $V(\tau', \chi_N)$, is considered to be dependent on three parameters, CTIB = cis–trans isomerization barrier, IB = pyramidal inversion barrier of sp^3 nitrogen, and QP = force constant for the out-of-plane bending of the sp^2 nitrogen. The function has zero value at the origin, corresponding to the equilibrium geometry of the group. For $\tau' = 0°$ it increases linearly with χ_N^2, representing the elastic out-of-plane deformation energy of the planar sp^2 nitrogen; for $\chi_N = 0°$ and $\tau' = 180°$ the function has the value CTIB + IB, which differs from CTIB by the energy needed to make planar the sp^3 nitrogen, the more stable form at $\tau' = 180°$. Finally it assumes exactly the value of CTIB for $\tau' = 180°$ and $\chi_N = 60°$ (hypothetical transition-state geometry). The expressions (1 + cos τ') and (1 − cos τ') appearing in the second and third terms of eq 3 are introduced in order to cancel progressively out the second term, replacing it by the third one while τ' changes from zero, where the stable nitrogen form is the planar one, to 180°, where the stable form is pyramidal. The CTIB value (see above) is in the range 5–21 kcal mol^{-1}, IB can be assimilated to the inversion barrier in ammonia (usually reported to be 6 kcal mol^{-1} [21]), and QP can be evaluated by a variety of spectroscopic or molecular mechanical data to be of the order of magnitude of 5–10 kcal mol^{-1} rad^{-2} (see ref 11). The choice of reasonable values for these parameters accounting for all the compounds studied is clearly impossible. Average values have been chosen as CTIB = 14 kcal mol^{-1}, IB = 8 kcal mol^{-1}, and QP = 8.0 kcal mol^{-1} rad^{-2}.

The potential energy surface calculated with these parameters is reported in Figure 6. It shows an energy valley which is compatible with the distribution of observed data of Figure 4 but with the discrepancy that the transition state is forseen at (180, 60) of (τ', χ_N) instead of the observed value of nearly (180, 50). The reason for that can be sought for in the neglect of nonbonded van der Waals interactions among third neighbors, that is the function to be reckoned is to be expressed as

$$V'(\tau', \chi_N) = V(\tau', \chi_N) + E_{nb}(\tau', \chi_N) \qquad (4)$$

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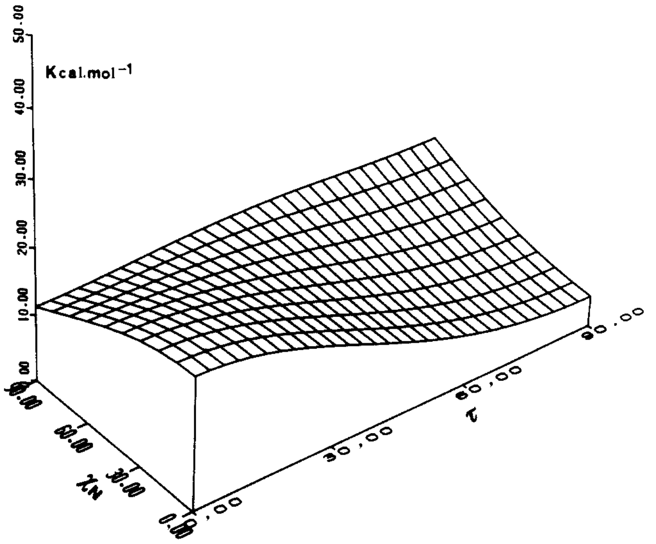

Figure 7. Nonbonded interaction potential energy, E_{nb}, calculated as a function of $\tau = \tau'/2$ and χ_N.

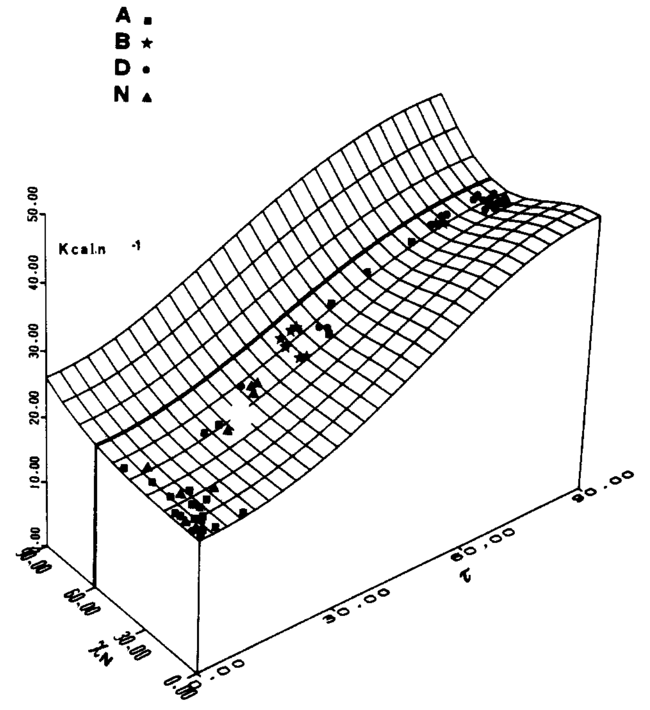

Figure 8. The total energy surface as a function of $\tau = \tau'/2$ and χ_N calculated according to eq 4. The experimental points have been reported on the surface for all compounds but amides and thioamides (some points are missing owing to superimposition).

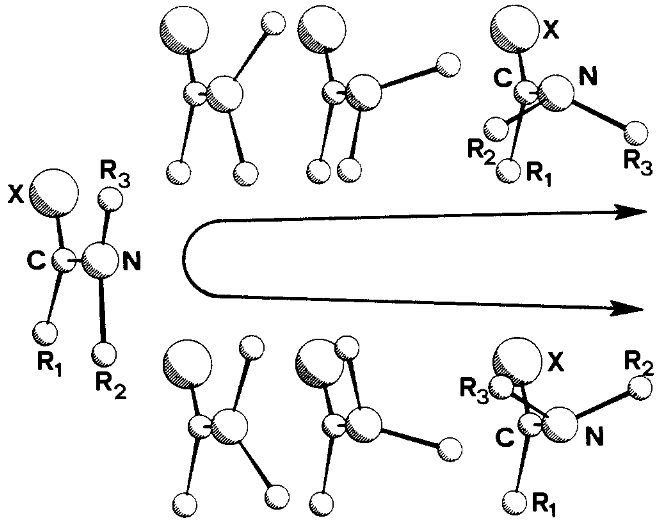

Figure 9. A final sketch of the reaction path worked out in the present paper. The figure shows the steps carrying from the planar conformation to the two enantiomeric transition states. Further rotation around the C–N bond would transform the cis isomer on the left into the unshown trans isomer on the right.

where the E_{nb} term can be evaluated in a simple model of atom–atom potentials. Potentials used here are those given by Giglio.[22] An average representative molecular formula has been considered, having $R_1 = R_2 = R_3$ = methyl and X equal to a nonexisting atom of van der Waals radius intermediate between oxygen and a methyl group. The E_{nb} function calculated with these parameters is shown in Figure 7. It has maximum value for the planar conformation and slowly decreases both with χ_N and τ' assuming a minimum value for $(\tau', \chi_N) = (180, 0)$. Evaluation of V' without changing the assumed value of 14 kcal mol^{-1} for the cis–trans isomerization barrier requires that the CTIB value be incremented by the energy difference between $E_{nb}(180, 50)$ and $E_{nb}(0,0)$. The V' function calculated in such a way is shown in Figure 8. It represents the energy surface of the $C(sp^2)-N(sp^3)$ system as a function of τ' and χ_N for an imaginary molecule intermediate among all the compounds taken into account and, therefore, can be considered to have only an indicative value. However, it has the expected form, and the agreement is much more convincing when the experimentally determined points are plotted on it. All of them are nicely located along the energy valley leading from the planar conformation to the transition state which is now more realistically located at $(\tau', \chi_N) = (180, \simeq 50)$.

Conclusions

It can be concluded that such a correspondence between the experimental findings and the simple theoretical model used seems to be of some relevance as it is one of the few proofs[23] that the structure correlation method is actually able to foresee both reaction paths and transition-state geometries at least in the simplest case where the "reaction" does not imply variations of atomic connectivities but only stereochemical rearrangements as it happens in the present case or in the well-described Berry rearrangement of pentacoordinate compounds.[24] A conclusive sketch of the hypothesized pathway worked out in the present paper is reported in Figure 9.

Supplementary Material Available: Table S1, listing references for the crystal structures used, and Table S2, listing geometric parameters for 90 $C(sp^2)-N(sp^3)$ fragments (6 pages). Ordering information is given on any current masthead page.

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