Theoretical Study of Conformational Changes in Simple Hydrazones

Rois Benassi and Ferdinando Taddei *
Istituto di Chimica Organica, Università, Via Campi 183, 41100 Modena, Italy

An *ab initio* MO study was carried out in order to predict the conformational properties of *C*-substituted hydrazones. The order of stability found for the stereoisomers of these compounds changes when a methyl group bonded to the imine carbon atom is replaced by fluorine, the *Z*-form being more stable in the latter case. The $E \rightleftharpoons Z$ isomerization process turns out to have an inversion pathway, and the energy barrier depends on the substitution at the carbon atom. The mechanism of inversion of the amino nitrogen, which is only slightly distorted from planarity, requires small activation energies which differ in the two stereoisomers of the compounds examined.

The conformational requirements and electronic properties of hydrazones are relevant in connection with their pharmacological acitivity,[1] and also of interest in view of their chemical importance as intermediates for diastereo- and enantio-selective C–C bond formation.[2,3]

From n.m.r.[4] and u.v.[5] investigations it has been found that *N,N*-dimethyl- and *N*-methyl-hydrazones of aldehydes are present almost exclusively in the *E*-stereoisomers (aldehydic proton *syn* to the amino group), whereas a mixture of *E*- and *Z*-isomers is present in the case of the corresponding derivatives of ketones. More recently[6] an n.m.r. study of a number of *N*-acetyl hydrazones of aromatic aldehydes has evidenced that an almost equimolecular mixture of *E*- and *Z*-isomers is present, and a thermal isomerization process has also been detected. As regards the amino group, a planar conformation with extended conjugation of the lone pair and the double bond seems to be preferred[5] in the hydrazones with no amino-substitution.

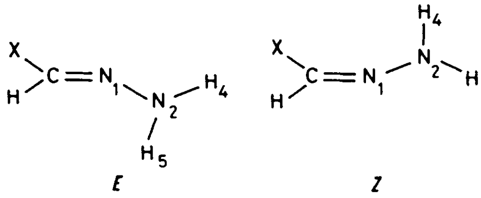
In principle, the $E \rightleftharpoons Z$ thermal isomerization of imino compounds may be ascribed to various mechanisms: (i) inversion at the imine nitrogen through a linear transition state in which the nitrogen is *sp*-hybridized (lateral shift mechanism); (ii) torsion about the C=N double bond with a 90° transition state; (iii) an intermediate mechanism with both torsional and inversional components.

Ab initio calculations applied to methyleneamine[7] indicate the inversion mechanism to be the more probable, since the energy content is 108.7—117.52 kJ mol^{-1} above the ground state for the linear transition state, and 238.5 kJ mol^{-1} for the 90° transition state. The linear transition state is also less polar than the perpendicular one.[7]

Introduction at the carbon atom of the C=N group of one heteroatom having a lone-pair substantially lowers[8] the barrier for $E \rightleftharpoons Z$ isomerization, and the results of CNDO/2 calculations[9] show that the energy barrier for the torsional mechanism is depressed while the one corresponding to the inversion mechanism is almost unaffected. From these findings a mechanism involving inversional and torsional components has been postulated as the most probable.

From *ab initio* calculations[10,11] the heteroatom effect seems to consist of a marked lowering of the activation energy for inversion, thus showing, for these molecules, a result opposite to that given by the semiempirical approach. The *ab initio* results[10,11] also show that an electron-withdrawing substituent on the imine nitrogen atom increases the energy required for inversion.

We report here an *ab initio* MO study of the conformational changes, regarding both C=N and N–N bonds, in the simple hydrazones (**1**)—(**3**).



(**1**) X = H
(**2**) X = CH_3
(**3**) X = F

Results and Discussion

The energies of the individual conformations and first-order electronic properties were obtained by the Gaussian-80 program.[12] The minima corresponding to *E*- and *Z*-stereoisomers were located using the 4-31G basis set[13] in the analytical gradient-optimization method.[14] Transition states were characterized as saddle-points[14] in the potential-energy surface by finding one negative eigenvalue of the analytic force constant matrix. The 4-31G-optimized geometries were then used for single-point energy calculations with the more extensive 6-31G** basis set[15] containing *d*-type polarization functions on heavy atoms and *p*-type polarization functions on hydrogen atoms. The effect of valence-electron correlation on the 6-31G** basis set, 6-31G**MP2,[16] was tested as well, in the case of compounds (**1**) and (**3**); for compound (**2**) this was not feasible owing to molecular size. Previous studies[17] have proved the validity of the assumption that the optimized geometries obtained at a lower level will be not significantly different from those obtained with the more extensive basis set, and hence the validity of using a single-energy calculation with 4-31G-optimized geometries to estimate the effect of basis-set size and polarization function implement on the relative stability of conformers and on energy barriers. This has been verified by comparison with the optimized geometries and the relative energetics obtained for the same molecules in the minimal STO-3G basis set (not reported). Geometries, molecular orbitals, and gradients obtained were then employed as input parameters for the optimization in the more extensive basis set.

Ground-state Stabilities.—We focused our attention first on the problem of the stability of ground states of the molecules examined, in connection with the orientation of the amino group and the geometrical structure of the corresponding nitrogen atom. In CNDO/2 calculations applied to the guanidine molecule[9] the amino nitrogen was assumed to have a planar sp^2 configuration; however, for formaldehyde hydrazone[18] the results agree better with a pyramidal structure having an inversion barrier slightly lower than that for the ammonia molecule.

Table 1. Energy values relative to the ground states, transition states for the $E \rightleftharpoons Z$ isomerization and inversion at the amine nitrogen, relative stereoisomer stabilities, and energy barriers relative to compounds (**1**)—(**3**) calculated *ab initio* in various basis sets

		Ground state (a.u.)		Transition state $E \rightleftharpoons Z$ isomerization (a.u.)	Transition state nitrogen inversion (a.u.)		$\Delta E(E-Z)$ kJ mol^{-1}	$\Delta E^*_{\text{isom.}}$ kJ mol^{-1}	$\Delta E^*_{\text{inv.}}$ kJ mol^{-1}	
Compd.	Basis set	*E*	*Z*		*E*	*Z*			*E*	*Z*
(**1**)	4-31G	−148.801 79		−148.749 29	−148.801 78			137.11	0.03	
	6-31G**	−149.035 70		−148.976 35	−149.035 06			155.00	1.66	
	6-31G**MP2	−149.510 77		−149.451 19	−149.510 18			155.61	1.54	
(**2**)	4-31G	−187.787 17	−187.785 77	−187.733 47	−187.786 89	−187.785 54	−3.66	140.25	0.73	0.60
	6-31G**	−188.082 16	−188.080 17	−188.020 21	−188.079 54	−188.077 82	−5.20	161.80	6.84	6.14
(**3**)	4-31G	−247.530 55	−247.540 02	−247.501 43	−247.530 34	−247.540 02	24.73	76.05	0.55	0
	6-31G**	−247.886 73	−247.891 60	−247.844 81	−247.884 07	−247.891 61	12.72	109.48	6.95	0.03
	6-31G**MP2	−248.527 71	−248.534 61	−248.487 21	−248.525 10	−248.534 61	18.02	105.77	6.82	0

Table 2. Geometries of the ground-state conformations and of the transitions states relative to the process of thermal isomerization, calculated in various basis sets for compounds (**1**)—(**3**)

Compound	Molecular state[a]	C–X	C–N	N–N	C–H	N–H(4)	N–H(5)
(**1**)	G	1.068	1.260	1.351	1.078	0.985	0.993
	TT	1.083	1.240	1.289	1.083	0.991	0.991
	TI	1.067	1.260	1.348	1.078	0.984	0.992
(**2**)	G(*E*)	1.493	1.259	1.367	1.082	0.987	0.994
	G(*Z*)	1.501	1.262	1.367	1.070	0.992	0.987
	TT	1.512	1.238	1.295	1.087	0.990	0.990
	TI(*E*)	1.492	1.260	1.356	1.082	0.984	0.991
	TI(*Z*)	1.501	1.236	1.355	1.070	0.989	0.984
(**3**)	G(*E*)	1.362	1.237	1.361	1.069	0.987	0.993
	G(*Z*)	1.384	1.239	1.346	1.060	0.989	0.984
	TT	1.410	1.201	1.299	1.069	0.988	0.989
	TI(*E*)	1.364	1.237	1.350	1.069	0.984	0.990
	TI(*Z*)	1.384	1.239	1.346	1.060	0.989	0.984

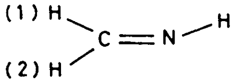
		Angles							Methyl group		
										Angles	
Compound	Molecular state[a]	XCN	HCN	CNN	NNH(4)	NNH(5)	CNNH(4)	CNNH(5)	C–H	CCH	HCCN
(**1**)	G	118.43	123.34	121.04	115.91	121.57	+172.88	+9.06			
	TT	122.36	122.36	180.00	120.14	120.14	0.0	0.0			
	TI	118.40	123.36	121.07	116.43	122.20	180.0	0.0			
(**2**)	G(*E*)	121.57	121.14	120.54	114.01	119.65	+196.42	+341.83	1.083	110.71	121.31; 0.82; −119.64
	G(*Z*)	126.02	115.48	120.75	120.76	113.59	+338.44	+189.44	1.084	111.21	66.55; −53.50; −173.81
	TT	124.89	120.73	179.89	120.11	120.04	+0.02	+179.99[b]	1.087	110.85	121.47; 0.92; −119.59
	TI(*E*)	121.51	121.09	120.87	116.31	122.22	+180.01	+359.98	1.083	110.75	121.21; 0.72; −119.74
	TI(*Z*)	125.95	115.47	121.27	123.32	115.81	+359.95	+180.01	1.084	111.27	60.05; −60.06; −179.99
(**3**)	G(*E*)	119.25	128.80	122.15	113.69	118.71	−19.69	+190.52			
	G(*Z*)	121.26	125.45	122.85	121.69	116.04	+0.20	+179.84			
	TT	122.33	130.12	180.00	119.40	119.28	0.00	180.00[b]			
	TI(*E*)	119.20	128.82	122.66	115.80	122.68	180.00	360.00			
	TI(*Z*)	121.26	125.43	122.85	121.69	116.04	0.00	180.00			

[a] G refers to the the ground states of the *Z*- and *E*-stereoisomers, TT to the transition state for thermal isomerization, and TI to the transition state for the inversion process at the amine nitrogen. [b] Since the C–N–N group is linear, the torsion angle is defined by the position of the atom X.

The results of energy calculations in the different basis sets are reported in Table 1; in Table 2 are collected the geometrical parameters optimized in the 4-31G basis set for the ground-state conformations and for the transition states.

The bond angles and torsion angles for the ground-state conformations show that the configuration of the nitrogen atom of the amino group is close to planarity, and this feature is enhanced in the transition state for $E \rightleftharpoons Z$ isomerization. Bond lengths are almost identical in the *E*- and *Z*-stereoisomers; however, a small but significant difference (3—5°) is found for the bond angles relative to the imine nitrogen, for which angles closer to 120° in the more stable stereoisomer are assumed.

The energy values relative to the ground states of compounds (**2**) and (**3**) indicate that the relative stabilities of the *E*- and *Z*-stereoisomers, in both the 4-31G and the 6-31G** basis sets, are opposite for the fluorine derivative as compared with the methyl compound; this also occurs in the imine derivative.[19] A comparison with previous calculations[19] performed on XHC=NH molecules shows that for ethylideneamine (X = CH_3) and formimidoyl fluoride (X = F) the same stability order is found regarding the relative position of the imino lone-pair and the substituent on the carbon atom. This result seems to indicate that the presence of the amino group on the imine nitrogen does not change the relative stabilities of the isomers determined by substituents on the carbon atoms of XCH=NH derivatives. The relative isomer stability of these compounds has been attributed to consistent stabilizing contributions from σ conjugative effects.[20,21] In the CH_2=NH system,[21] the C–H(1) overlap population is somewhat smaller than that of the C–H(2) bond [see (A)], and H(1) is more negative than H(2). When fluorine substitution is made, the low-energy conformer is the one having the electronegative F atom at the site occupied by the most negative hydrogen atom in the parent molecule.



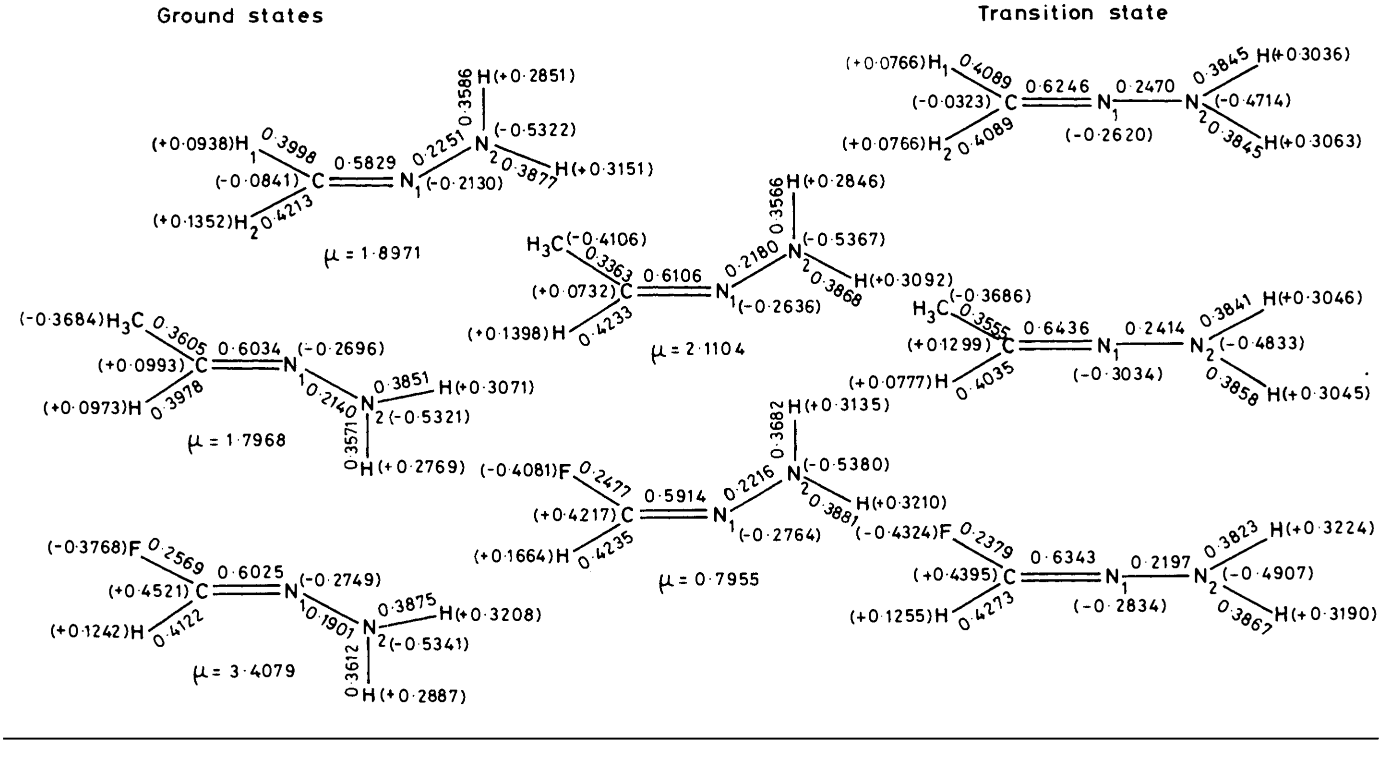
(A)

For the compounds here examined we obtain in the 6-31G** basis set the charge distributions and bond-overlap populations reported in Table 3. In compound (1) the charges on the hydrogen atoms and the C–H overlap populations show the same trend as found[21] for CH_2=NH. Assuming that the hyperconjugative effect[20,21] determines the electronic distribution in these compounds, this effect seems to be enhanced by the introduction of an amino group on the nitrogen atom. It thus seems reasonable to accept that the same interpretation given to explain the relative stabilities of the *E*- and *Z*-stereoisomers of formimidoyl fluoride[20,21] should also apply to compound (3). Since the σ electron-withdrawal effect of the methyl group is opposite to that of the fluorine atom, it might be expected on this basis that the relative isomer stability, in the case of compound (2), should be the opposite to that of compound (3), while π-type interactions should agree with the same stability order of the stereoisomers of the two derivatives. The calculated dipole moments, also collected in Table 3, show that the more stable conformer is the one having the lower polarity. The effect of expanding the basis set and introducing polarization functions does not result in a change in the stability order of conformers, even though the energy changes are different in the *E*- and *Z*-stereoisomers.

Conformational Changes.—The geometry of the transition state for the $E \rightleftharpoons Z$ thermal isomerization, characterized as a saddle-point in the potential-energy surface,[14] is linear in character, and involves inversion at the imine nitrogen atom. In compounds (1) and (3) the process does not possess an appreciable torsional component, and in the transition state the amino group is essentially planar. For compound (2) the amino group is slightly distorted from planarity and this could indicate a small torsional component in the inversion process. These findings agree with the results from the calculations applied to the topomerization process of methyleneamine.[10] The transition state is characterized by an increase in the C–X bond length, whereas a shortening of those of C=N and N–N is found: these changes correspond to a decrease and an increase (Table 3) in bond-overlap populations in the former and the latter case, respectively. From atomic charge distributions, in the transition state, electron transfer from the amino to the imine nitrogen is apparent, as also is an increase in electronic charge on the fluorine atom; no appreciable change occurs on the methyl group. Electron withdrawal from the amine nitrogen found in the case of the fluorine substituent should also reflect a lowering of the energy of the linear transition state due to conjugative effects: while the methyl group does not introduce an appreciable change in the ΔE^* value relative to compound (1), the fluorine substituent causes a significant lowering of this quantity.

The substituent X, beside exerting an influence on the relative stabilities of *E*- and *Z*-stereoisomers and on the energy barrier for their interconversion, also affects the geometrical environ-

Table 3. Atomic charge distribution, bond-overlap population, and dipole moment in compounds (1)—(3) (6-31G** basis set) referred to the ground states and to the transition state for thermal isomerization



ment and the inversion barrier of the amine nitrogen. In compound (**1**) the configuration of this atom is slightly distorted from planarity, as apparent from Table 2, and an energy barrier is determined relative to the planar transition state (located as a saddle-point in the potential-energy surface). The energy barriers increase on going from 4-31G to 6-31G** basis set; introducing valence-electron correlation (6-31G**MP2) does not result in an appreciable further enhancement. This is verified for the compounds examined, particularly for derivatives (**1**) and (**3**) where calculations with the three basis sets were performed: comparisons of the ΔE^* values should thus be restricted within the same basis set approach.

The presence of the methyl group [compound (**2**)] increases the deviation from planarity of the amino group and, as a consequence, the energy barrier for nitrogen inversion also increases. The effects are very similar in the *E*- and *Z*-stereoisomers, and the energy barrier is higher than in the unsubstituted compound. In compound (**3**) the amino group is very nearly planar in the *Z*-stereoisomer, while the degree of distortion from planarity in the *E*-stereoisomer is close to that of compound (**2**). The barrier for nitrogen inversion behaves as expected. The high planarity of the *Z*-stereoisomer of compound (**3**) is associated also with the higher stability with respect to the *E*-stereoisomer; this property may also be related to stabilization due to hydrogen bonding involving fluorine and one of the hydrogen atoms of the amino group.

In conclusion, the calculations here performed on *C*-substituted hydrazones show that: (i) the stabilities of *E* and *Z* ground states are in the opposite order for the fluorine-substituted derivative from that for the methyl-substituted compound: electronic hyperconjugative effects are probably the origin of this stability order and in the case of the fluorine substituent hydrogen-bond effects could contribute towards stabilizing the *Z*-stereoisomers; (ii) the $E \rightleftharpoons Z$ isomerization process shows a pure inversion path and an electronegative substituent on the imine carbon atom lowers the energy barrier; (iii) inversion at the amine nitrogen shows low energy barriers which are affected by substitution on the carbon atom: while the methyl group increases the activation energy of the process, for the fluorine substituent this is found only in the less stable *E*-stereoisomer; distortion from planarity of the configuration of the amine nitrogen in the ground states of the molecules seems to be the origin of this behaviour.

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