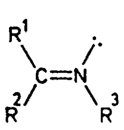
Dynamic Stereochemistry of Imines and Derivatives. Part VIII.[1] Barriers to Rotation around the Carbon–Nitrogen Bond in Imine *N*-Oxides (Nitrones)

By **W. Brian Jennings,*** Department of Chemistry, University of Birmingham, P.O. Box 363, Birmingham B15 2TT
Derek R. Boyd and **Lionel C. Waring,** Department of Chemistry, Queen's University of Belfast, Belfast BT9 5AG

Semiempirical molecular orbital calculations (CNDO/2 and INDO) are reported for methyleneamine *N*-oxide, *N*-(benzylidene)methylamine *N*-oxide, and diphenylmethyleneamine *N*-oxide. The calculated dipole moments and the energy difference between *E*- and *Z*-isomers are in good agreement with experimental data in solution. The calculated barriers to rotation around the C=N bond are about twice the measured barriers to *E*–*Z*-interconversion in closely related nitrones. Experimental data for *E*–*Z*-isomerization in *N*-(9-anthrylmethylene)methylamine *N*-oxide shows the entropy of activation to be close to zero as expected for a rotational process.



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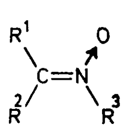

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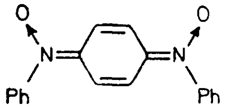
THE phenomenon of E–Z isomerism about the C=N bond in imines (1; R^3 = alkyl or aryl), oximes (1; R^3 = OR), and hydrazones (1; $R^3 = NR_2$) has been recognised for almost a century[2] and has been the subject of considerable research.[3] Interconversion of the isomers can take place by rotation through 180° around the double bond, by a planar inversion at nitrogen (a lateral shift), or by imine–enamine tautomerism.[4] However, in the case of imine *N*-oxides (nitrones) (2) the inversion mechanism is not available. It is clear from the available literature on double bond isomerization[3] and on nitrone chemistry[5-7] that there have been few investigations of E–Z isomerization in the latter. The activation energy of Z–E isomerization in the nitrone (2; R^1 = CN, $R^2 = R^3$ = Ph) has been measured to be 24.6 kcal mol^{-1} at 117°.[8] An n.m.r. study of the bis-nitrone (3) has indicated that the isomerization barrier ($\Delta G^‡$) is *ca.* 12 kcal mol^{-1}.[9] Both these examples can be considered to be atypical of nitrones in general. Recently however, Whitham *et al.*[10] have estimated by n.m.r. spectroscopy that $\Delta G^‡ = 23.2$ kcal mol^{-1} at 180° for configurational exchange of the vinyl protons in the nitrone (4). Subsequent investigation by Grubbs and his co-workers[11] on ketonitrones have shown considerably higher activation energies for isomerization (*ca.* 33.6 kcal mol^{-1}). Recently, the barrier to interconversion in compound (5) has been determined to be $\Delta G^‡ = 34.6$ (Z to E) and 33.1 kcal mol^{-1} (E to Z) at 147°.[12] The above barriers to E–Z isomerization in nitrones vary over a considerable range and are much lower than the corresponding barriers measured in E-1,2-dideuterioethene and in Z-1,2-diphenylethene (E_a 65.0 and 42.8 kcal mol^{-1} respectively).[13,14] We now report the results of a self-consistent molecular orbital study of CN bond rotation in nitrones using the CNDO/2[15] and INDO[16] methods, and some further experimental data for E–Z isomerization in an aldonitrone.



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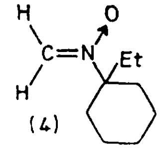

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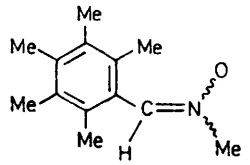

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The semiempirical CNDO/2 and INDO procedures have been widely used and generally provide quite a good representation of valence electron distribution in organic compounds, although the calculated energies of formation are often in poor agreement with experimental data.[17,18] There have been numerous such

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calculations of the *relative* energy changes involved in conformational processes, including rotation or inversion in imines,[19-21] guanidine,[19] immonium ions,[21-23] oxime anions,[24] carbodi-imide,[25] and azacumulenes.[25]

RESULTS AND DISCUSSION

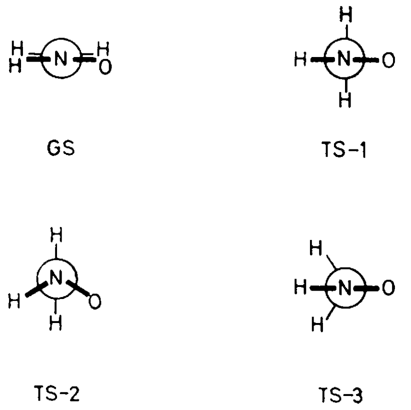
The results of CNDO/2 and INDO calculations on the unsubstituted nitrone (2; $R^1 = R^2 = R^3 = H$) are summarised in Table 1. The CN and NO bond lengths were optimised consecutively in the CNDO/2 treatment and the INDO calculations were performed on the latter optimised geometry. Both methods gave very similar results, the only significant difference being in the energy of the various conformations. Attempts were made to lower the energy of the twisted conformation TS-1 (Figure) by relaxing the nitrogen or carbon geometry to tetrahedral. Changing the former (TS-2) had little effect on the total energy but in line with the carbanion character of carbon in TS-1, relaxation of the latter to tetrahedral (TS-3) appreciably lowered the total energy (Table 1). The electronic structure of nitrones is commonly represented as a hybrid between the valence bond structures (6) and (7).[5,6] The calculations on the ground state (GS) indicate a high charge density at oxygen and a CN π-bond order of 0.86. This would be consistent with a major contribution from structure (6), although the NO π-bond order was 0.5. The twisted conformations TS-1 and TS-3 appear to be well represented by structure (7) since there is a high charge density at carbon and a NO π-bond order of 0.94. The theoretical dipole moments are close to the measured values of 3.37—3.47 D in substituted nitrones;[26] a previous *ab initio* calculation on (6) gave a dipole moment of 4.99 D.[27]

TABLE 1

CNDO/2 and INDO results for nitrone (6)

Conformation [a]	GS	TS-1	TS-3
CN bond length (Å)	1.31	1.38	1.39
NO bond length (Å)	1.25	1.20	1.19
CNDO/2 Energy (kcal mol^{-1})	0.0 [b]	81.1	61.1
INDO Energy (kcal mol^{-1})	0.0 [c]	93.0	78.8
Dipole moment (D)	4.03	3.66	5.40
	(3.86)	(3.34)	(4.93)
Atomic charge [d] O	−0.40	−0.10	−0.10
	(−0.44)	(−0.13)	(−0.13)
N	+0.31	+0.44	+0.42
	(+0.38)	(+0.54)	(+0.53)
C	−0.09	−0.52	−0.43
	(−0.07)	(−0.54)	(−0.47)

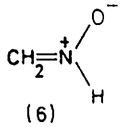
[a] The conformations are depicted in the Figure as Newman projections. [b] Total energy −39.316 7 a.u. [c] Total energy −37.734 0 a.u. [d] Open figures are CNDO/2 results and values in parentheses are INDO data.



GS TS-1

TS-2 TS-3

Conformations of nitrone (6)



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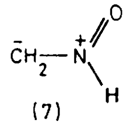

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The calculated rotational barrier in (6) is *ca.* 60 (CNDO/2) and *ca.* 80 kcal mol^{-1} (INDO) on the basis of TS-3 as the transition state. These estimates are clearly much higher than the measured *E–Z* isomerization barriers in substituted nitrones (23—35 kcal mol^{-1}, see Introduction), although the presence of conjugating substituents might be expected to lower the barrier to rotation around the CN bond. Accordingly, semi-empirical molecular orbital calculations were also carried out on the nitrone (2; R^1 or R^2 = Ph, R^2 or R^1 = H, R^3 = Me), and the results are given in Table 2. Both the *Z*- and *E*-isomers were considered with the phenyl ring either coplanar or orthogonal to the imino-system. The INDO and CNDO/2 energies suggest that the phenyl ring in the *Z*-isomer prefers to be coplanar rather than orthogonal. On the other hand the coplanar conformation in the *E*-isomer is destabilised (relative to the orthogonal conformation) by *ca.* 30 kcal mol^{-1}, though it is probable that this figure could be considerably reduced in practice by distortion of the geometry from ideal. Nevertheless, these calculations indicate that the phenyl ring is close to orthogonal in the *E*-isomer, presumably due to non-bonded repulsions between the proximate *C*-phenyl and *N*-methyl groups. The *Z*-isomer (GS-1) is predicted to be more stable than the *E*-isomer (GS-2) by 3—4 kcal mol^{-1}, and this is in agreement with *X*-ray and n.m.r. evidence that *N*-(4-chloro- and *N*-(4-nitrobenzylidene)methylamine *N*-oxide

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exist exclusively in the Z-configuration.[28,29] An energy difference of 3—4 kcal mol^{-1} corresponds to an equilibrium concentration of the E-isomer of $<1\%$. It is interesting to consider the anomalous behaviour of *ortho*-disubstituted C-aryl aldonitrones which show a significant proportion of the E-isomer at equilibrium.[12] Steric interactions between the *ortho*-substituents and the neighbouring oxygen and vinyl hydrogen atoms will cause the aryl ring in the Z-isomer to adopt a conformation close to the orthogonal GS-2. It can be seen from the results in Table 2 that the potential energy difference between the orthogonal GS-2 of the Z- and E-isomers is only 0.6 (CNDO) or 1.3 kcal mol^{-1} (INDO), corresponding to an equilibrium proportion of 25 or 10% E-isomer at ambient temperature. These estimates are probably fortuitously close to the observed isomer distributions of *ortho*-disubstituted aldonitrones in solution [*e.g.* 17% E-nitrone (5) in deuteriochloroform].[12]

TABLE 2

CNDO/2 and INDO results for N-(benzylidene)methylamine N-oxide

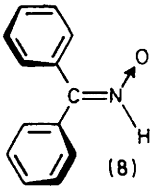
	Z-isomer		E-isomer			
Conformation [a]	GS-1	GS-2	GS-1	GS-2	TS-1	TS-3
CNDO/2 energy (kcal mol^{-1})	0.0 [b]	2.51	33.07	3.14	60.68	53.53
INDO energy (kcal mol^{-1})	0.0 [c]	3.14	33.26	4.39	72.23	71.60
Dipole moment (D) [d]	4.2	4.4	4.1	4.6	6.2	6.1
	(3.9)	(4.2)	(4.0)	(4.5)	(6.1)	(5.8)

[a] GS-1 is the ' ground state ' with the phenyl ring and imino systems coplanar; GS-2 has the phenyl ring orthogonal to the coplanar imino system; TS-1 is the twisted conformation (Figure) with the phenyl ring coplanar with the H–C–N moiety; TS-3 is the twisted conformation with tetrahedral carbon (Figure)and the plane of the phenyl ring perpendicular to the plane bisecting the angle HCN [b] Total energy $-93.706\,7$ a.u. [c] Total energy $-90.344\,7$ a.u. [d] Open figures are CNDO/2 results and values in parentheses are INDO data.

The calculated dipole moment of 4.2 (CNDO) or 3.9 D (INDO) in the planar GS-1 conformation of Z-N-(benzylidene)methylamine N-oxide is also in close agreement with the experimental value of 3.55 D.[30] The dipole moments in the isomers of aldonitrone (5) have been determined to be 3.88 and 4.84 D for the Z- and E-forms respectively. These dipole moments provide further evidence of the E- and Z-isomeric structures and are again in good agreement with the calculated moments for the orthogonal GS-2 conformations of Z- and E-N-(benzylidene)methylamine N-oxide (Table 2). Comparison of the relative energies of the twisted CN conformations (TS-1 or TS-3) for N-(benzylidene)methylamine N-oxide (Table 2) with similar data for the unsubstituted nitrone (Table 1) indicates that the rotational barrier is lower in the former by *ca.* 10 kcal mol^{-1}.

CNDO/2 Calculations were also carried out for the nitrone (8) using a geometry with both phenyl rings twisted 30° out of the imino-plane in opposite directions. Diphenyl ketone adopts a similar conformation in the solid state presumably due to unfavourable interactions between the *ortho*-hydrogen atoms on adjacent rings.[31] The calculated rotational barrier (maintaining trigonal geometry) was 66 kcal mol^{-1} and the dipole moment in the ground state was 4.1 D.

The free energy barrier for Z to E isomerization in aldonitrone (5) has been reported to be 34.6 kcal mol^{-1} at 147°.[12] The calculated potential energy difference between GS-2 (phenyl ring orthogonal) and the twisted TS-3 configuration in N-(benzylidene)methylamine N-oxide is 51 (CNDO) or 68 kcal mol^{-1} (INDO). Similarly the calculated CN rotational barrier in (8) is higher than the measured barriers to E–Z isomerization in N-(diarylmethylene)alkylamine N-oxides (*ca.* 34 kcal mol^{-1}).[11] It would appear that these molecular orbital calculations considerably overestimate the CN rotational barrier. An alternative possibility however is that E–Z isomerization occurs more easily by another route. Some aspects of the reported isomerization data might be cited in support of the latter possibility. Thus it is difficult to see why the measured barrier in nitrone (4) should be *ca.* 10 kcal mol^{-1} lower than in nitrone (5). Even if the ground state in (4) is more hindered than in (5), 10 kcal mol^{-1} might be considered to be excessive for this type of interaction when compared with steric effects in imines.[3,4] Secondly, it has been noted that the isomerization barrier in nitrone (5) was lowered by *ca.* 9 kcal mol^{-1} when a small quantity of benzoic acid was added to the sample.[12] It would seem therefore, at least in the presence of benzoic acid, that an alternative mechanism is available to interconvert the E- and Z-isomers. A similar effect of benzoic acid has been reported in imine isomerization, and it was suggested that the isomers may interconvert *via* an intermediate containing a single carbon–nitrogen bond where rapid rotation could occur readily.[23]



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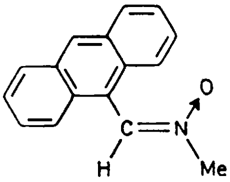

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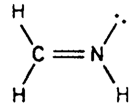

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However, if the nitrones were isomerizing by a route involving catalysis by trace impurities in solution, this should be reflected in the entropy of activation. First-order thermal isomerizations usually have activation entropies close to zero,[3,32] whereas second-order acid catalysed imine isomerizations show a large negative entropy of activation.[23] Grubbs *et al.*[11] have reported that $\Delta S^{\ddagger} = -4 \pm 4$ cal mol^{-1} K^{-1} for Z–E isomerization in N-[phenyl-(4-tolyl)methylene]benzylamine N-oxide, a value consistent with a C=N rotational process. We have obtained kinetic data for the equilibration of the nitrone (9) under acid-free conditions and the results are given in Table 3. The aldonitrone was selected for study as it shows a relatively high proportion of the E-isomer at equilibrium.[12] Poor solubility in most suitable solvents necessitated the use of deuteriochloroform solutions in sealed tubes at high temperature. The near zero entropy of activation (Table 3) is again quite consistent with an intramolecular bond rotational process.

TABLE 3

Activation parameters for Z–E isomerization in nitrone (9) determined in deuteriochloroform solution (sealed tube) [a]

Temperature (°C)	101.9	146.4
k_f/s^{-1}	0.443×10^{-6}	0.478×10^{-4}
k_r/s^{-1}	1.07×10^{-6}	1.16×10^{-4}
$\Delta H_f^{\ddagger}$/kcal mol^{-1}	32.0 ± 1.0	
$\Delta H_r^{\ddagger}$/kcal mol^{-1}	32.0 ± 1.0	
$\Delta S_f^{\ddagger}$/cal mol^{-1} K^{-1}	-2.5 ± 3.0	
$\Delta S_r^{\ddagger}$/cal mol^{-1} K^{-1}	-0.7 ± 3.0	

[a] Parameters with subscript f refer to the Z–E process, and those bearing subscript r refer to the reverse process.

Accordingly, on balance it would seem that the CNDO/2 and INDO calculations may overestimate the CN rotational barrier by about a factor of two. Previous CNDO/2 calculations on methyleneamine (10) have given a CN rotational barrier of 61 kcal mol^{-1} and a barrier to nitrogen inversion of 31 kcal mol^{-1}.[19] Measured E–Z isomerization barriers in N-alkylimines are generally in the range 25—28 kcal mol^{-1} supporting the view that they interconvert largely by planar inversion. However it should be noted that if the CNDO/2 method also overestimates the CN rotational barrier in these systems by a factor of two, the conclusions would be very different. It is true that *ab initio* calculations on imine (10) also indicate a high rotational barrier (57.5 kcal mol^{-1}),[33] though similar calculations overestimate the C=C rotational barrier in ethylene by a factor of at least two [34-36] (reduced somewhat by including configuration interaction).

EXPERIMENTAL

MO Calculations were carried out on the ICL 1906A computer at Birmingham University. The CNDO/2 and INDO programmes were modified versions of QCPE-91 with standard parameters. The bond lengths used were as follows (Å): N–H 1.01, trigonal C–H 1.08, tetrahedral C–H 1.09, aromatic C–C 1.40, C-phenyl 1.45, N–CH_3 1.50. The NO bond length in the unsubstituted nitrone (6) was initially taken to be 1.28 Å as found in the crystal of N-(4-chlorobenzylidene)methylamine N-oxide and the CN bond length varied (in steps of 0.02 Å) to minimise the total CNDO/2 energy of each configuration. Using the optimum CN bond length the NO bond length was then optimised (in steps of 0.02 Å). These optimised bond lengths were then used in the INDO calculations and in the calculations on substituted nitrones. Standard trigonal or tetrahedral bond angles were used as appropriate, and singlet states only were considered.

N-(9-*Anthrylmethylene*)*methylamine* N-*Oxide* (9).—Condensation of N-methylhydroxylamine hydrochloride and 9-anthraldehyde in aqueous methanol containing sodium hydroxide afforded the nitrone in quantitative yield. Recrystallisation from methanol containing a trace of sodium methoxide gave yellow ***needles***, m.p. 225° (Found: C, 81.8; H, 5.55; N, 5.9. $C_{16}H_{13}NO$ requires C, 81.7; H, 5.6; N, 5.95%). The crystalline material on dissolution in deuteriochloroform showed n.m.r. signals due only to the Z-isomer.

Equilibration.—A solution of the nitrone in deuteriochloroform was degassed and sealed *in vacuo* in a base washed n.m.r. tube. The deuteriochloroform was purified by passage through short columns of alumina and magnesium carbonate prior to distillation in base washed apparatus. The equilibration of the Z-isomer was carried out in a thermostatically controlled oil bath (±0.1 °C) and monitored using the integrated intensities of the N-methyl signals at δ 4.12 (E) and 3.45 (Z).

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