Oxidation of *N*-benzyl-*N*-methylhydroxylamines to nitrones. A mechanistic study

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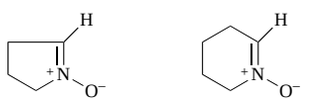
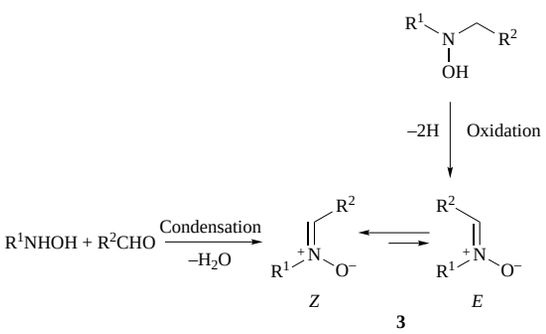
Oxidation of various *N*- (*o*-, *m*-, *p*- substituted benzyl)-*N*-methylhydroxylamines has been carried out using mercury(II) oxide and *p*-benzoquinone (*p*-BQ) as oxidants. Hammett plots have been obtained with negative ρ values, showing the development of a positive centre in the transition state. The unstable *E* nitrones, which readily isomerize to the more stable *Z* nitrones, are obtained in appreciable quantities and in some cases as the major product. A considerable deuterium isotope effect is observed in the oxidation process. The overall picture of the mechanistic pathway involves electron transfer from nitrogen to the oxidant followed by hydrogen abstraction.

Nitrone functionality has etched a place of distinction in organic synthesis due to its ability to incorporate multiple stereocentres in a single cycloaddition step with alkenes.[1,2] While the widely used cyclic aldonitrones **1** and **2** must remain in the *E*



1 **2**

geometry due to structural constraints, their acyclic counterparts **3** are involved in *E*–*Z* isomerization at higher temperatures with equilibrium constants overwhelmingly favouring the more stable *Z* form [3] (Scheme 1). With rare exceptions,[4,5] it is the

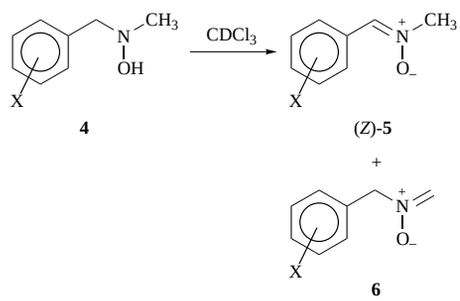


Scheme 1

Z form which undergoes cycloaddition reactions thus dictating the stereochemical outcome. The addition of the *E* isomer (which is expected to be much more reactive [4] than the *Z* form) on the other hand would lead to cycloadducts with different stereochemistry. Condensation of primary hydroxylamines with aldehydes, used in the preparation of the aldonitrones, almost always leads to exclusive formation of the *Z* isomers **3**, except in the cases where the terminal carbon of the nitrone is attached to a 2,6-disubstituted phenyl ring or electron withdrawing conjugated substituents.[5–7] Oxidation of secondary hydroxylamines, like the condensation process, also leads to the more stable *Z* nitrones **3** (Scheme 1). In a few cases some unstable *E* nitrones have been generated by irradiation of the *Z* isomers.[8] The mechanistic investigation of this widely used oxidation process has not been studied to any meaningful extent.[9] Herein we report a systematic study of the oxidation of various *N*-benzyl-*N*-methylhydroxylamines **4** using mercury(II) oxide and *p*-benzoquinone (*p*-BQ) as oxidants. Efforts are being made to generate and study the unstable *E* nitrones and subsequent *E*–*Z* isomerization.

Results and discussion

Regiochemistry of the oxidation of the hydroxylamines **4** with various substituents in the benzene ring is included in Table 1 (Scheme 2). As is evident from Table 1 the composition of



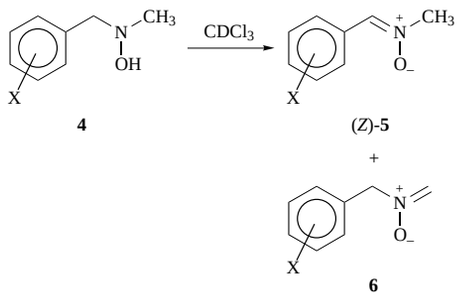
4 **(*Z*)-5** **6**

Scheme 2

the nitrones depends on the nature of the substituent X but is somewhat independent of the nature of the oxidant, mercury(II) oxide or *p*-BQ. As the electron withdrawing ability of the substituent X increases, the percentage of the conjugated nitrones **5** also increases indicating either free radical or carbanion character at the benzylic position during H abstraction. Hydride abstraction would have placed a positive charge on the benzylic position in which case the electron donating group (X) would have preferred that situation to give nitrones with increased percentage of the conjugated nitrone **5**. While the nitro substituent favours the formation of the conjugated nitrone **5** in a 9:1 ratio, the electron donating substituents (methoxy or dimethylamino) led to the formation of the nonconjugated nitrones **6** in almost a 1:1 ratio (in the case of *o*-methoxy group it even becomes the major isomer). It is also to be noted that whatever the substituent X, one would have expected the abstraction of the benzylic H to be overwhelmingly preferred, leading to the formation of the conjugated nitrone **5** as the sole product. Formation of the nonconjugated nitrones **6** in considerable amounts thus implicates kinetic factors in a significant way in the abstraction of the hydrogen.

Next we focused our attention on determining the relative rate (k_X/k_H) of oxidation of the hydroxylamines using HgO and *p*-BQ. A mixture of one equivalent each of **4a** (X = H),

Table 1 Composition of nitrones in the oxidation of hydroxylamine **4** with HgO at −20 °C and *p*-benzoquinone at +20 °C[a]



	Composition of the nitrones			
	Using *p*-benzoquinone		Using HgO	
Hydroxylamine	**5**	**6**	**5**	**6**
4a (X = H)	65	35	60	40
4b (X = *p*-NO_2)	88	12	80	20
4c (X = *p*-Cl)	77	23	68	32
4d (X = *p*-OMe)	60	40	54	46
4e (X = *p*-Me)	60	40	59	41
4f (X = *p*-NMe_2)	53	47	59	41
4g (X = *m*-NO_2)	90	10	83	17
4h (X = *o*-OH)	68	32	60	40
4i (X = *o*-OMe)	30	70	44	56

[a] The experimental conditions and procedure are described in the Experimental section.

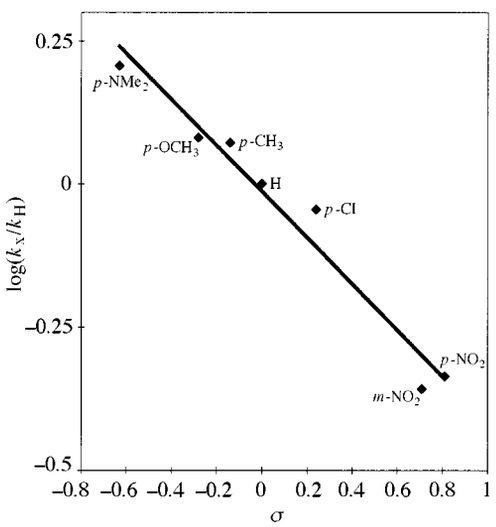


Fig. 1 Hammett plot for the HgO oxidation of *N*-benzyl-*N*-methylhydroxylamines **4**

4 (X ≠ H) and the oxidant was reacted in $CDCl_3$ and using integration of several proton signals the amounts of unreacted hydroxylamines were determined. Application of the Ingold and Shaw[10] equation provided the relative rates k_X/k_H. As is evident from Table 2, the rate of oxidation increases with the electron donating ability of the substituents X. Hammett plots for the oxidation process are shown in Figs. 1 and 2. A good linear free energy relationship is obtained with ρ values of −0.403 and −0.483 using HgO and *p*-BQ, respectively. The negative ρ values indicate the development of positive charge on the nitrogen in the transition states. Had it been on the benzylic carbon by hydride transfer in the first step, the ρ values would be substantially higher by virtue of direct resonance of the aromatic π-cloud with the benzylic carbon. In the subsequent step, however, the compounds with electron withdrawing substituents should facilitate H abstraction from the benzylic position by stabilizing the second transition state.

Table 2 Relative rates of oxidation of the hydroxylamines **4** in $CDCl_3$[a]

	Using *p*-benzoquinone		Using HgO	
Hydroxylamine	k_X/k_H	log (k_X/k_H)	k_X/k_H	log (k_X/k_H)
4b *p*-NO_2	0.425	−0.372	0.461	−0.336
4c *p*-Cl	0.835	−0.0781	0.901	−0.0452
4d *p*-OMe	1.43	0.156	1.21	0.0811
4e *p*-Me	1.15	0.0627	1.18	0.0714
4f *p*-NMe_2	1.83	0.263	1.61	0.207
4g *m*-NO_2	0.387	−0.412	0.412	−0.358
4h *o*-OH	0.540	−0.267	0.892	−0.0496
4i *o*-OMe	0.479	0.320	1.415	0.151

[a] The experimental conditions and procedure are described in the Experimental section.

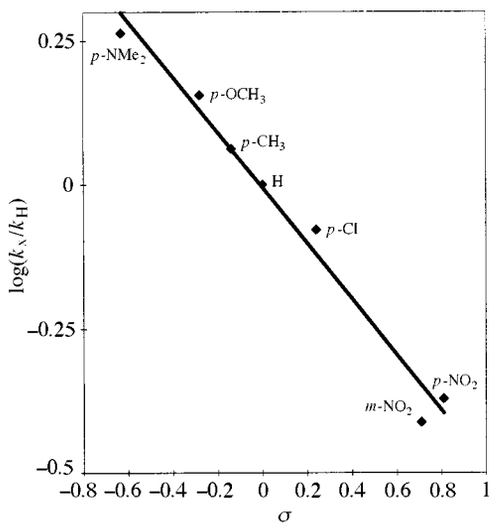
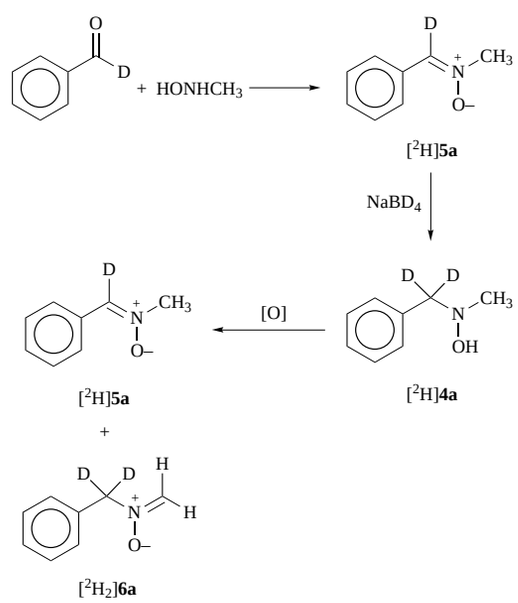


Fig. 2 Hammett plot for the *p*-benzoquinone oxidation of *N*-benzyl-*N*-methylhydroxylamines **4**

This is why the nitro substituent provides a higher percentage of the conjugated nitrone (Table 1).

In order to shed more light on the oxidation process, the hydroxylamine deuteriated at the benzyl position was prepared as shown in Scheme 3. Condensation of *N*-methylhydroxylamine with PhCDO afforded the nitrones [^{2}H]**5a**, which on reduction with $NaBD_4$ gave the hydroxylamine [$^2H_2$]**4a**, with the



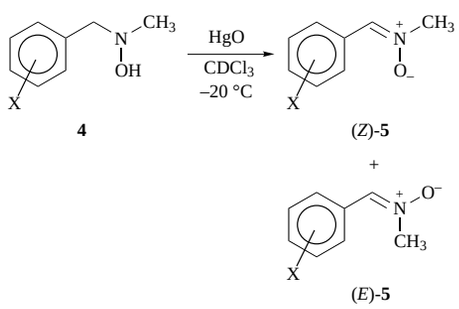
Scheme 3

Table 3 Regiochemistry and reactivity of hydroxylamines in oxidation using HgO (0 °C) and *p*-benzoquinone (*p*-BQ) (20 °C) in $CDCl_3$[a]

Hydroxylamine	Oxidant	Composition of nitrones[a] (%)				Rate ratio[a] $k_{5a}/k_{[^2H_2]5a}$	
						HgO	*p*-BQ
$PhCH_2N(OH)CH_3$	HgO	**5a**	57	**6a**	43		
4a	*p*-BQ	**5a**	65	**6a**	35	1.34	1.15
$PhCD_2N(OH)CH_3$	HgO	[^{2}H]**5a**	17	[$^2H_2$]**6a**	83		
[$^2H_2$]**4a**	*p*-BQ	[^{2}H]**5a**	33	[$^2H_2$]**6a**	67		

[a] The experimental conditions and procedure are described in the Experimental section.

Table 4 Composition of the nitrones in the oxidation of *N*-methylhydroxylamines **4** with HgO in $CDCl_3$ at −20 °C



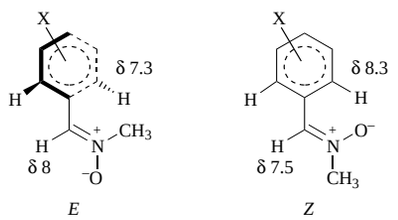
4 (*Z*)-**5** + (*E*)-**5**

Hydroxylamine	*Z*:*E*[a]	*Z*:*E*[b]
4a H	70:30	55:45
4b *p*-NO_2	85:15	80:20
4c *p*-Cl	67:33	63:37
4d *p*-OMe	56:44	50:50
4e *p*-Me	68:32	53:47
4f *p*-NMe_2	58:42	40:60
4i *o*-OMe	68:32	50:50

[a] Ratio of *E*/*Z* isomers at −20 °C at the end of the reaction (see Experimental section). [b] *In situ* experiment in the NMR probe at −20 °C (see Experimental section).

benzyl position dideuteriated. While the hydroxylamine **4a** on oxidation with HgO and *p*-benzoquinone afforded a mixture of the nitrones **5a** and **6a** in a ratio of 57:43 and 65:35, respectively (Table 3), with either oxidant the regiochemistry of the oxidation of [$^2H_2$]**4a** is reversed providing the nitrones [^{2}H]**5a** and [$^2H_2$]**6a** in a respective ratio of 17:83 and 33:67. When a 1:1:1 mixture of **4a**, [$^2H_2$]**4a** and the oxidant was allowed to react, analysis of the ^{1}H NMR spectrum revealed the amounts of unreacted hydroxylamines; using the rate equation of Ingold and Shaw,[10] the rate ratios were determined and are listed in Table 3. In HgO oxidation the hydroxylamine **4a** was found to react 1.34 times faster than its deuteriated counterpart [$^2H_2$]**4a**. In both cases the rate of formation of the nonconjugated nitrones **6a** and [$^2H_2$]**6a** is more or less the same while it is the benzylic part where they differ in reactivity. So the magnitude of the isotope effect can be realized when the rate constants for the abstraction of benzylic H (and D) alone are considered.

Previous workers including ourselves[9] probably did not notice the formation of the *E* isomer in the HgO (0 °C) or *p*-BQ (20 °C) oxidation because of the time lapse between the completion of the reaction and NMR recording (at room temperature) by which time the unstable *E* isomers, if any, might have isomerized to the more stable *Z* isomer. The NMR spectrum of the *Z* nitrone **5a**, derived from the oxidation of the hydroxylamine **4a** displays signals at δ 3.93 (N–CH_3), 7.50 (CH=N). Luckily, in one instance, the reaction mixture, resultant nitrone(s) and the NMR probe were all kept at −20 °C throughout. Surprisingly, the ^{1}H NMR spectrum revealed new signals at δ 3.83 (N–CH_3) and 8.04 (CH=N) in addition to the corresponding signals due to the *Z* nitrones. The intensity of the additional signals, attributed to the presence of the *E* isomer, decreased with time with concomitant increase in the intensity of the signals due to the *Z* isomer. Table 4 displays the *E*, *Z* isomeric distribution in the HgO oxidation of several hydroxylamines carried out at −20 °C. As is evident from Table 4 20–60% of the nitrone **5** is formed as the unstable *E* isomer. In the oxidation of hydroxylamine **4f** it is the *E* isomer which predominates. It is to be noted that aromatic rings with electron withdrawing substituents tend to give a smaller amount of the unstable *E* isomer. This could either be attributed to the higher rate of the isomerization of the *E* form during work-up or it is inherent in the oxidation process, which would give smaller amounts of the unstable *E* nitrones.

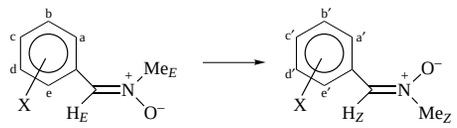


E *Z*

Fig. 3 The conformation and configuration of *E* and *Z* nitrones

The *E* isomer equilibrates completely to the *Z* isomer, so we were not able to determine the equilibrium constant. An energy difference of 13–17 kJ mol^{-1} would correspond to an equilibrium concentration of <1% for the *E* isomer which would evade the NMR detection limit. The free energy difference between the *E* and *Z* isomers may well be higher than 13–17 kJ mol^{-1}. ^{1}H NMR signals of various *E* and *Z* isomers are given in Table 5. The aromatic *ortho* protons of the *E* nitrones appear almost 1 ppm upfield from the corresponding *Z* nitrones. The downfield shift of the *ortho* protons in the *Z* isomers thus indicates the conjugation of the electron withdrawing nitrone functionality with the aromatic ring, whereas in the *E* nitrone such conjugative deshielding is absent. The methine hydrogen (CH=N) in the *E* isomers is shifted downfield by 0.5–0.6 ppm (in comparison to the *Z* nitrones) indicating a *cis* relationship between the methine H and the negatively charged O, which is known to deshield the proton.[11–13] Based on the proton chemical shifts the conformation and configuration of the *E* and *Z* nitrones can be drawn as shown in Fig. 3. The *E* nitrone has the aromatic plane perpendicular to the plane of the nitrone functionality whereas they are coplanar in the *Z* nitrones. In order to avoid steric congestion between the aromatic *ortho* protons and the methyl group, the *E* isomer adopts a perpendicular conformation. This is, to our knowledge, the first comprehensive study of *E*, *Z* isomeric nitrones where the aromatic *ortho* (2, 6) positions are not substituted. Previous studies[7] dealt with nitrones that remained in the perpendicular conformation in both the *E* and *Z* isomers due to the presence of substituents. The *Z* nitrones in those cases also adopt the perpendicular noncoplanar conformation in order to avoid crowding between the methine H and the *ortho* substituents. The present study provides us with the opportunity to compare the NMR chemical shifts between the noncoplanar *E* and coplanar *Z* and also to study the kinetics of $E \rightleftharpoons Z$ isomerization (*vide infra*).

Table 5 ^{1}H chemical shifts of *E* and *Z* nitrones **5** in $CDCl_3$ at −10 °C



(*E*)-**5** (*Z*)-**5**

Nitrones **5**	$\delta_H(E)$			$\delta_H(Z)$		
	Aromatic protons	H_E	Me_E	Aromatic protons	H_Z	Me_Z
a X = H	7.5 (a–e)	8.04	3.89	8.30 (a′, e′) 7.50 (b′, d′)	7.50	3.93
b X = *p*-NO_2	7.72 (a, e) 8.35 (b, d)	8.05	3.95	8.46 (a′, e′) 8.34 (b′, d′)	7.63	3.99
c X = *p*-Cl	7.33 (a, e) 7.50 (b, d)	7.98	3.87	8.26 (a′, e′) 7.44 (b′, d′)	7.44	3.92
d X = *p*-OMe[a]	7.28 (a, e) 7.02 (b, d)	7.96	3.84	8.28 (a′, e′) 6.98 (b′, d′)	7.37	3.87
e X = *p*-Me[b]	7.30 (a, b, d, e)	8.00	3.87	8.20 (a′, e′) 7.28 (b′, d′)	7.42	3.90
f X = *p*-NMe_2[c]	7.26 (a, e) 6.74 (b, d)	7.92	3.89	8.22 (a′, e′) 6.74 (b′, d′)	7.27	3.84
g X = *m*-NO_2	—	—	—	8.74 (a′), 7.68 (b′) 8.33 (c′), 9.08 (e′)	7.79	4.04
h X = *o*-OH[d]	—	—	—	6.88–7.58 (a′–d′)	7.66	3.94
i X = *o*-ONe[e]	~7 (b, c) 7.28 (d) 7.45 (a)	8.02	3.87	9.30 (a′), 7.45 (c′) 7.08 (b′), 6.94 (d′)	7.92	3.92

[a] OCH_3 signal at δ 3.84(*E*) and 3.87(*Z*). [b] CH_3 signal at δ 2.41(*E*, *Z*). [c] NMe_2 signal at δ 2.99(*E*) and 3.02(*Z*). [d] OH signal at δ 12.40. [e] OCH_3 signal at δ 3.87(*E*, *Z*).

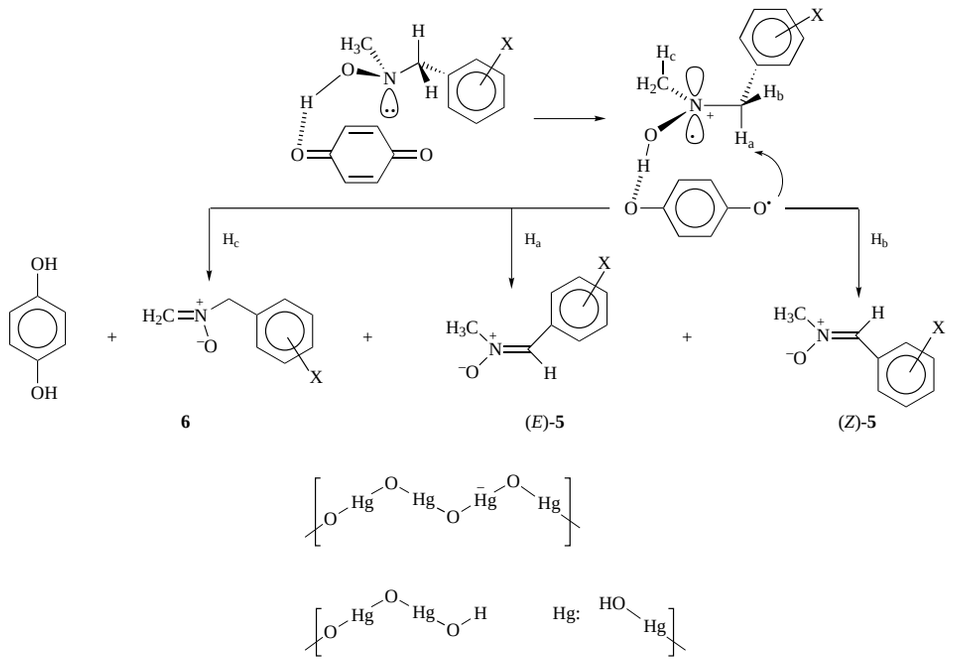
The difference of 0.04 ppm between the chemical shifts of N–CH_3 proton signals of the *E* and *Z* nitrones are found to be less than the difference (0.5 ppm) found in the study involving noncoplanar *E*, *Z* nitrones. The shielding effect of the aromatic π-cloud in the noncoplanar *E* nitrones is assumed to induce an upfield shift of the N–CH_3 signals. However, in the present study this upfield shift was found to be a mere 0.04 ppm. In the case of the nitrone **5f** (X = NMe_2) this upfield trend of the *N*-methyl signal is even reversed. An aromatic π-cloud with increased π density due to electron donation by an NMe_2 group even caused the *N*-methyl signal in the *E*-isomer to appear downfield (increased electron density should have shielded the *N*-methyl protons). While the aromatic π-cloud in the noncoplanar *E* nitrone **5f** shields the N–CH_3 protons, π-electron donation from the aromatic ring (possible only in the planar form) to the nitrone functionality makes the nitrogen richer in electron density inducing a greater upfield shift in the *N*-methyl signals of the *Z* nitrone. Semiempirical molecular orbital calculations[14] on the nitrone **5a** predicted that the *Z* isomer with a coplanar arrangement is more stable than the *E* isomer with an orthogonal geometry by 13–17 kJ mol^{-1}. Our experimental findings of non-detectable amounts of the *E* isomer after equilibration supports the calculation. It was calculated that the planar arrangement in the *E* isomer is destabilized by *ca*. 126 kJ mol^{-1} in comparison with the orthogonal geometry.

Oxidation processes can follow a single electron transfer (SET) pathway[15,16] or a polar (S_N2) mechanism. However, in order to accommodate our experimental findings we envisaged a rate determined by more than one step.

Accumulated evidence so far has led us to depict a probable mechanistic pathway the oxidation process traverses. As presented in Scheme 4 the approach of oxidant towards the nitrogen lone pair would occur from the least hindered side. Some kind of hydrogen bonding would increase the effective size of the hydroxy group and as such the conformer with the disposition of phenyl ring in the *anti* position would facilitate such an approach of the oxidant. A single electron transfer from non bonding electrons in the nitrogen would lead to the formation of radical-cation–radical-anion pair, which would abstract a hydrogen atom H_a, H_b or H_c in its vicinity leading to the formation of the nitrone (*E*)-**5**, and (*Z*)-**5**, and **6**, respectively. When a 0.1 M solution the hydroxylamine and *p*-BQ in $CDCl_3$ was mixed in an EPR tube at −30 °C, no EPR signal could be seen. But upon gradual warming to 20 °C a strong EPR signal was observed, indicating the formation of radical ions. The spectrum persisted as long as the blue complex remained in the reaction mixture. After 20 min the blue complex disappeared with the formation of colourless needles of hydroquinone and no EPR signal was then observed. Formation of the cationic radical is demonstrated by the negative ρ values obtained in the Hammett plots (Figs. 1 and 2). The magnitude of the ρ values are small but this is expected as the cationic centre is removed from the aromatic ring by the intervening two σ bonds. For HgO oxidation the relevant radical anion and subsequent reduced metal (Hg^0) are shown in Scheme 4.

Anodic methoxylation of *N*,*N*-dimethylbenzylamine in methanol is known[15] to give α-methoxy-*N*,*N*-dimethylbenzylamine as the minor and *N*-methoxymethyl-*N*-methylbenzylamine as the major product by preferential abstraction of hydrogen on the methyl group of the aminium cation radical. In this case the proposed mechanism also involved the formation of a cation radical by single electron transfer (SET) from the amine substrate. In our case, however, preferential abstraction of benzylic hydrogen is observed except in compound **4i** where increased steric crowding around the benzylic proton leads to preferential attack on the methyl group of the cation radical (Table 1).

If one envisages the formation of radicals and hydrogen abstraction as two discrete irreversible steps, with two transition states, then the oxidation rate ratio for the pair **5a**/[$^2H_2$]**5a** should not demonstrate a considerable isotope effect in the present experimental set-up as described. The rate of formation of cation radical should be approximately equal in each pair (there will be some difference due to secondary isotope effects). Abstraction of H or D in the second step would of course have different energy requirements. For a two-step process (Fig. 4) reversible formation of the radical pair in the first step would demonstrate a primary isotope effect. Formation of a blue



6 (*E*)-**5** (*Z*)-**5**

Scheme 4

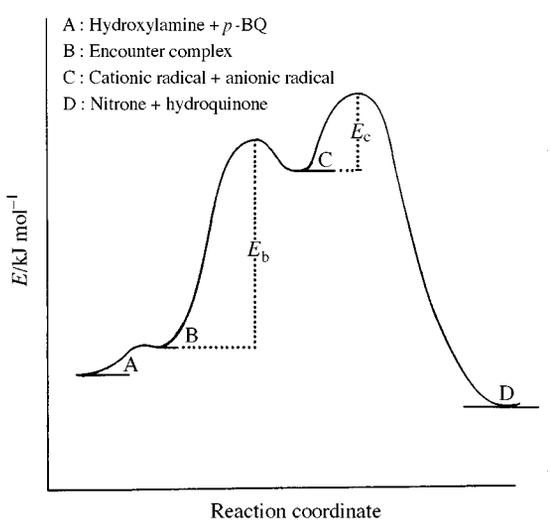


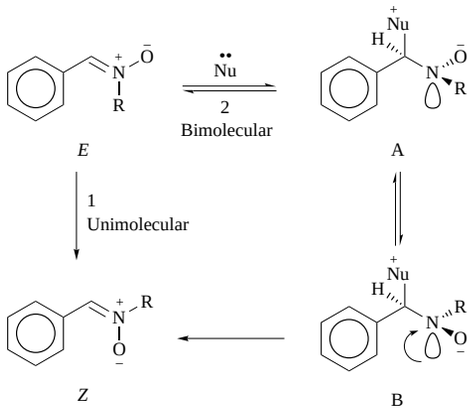
Fig. 4 Energy diagram for the oxidation process

solution in the oxidation using *p*-BQ indicated the formation of the radical-cation–radical-anion pair by a SET mechanism.[16,17] To a great extent the abstraction of H is determined by steric factors around the H to be abstracted. Combined energy requirements for the two steps determine the energy of activation (Fig. 4).

The formation of a considerable amount of the *E* isomer in the oxidation of hydroxylamines provided us with the opportunity to study the kinetics of *E*–*Z* isomerization. Unlike other studies[2,6] involving the kinetics of nitrone *E*–*Z* isomerization, we cannot in our study obtain the *E* isomers in pure isolated form. The HgO oxidation of a 0.2 M solution of the hydroxylamines **4** in $CDCl_3$ (at −15 to −20 °C, 2 h) afforded a mixture of the *E* and *Z* nitrones **5** and the regioisomeric nitrones **6** along with the unreacted starting hydroxylamines (5–15%). In order to ensure the complete consumption of the hydroxylamines the oxidation process needed to be run for longer which would jeopardize the presence of the *E* nitrone required for the kinetic runs. As soon as the nitrones are formed, the *E*–*Z* isomerization would occur in the reaction flask. Kinetic runs were run in base-(NH_3) washed NMR tubes, by NMR techniques. Changes of the intensity of N–CH_3, N–CH_2–, CH=N, aromatic *ortho* protons were monitored and the first-order rate constants for the *E*–*Z* isomerization process were determined by linear regression analysis. Excellent correlation coefficients were obtained in all cases. Isomerization of the *E* nitrone **5a** in the temperature range −10 to 10 °C revealed the values of E_a, $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}_{(273\ K)}$, $\Delta S^{\ddagger}$ as 40.0, 37.8, 86.2 kJ mol^{-1}, and −177 J mol^{-1} K, respectively. Low values of E_a and $\Delta G^{\ddagger}$ and very large negative values of entropy of activation cast doubt on the validity of the assumption that the isomerization is a unimolecular process. In any unimolecular process the entropy of activation should be close to zero;[11,14] while second-order isomerization is expected to have high negative values of entropy of activation.[18] The kinetic runs for each hydroxylamine were repeated several times and the rate constants were not reproducible.

In a series of experiments with a mixture of two nitrones (*E*)-**5** (X = H, *p*-CH_3, *p*-Cl, *p*-OCH_3 and *p*-NO_2) and (*E*)-**5f** in the same NMR tube the rate constants for the individual isomerization were measured. The presence of two nitrones in the same NMR tube would experience almost similar effects (whatever those effects may be). However the rate constants for the isomerization of (*E*)-**5f** varied from 4.70×10^{-5} to 25.0×10^{-5} s^{-1} and were not reproducible. Even though the rate constants were not reproducible, the rate of the isomerization of (*E*)-**5f** was found to be slower (2 to 5 times) than that of the other *E* nitrones with different X substituents.

Evidence presented so far indicate the isomerization to be a bimolecular process. Nucleophilic addition to the *E* nitrone would lead to the reversible formation of the tetrahedral addition product **A** which could either go back to the starting *E* nitrone or to the stable nitrone *Z* *via* the conformer **B** (obtained from **A** by C–N rotation) (Scheme 5). This isomerization scheme clarifies various points. The slower isomerization of the nitrone (*E*)-**5f** could be attributed to the destabilization of the electron rich nitrogen by the electron donating NMe_2 group. Bimolecular processes would lead to a large negative entropy of activation. Addition of nucleophile to the electron rich (*E*)-**5f** is expected to be slower. With regard to the nature of the nucleophilic species it could be the unreacted hydroxylamine, the nitrone itself or any basic entity present during the oxidation with HgO. Since the concentration of the nucleophile is unknown, the rate constants we obtained are pseudo-first-order constants and are not reproducible because of the variable concentration of the unknown nucleophiles from one kinetic run to the next.



Scheme 5

This is the first time a systemic study of the oxidation of *N*-benzyl-*N*-methylhydroxylamines has been made. Efforts are currently underway to find ways to stabilize the *E* nitrones and study their cycloaddition reactions. It would be interesting to study the effect on the regiochemistry of changing the *N*-methyl to another alkyl group (conjugated *vs.* nonconjugated nitrones) and stereochemistry (*E vs. Z*) of this oxidation process.

Experimental

Variable temperature ^{1}H NMR spectra were recorded on a Varian XL 200 NMR spectrometer operating at 200.05 MHz in the Fourier transform mode in $CDCl_3$ solutions using TMS as internal standard; *J* values in Hz. Elemental analyses were performed on a Fisons Instruments Elemental Analyser 1108. The preparation of the hydroxylamine derivatives that are used in our study has been described in our previous work.[19,20] Condensation reactions always provided the *Z* nitrones and using the known positions of the proton signals of the *Z* isomers, the chemical shifts of the *E* and the nonconjugated nitrones **6** are deduced from the spectra of their mixture. The hydroxylamines deuteriated at the benzyl position were prepared by using the same general procedure. The condensation of the hydroxylamines [^{2}H$_2$]**4a** with PhCDO gave the nitrone [^{2}H]**5a** which on reduction with $NaBD_4$ formed the required hydroxylamine.

***N*-[α,α-^{2}H$_2$]Benzyl-*N*-methylhydroxylamine [^{2}H$_2$]4a**

Colourless crystals mp 41–42 °C (diethyl ether–hexane) (Found: C, 68.8; H, 9.3; N, 10.0. $C_8H_9D_2NO$ requires C, 69.03; H, 9.41; N, 10.07%); ν_{max}(KBr)/cm^{-1} 3150, 2800, 2202, 2142, 2090, 1499, 1452, 1109, 932, 799 and 695; δ_H(+20 °C) 2.89 (3 H, s), 7.32 (5 H, s), 7.91 (1 H, br s), benzylic proton signals disappeared due to deuteriation.

***N*-Methyl [α-^{2}H]benzylideneamine *N*-oxide [^{2}H]5a**

Colourless crystals mp 82–83 °C (diethyl ether–hexane) (Found: C, 70.4; H, 7.35; N, 10.2. C_8H_8DNO requires C, 70.56; H, 7.40; N, 10.29%); ν_{max}(KBr)/cm^{-1} 3052, 2936, 2256, 1578, 1440, 1339, 1204, 1172, 1104, 920, 770 and 696; δ_H(+20 °C) 3.92 (3 H, s), 7.50 (3 H, s), 8.30 (2 H, m).

General procedure to determine the composition and the relative rates of HgO oxidation of the hydroxylamines

To a solution of the hydroxylamine **4a** (0.15 mmol) and X-$C_6H_4CH_2NOHMe$ (0.15 mmol) in $CDCl_3$ (2.0 cm^3) at 0 °C was added yellow HgO (40.0 mg, 0.185 mmol) and the mixture was stirred for 30 min or until the mercury salt turned greyish. The solution was passed through tightly packed glass wool with a bed of $MgSO_4$ in a pipette to remove the mercury salts. The ^{1}H NMR spectrum revealed the presence of starting materials along with product nitrones. Careful analysis of the spectrum helped to quantify each product and starting material, by integration of several proton signals. The *N*-alkyl protons of the nitrones and hydroxylamines are well separated and there are many other non-overlapping signals of the starting materials and products. ^{1}H NMR data of the individual nitrones and that of hydroxylamines are reported. Before the addition of the HgO, the ^{1}H NMR spectra of the reaction mixture were taken in order to check the quantities of the starting materials by integration. After recording the spectra the content of the NMR tube was quantitatively transferred into the reaction flask. At the end of the oxidation and quantification of the individual compounds, about 7 mg of the hydroxylamine $PhCH_2NOHMe$ was mixed with the contents of the NMR tube. Peak enhancement of the unreacted $PhCH_2NOHMe$ ensured that the assignment of the signals to the starting hydroxylamines was correct. Using the rate equation of Ingold and Shaw[10] the relative rates were determined. The same procedure was repeated to determine the relative rates of oxidation of the hydroxylamines **4a** and [^{2}H$_2$]**4a**.

General procedure to determine the composition and relative rates of *p*-BQ oxidation of the hydroxylamines

To a stirred solution of the hydroxylamine **4a** (0.15 mmol) and X-$C_6H_4CH_2NOHMe$ (0.15 mmol) in $CDCl_3$ (1.0 cm^3) at 20 °C was added dropwise a solution of *p*-BQ (0.15 mmol) in 1 cm^3 of $CDCl_3$ over a period of 3–5 min. The solution immediately turned dark blue and after 10–20 min it became colourless with the separation of white crystals of hydroquinone. After passing through glass wool (tightly packed in a pipette) to remove the hydroquinone the reaction mixture was analysed by ^{1}H NMR and relative rates determined as described above in the case of HgO oxidation. The same procedure was repeated to determine the relative rates of oxidation of the hydroxylamines **4a** and [^{2}H$_2$]**4a**.

General procedure to determine the composition of nitrones

(*i*) HgO oxidation of the hydroxylamines. To a solution of hydroxylamine **4** (0.3 mmol) in $CDCl_3$ (2.0 cm^3) at −20 °C was added yellow HgO (1.0 mmol). The mixture was stirred for 2 h. The solution was then passed through tightly packed glass wool with a bed of $MgSO_4$ in a precooled pipette (to prevent rapid isomerization) to remove the mercury salts. The solution was filtered into a base-washed precooled NMR tube. The NMR spectra at −20 °C revealed the composition of the isomers present (Table 4).

(*ii*) *In situ* HgO oxidation. To a solution of hydroxylamine **4** (0.1 mmol) in $CDCl_3$ (1.5 cm^3) at −20 °C was added yellow HgO (0.3 mmol). NMR spectra were recorded immediately after the addition of the oxidant to see the composition of nitrones at the beginning of the oxidation process (Table 4).

^{1}H NMR chemical shifts of the nonconjugated nitrones 6

These were deduced from the spectrum of their mixture with the conjugated nitrones **5**. *J* values are in Hz.

***N*-Benzylmethyleneamine *N*-oxide 6a.** δ_H(−10 °C) 4.98 (2 H, s), 6.32 (1 H, d, *J* 8.0), 6.64 (1 H, d, *J* 8.0), 7.5 (5 H, m).

***N*-(4-Nitrobenzyl)methyleneamine *N*-oxide 6b.** δ_H(−10 °C) 5.10 (2 H, s), 6.56 (1 H, d, *J* 7.0), 6.68 (1 H, d, *J* 7.0), 7.60 (2 H, d, *J* 8.0), 8.34 (2 H, d, *J* 8.0).

***N*-(4-Chlorobenzyl)methyleneamine *N*-oxide 6c.** δ_H(−10 °C) 4.94 (2 H, s), 6.38 (1 H, d, *J* 7.0), 6.62 (1 H, d, *J* 7.0), 7.44 (4 H, overlapping AB).

***N*-(4-Methoxybenzyl)methyleneamine *N*-oxide 6d.** δ_H(−10 °C) 3.84 (3 H, s), 4.88 (2 H, s), 6.24 (1 H, d, *J* 8.0), 6.58 (1 H, d, *J* 8.0), 6.98 (2 H, d, *J* 9.0), 7.39 (2 H, d, *J* 9.0).

***N*-(4-Methylbenzyl)methyleneamine *N*-oxide 6e.** δ_H(−10 °C) 2.39 (3 H, s), 4.94 (2 H, s), 6.26 (1 H, d, *J* 8.0), 6.60 (1 H, d, *J* 8.0), 7.30 (4 H, AB).

***N*-(4-Dimethylaminobenzyl)methyleneamine *N*-oxide 6f.** δ_H(−10 °C) 2.99 (6 H, s), 4.85 (2 H, s), 6.19 (1 H, d, *J* 8.0), 6.60 (1 H, d, *J* 8.0), 6.76 (2 H, d, *J* 9.0), 7.30 (2 H, d, *J* 9.0).

***N*-(3-Nitrobenzyl)methyleneamine *N*-oxide 6g.** δ_H(−10 °C) 5.14 (2 H, s), 6.67 (2 H, s).

***N*-(2-Hydroxybenzyl)methyleneamine *N*-oxide 6h.** δ_H(−10 °C) 5.10 (2 H, s), 6.70 (2 H, s), 6.68–7.58 (4 H, m).

***N*-(2-Methoxybenzyl)methyleneamine *N*-oxide 6i.** δ_H(−10 °C) 3.87 (3 H, s), 5.00 (2 H, s), 6.27 (1 H, d, *J* 8.0), 6.60 (1 H, d, *J* 8.0), 6.92–7.45 (4 H, m).

Acknowledgements

Facilities provided by the King Fahd University of Petroleum and Minerals, Dhahran, are gratefully acknowledged.

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Paper 7/04761D
Received 4*th July* 1997
Accepted 11*th November* 1997