The Reactivities of Some Cyclic Nitrones in 1,3-Dipolar Cycloaddition Reactions

Sk. Asrof Ali* and Mohammed I. M. Wazeer
Department of Chemistry, University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

Rate constants for the cycloaddition of 1-pyrroline 1-oxide, (**1**), 3,4,5,6-tetrahydropyridine 1-oxide (**2**), and 3-oxo-3,4,5,6-tetrahydropyridine 1-oxide (**3**) to methyl acrylate, ethyl vinyl ether, and hex-1-ene have been determined at different temperatures by ^{1}H n.m.r. spectroscopy. The activation parameters and solvent effect on rate constant indicate the concerted nature of the reaction. Strain energy in the transition state plays an important role in the addition reactions of these cyclic nitrones. It is found that (**2**) is the most reactive among these cyclic nitrones. Methyl acrylate and ethyl vinyl ether are found to react faster than hex-1-ene. The presence of a protic solvent minimizes the dimerization of nitrone (**2**).

1-3-Dipolar cycloaddition of nitrones with dipolarophiles is useful for constructing five-membered heterocyclic rings.[1] The highly regio- and stereo-selective nature of this useful reaction enables one to incorporate several stereochemical centres in a single step.[2] Both intra- and inter-molecular nitrone cycloadditions have been utilized as the key step in achieving syntheses of various natural products.[3] The frontier orbital treatment is remarkably successful in explaining the regioselectivity and reactivity phenomena of 1,3-dipolar cycloadditions.[4—9] Fisera *et al.*[10,11] determined the rate constants for the additions of *C*-benzoyl-*N*-phenylnitrone with several furan derivatives. The second-order rate constants are correlated with energies of the frontier orbitals of the reactants and the cycloadditions are found to be controlled by a dominant interaction between the lowest unoccupied molecular orbital (LUMO) of nitrone and the highest occupied molecular oribital (HOMO) of furan. In acyclic nitrones, where $E \rightleftharpoons Z$ isomerization is possible at high temperature, the *E* isomer undergoes cycloaddition faster than the *Z* isomer due to steric reasons.[12] At room temperature usually the stable *Z* isomer exists. However, the cyclic nitrones, where only *E* isomer is possible because of structural constraints, should undergo cycloaddition much faster than their acylic counterpart.[13]

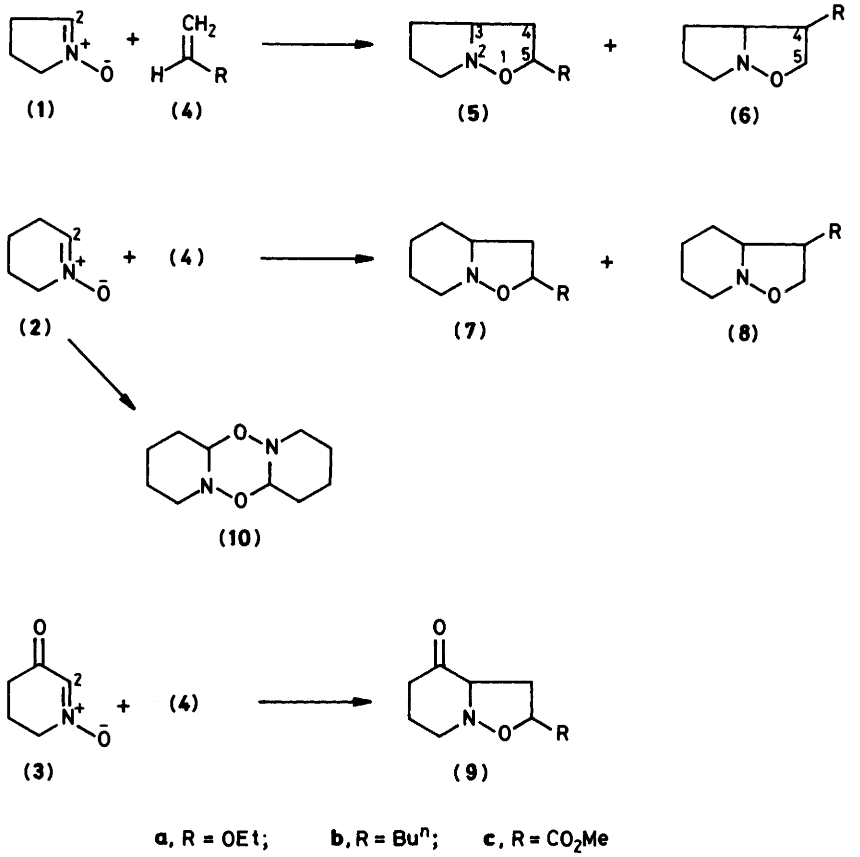
Alkaloids containing pyrrolidine and piperidine rings are widespread in nature. These rings could be elaborated using the cycloaddition reaction of 1-pyrroline 1-oxide (1), 3,4,5,6-tetrahydropyridine 1-oxide (2), and 3-oxo-3,4,5,6-tetrahydropyridine 1-oxide (3). Detailed knowledge of their rates of addition to monosubstituted alkenes would indeed be helpful for the proper utilization of these high yielding reactions. Hence we undertook a systematic kinetic study of these cycloaddition reactions, using a high-field ^{1}H n.m.r. technique which offers a convenient method for following these reactions.

Results and Discussion

Cycloaddition reaction of nitrone (1)—(3) with ethyl vinyl ether gave 5-substituted adducts (**5a**),[14] (**7a**), and (**9a**),[14] respectively. Addition of nitrones (1) and (2) to hex-1-ene were also regioselective and afforded 5-substituted isoxazolidine (**5b**)[14] and (**7b**) respectively, but ketonitrone (3) failed to give any characterizable adduct. The ^{1}H n.m.r. spectrum of a reaction mixture containing (3) and hex-1-ene in $CDCl_3$ at 36 °C darkened gradually, presumably due to extensive decomposition of the addition products. A different regiochemical behaviour is observed in the addition of electron-deficient alkene, methyl acrylate. The nitrone (3) afforded 5-substituted regiomer (**9c**) in good yield,[14] whereas a regiomeric mixture is obtained from the other two nitrones.[15,16] Thus nitrone (1) gave (**5c**) and (**6c**), while nitrone (2) afforded (**7c**) and (**8c**).

Measurement of the rate constants for the addition of nitrone (2) to alkenes is somewhat complicated by the competing dimerization process[17] to give (**10**). Spectral analysis revealed no dimer formation when the alkene is methyl acrylate. However, 6% dimer along with 94% adduct (**7a**) was produced during the addition of (2) onto ethyl vinyl ether. Kinetic data on nitrone (2)–hex-1-ene were not obtained because of the increased amount of dimer formation. ^{1}H N.m.r. analysis of $CDCl_3$ solution, initially 0.773M in nitrone (2) and 2.26M in hex-1-ene, revealed the presence of unreacted nitrone (2) and adducts (**7b**) and (**10**) in the ratio 27:55:18, respectively, after 14 h at 36 °C. The nitrone (2) dimerized on standing in $CDCl_3$ solution but not in CD_3OD containing 0.7M-nitrone even after 40 h at 26 °C. The presence of protic solvent thus minimizes the dimerization.

Kinetic results obtained for cycloaddition of the three nitrones with three different alkenes in $CDCl_3$ are shown in the Table. Cycloadditions were monitored at different temperatures by the disappearance of ^{1}H n.m.r. signals of 2-H of nitrone and α-H of alkene. These signals in the n.m.r. spectra were free of any overlapping signals. The 2-H signal of nitrones (1)—(3) appeared at δ 6.78, 7.18, and 7.25 respectively. The α-H signal of ethyl vinyl ether, hex-1-ene, and methyl acrylate were centred around δ 6.38, 5.69, and 6.10, respectively. The signals of 5-H of 5-substituted isoxazolidines (R = OEt, CO_2Me) were centred around δ 4.5—5.1 and were also free of any competing signals in the ^{1}H n.m.r. spectra of the reaction mixture containing adducts along with starting nitrone and alkene. The 5-H signal of isoxazolidines (R = Bu) overlaps other proton signals; however, a triplet (2 H) at δ 3.00 in (**5b**) was free of any competing signals. The ratio of the concentration of nitrone and alkene was determined from time to time and the second-order rate constants were obtained in the usual way by linear regression analysis. Cycloadditions were performed under mild kinetically controlled conditions in order to avoid any decomposition of the reactants and products. The low-temperature kinetic study virtually makes sure that cycloadducts do not go back to the starting reactants in a manner like a retro-Diels–Alder reaction. Towards the end of the kinetic run a known concentration of *p*-nitrobenzaldehyde was added to the reaction mixture and the integration of the aromatic proton, 2-H of nitrone, α-H of alkene, and in some cases 5-H of isoxazolidines revealed that the total concentration of products and unreacted nitrone (or alkene) was equal to the initial concentration of nitrone (or alkene). This result thus assured that the cycloaddition products, nitrones, and alkenes are all



a, R = OEt; b, R = Bu^n; c, R = CO$_2$Me

Scheme. Regiomeric distributions for reactions of cyclic nitrones with ethyl vinyl ether, hex-1-ene, and methyl acrylate

Table. Rate constants and activation parameters for the cycloaddition reactions

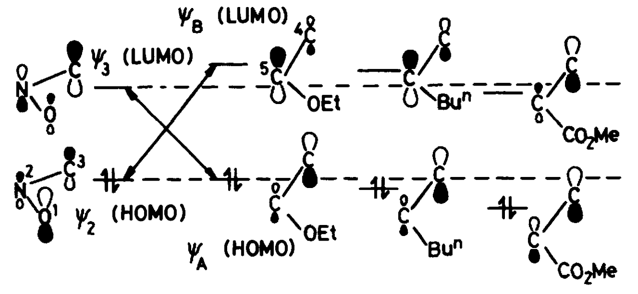
Nitrone	CH$_2$=CHR	Temp/°C	$10^5 k_2$/l mol^{-1} S^{-1}	E_a/kJ mol^{-1}	$\Delta H^{\#}$/kJmol^{-1}	$\Delta S^{\#}$/J mol^{-1} K^{-1}
(1)	R = CO$_2$Me	26.0 36.0	22.3 62.0	78.7	75.8	−61.3
(2)		26.0^a 36.0	188 340	45.6	43.8	−153
(3)		26.0 36.0	5.43 14.9	77.6	74.9	−75.6
(1)	R = OEt	36.0 56.0	0.295 1.63	72.3	69.7	−85.8
(2)		26.0 36.0	2.81 8.10	81.4	78.8	−68.2
(3)		26.0 36.0	0.668 1.84	77.9	75.4	−92.3
(1)	R = Bu^n	46.0 56.0	0.193 0.404	64.5	63.6	−156
(3)		36.0	0.589			

^{a} In CD$_3$OD solvent, k_2 59.7 × 10^{-5} l mol^{-1} s^{-1}.

stable under the reaction conditions and no products other than the normal cycloadducts were obtained.

The ratio of rate constants at 36 °C for the addition of nitrone (**1**)—(**3**) with methyl acrylate was found to be 4.2:23:1 respectively, while with ethyl vinyl ether the ratio was 1:27.5:6.2. Thus (**2**) is the most reactive among the cyclic nitrones towards both electron-rich and electron-deficient alkenes. However, nitrone (**1**) is more reactive than (**3**) toward methyl acrylate, while the reverse is the case with ethyl vinyl ether and hex-1-ene. The rate of cycloaddition is not markedly influenced by solvent polarity as would be expected in any concerted process.[13,18] Passing from CDCl$_3$ to CD$_3$OD the second-order rate constant of nitrone (**2**)–methyl acrylate addition at 26 °C is decreased by a factor of only 3.

Without detailed information on the HOMO – LUMO energy gap, orbital coefficients, substituents, steric effects *etc.* it would indeed be difficult to explain the differences in reactivity and regiochemical behaviour observed in these concerted, four-centred, addition reactions. However, a qualitative explanation can be put forward using the crude equation (1)[6,19] obtained by applying MO perturbation theory to the frontier orbital interactions (Figure). The interaction or stabilization energy, ΔE, of the transition state is determined by orbital coefficients (c and c' of HOMO and LUMO, respectively), resonance



Qualitative representation of the energies and orbital coefficients of nitrones and alkenes

$$\Delta E = \frac{2[c_1c'_5\beta_{\mathrm{O-C(5)}} + c_3c'_4\beta_{\mathrm{C(3)-C(4)}}]^2}{E_{\Psi_2} - E_{\Psi_B}} + \frac{2[c'_1c_5\beta_{\mathrm{O-C(5)}} + c'_3c_4\beta_{\mathrm{C(3)-C(4)}}]^2}{E_{\Psi_A} - E_{\Psi_3}} \quad (1)$$

integrals (β), and HOMO − LUMO energy gaps. An increase in ΔE increases the reaction rate. In the case of electron-rich alkenes both HOMO–LUMO combinations prefer the formation of a 5-substituted isoxazolidine by uniting larger terminal coefficients of the interacting atomic orbitals in the transition state.[9] With methyl acrylate these nitrones (1) or (2) gave both 4- and 5-substituted isoxazolidines.[16] The LUMO(nitrone)–HOMO(methyl acrylate) interaction dictates the formation of a 5-substituted isoxazolidine while the other HOMO–LUMO interaction favours the formation of the 4-substituted regiomer. However, due to the presence of the keto group in (3) the HOMO–LUMO orbital energies of (3) are lowered.[7,8] As a result, the LUMO(nitrone)–HOMO(alkene) interaction has a much greater say in regioselection. Thus, 5-substituted regiomers are obtained with all three alkenes.

The perturbation equation (1) has been simplified and used by other workers[6,10] by assuming that the numerators of the two terms are equal and the substituent changes the HOMO–LUMO energies of the alkene by the same amount. The kinetic data for several dipolar cycloaddition reactions and their HOMO–LUMO energies fit fairly well with the simplified equation. By making similar assumptions, one can see that switching from hex-1-ene to ethyl vinyl ether raises the orbital energies by an equal amount. Then a loss in the first term [due to an increase HOMO(nitrone) − LUMO(alkene) energy gap] will be more than compensated by a gain in the second term.[6] In the case of methyl acrylate the orbital energies are lowered in such a way that gain in the first term exceeds the loss in the second term. Thus, both in the cases of electron-rich and electron-deficient alkenes, an increased ΔE accelerates the reaction.

The frontier orbital interactions cannot alone explain why the six-membered cyclic nitrone (2) reacts faster than (1) or (3). This could probably be understood if one considers the role of strain energies in the transition state. Perturbation MO theory relates to an early point on the reaction co-ordinate and accounts only for a fraction of activation energy. Some constraints (or its relief) present in the reaction products must be introduced to give a better picture of the transition state.[19] Angular strain present in nitrone (1) is more than offset by the greater eclipsing strain (peculiar to cyclopentane systems)[20] introduced in the transition state due to a change in hybridization from sp^2 to sp^3. The presence of keto group in (3) introduces bond-opposition strain in the transition state similar to that present in a cyclohexanone system.[20] The absence of similar destabilizing strains in the transition states makes (2) the most reactive among these cyclic nitrones. Toward electron-rich alkenes, ketonitrone (3) is more reactive than (1), while their reactivities are reversed with electron-deficient alkenes. This observed reactivity is in accord with the prediction that can be made from the frontier orbital interactions (Figure) alone, since both transition states seem to have the same kind of destabilizing strain.

According to Sustmann's classification[5] the dominant interaction in Type I and Type III cycloaddition reactions are, respectively, HOMO (dipole)–LUMO (dipolarophile) and LUMO (dipole)–HOMO (dipolarophile). In our case cycloaddition reaction is of Type II where both HOMO–LUMO interactions can contribute to the stabilization of the transition state. The kinetic data we obtained for different alkenes fit quite well into the U-shaped dipolarophile activity scale inherent in Type II dipolar cycloadditions.[6,10]

Our activation parameters, shown in the Table, are derived from rate constants determined at two temperatures. Even though the rate constants are reproducible within 5%, the individual activation parameters may have larger uncertainties. However, our results are consistent with those reported for cycloaddition reactions involving acyclic nitrones.[13] These low activation energies and large negative entropies of activation are a necessary condition for multicentred concerted cycloaddition reactions.[6,21]

Experimental

The n.m.r. spectra were recorded on a Varian XL-200 n.m.r. spectrometer operating at a proton frequency of 200.0 MHz and in the pulse Fourier transform mode. Flip angle of 20°, digital resolution of 0.15 Hz, and four transients were employed in all measurements. The absolute intensity mode was used to measure integrals of interesting peaks, which were well separated without any overlap. Spectra at different times for the kinetic runs were obtained by arraying the pre-acquisition delay times. The temperature in the probe was controlled by standard Varian equipment and was accurate to ±0.5 °C. The temperature was calibrated by standard chemical shifts of methanol. Deuteriated chloroform (99.95% isotope purity) with Me_4Si as internal standard was used.

Solvent CH_2Cl_2 was passed through active alumina. Methyl acrylate, ethyl vinyl ether, hex-1-ene, *N*-hydroxypyrrolidine, and *N*-hydroxypiperidine were distilled prior to use. The ketonitrone (3) was prepared as described in the literature.[14,22] The nitrone was further purified by several crystallizations from dichloromethane–ether mixtures, m.p. 83—84 °C. All the cycloadducts except (**7a** and **b**) were prepared following literature procedures.[14–16]

Preparation of (1) *and* (2).—Nitrones (1) and (2) were prepared according to the reported procedures.[14,15] However, special care was taken to ensure the purity of the nitrones. In a typical run, yellow mercury(II) oxide (3 g, 14 mmol) was added to *N*-hydroxypiperidine (0.5 g, 5 mmol) in CH_2Cl_2 (50 ml) at 0 °C under nitrogen. Within 10 min the reaction was complete as indicated by t.l.c. (silica gel, ethyl acetate). Anhydrous $MgSO_4$ (*ca.* 4 g) was added to the mixture which was then filtered through a bed of Celite and anhydrous $MgSO_4$. The grey mercury salts were washed with cold (0 °C) CH_2Cl_2 (25 ml). The nitrone solution was kept at 0 °C in order to avoid dimerization. The solvent was removed *in vacuo* at 0 °C and to the thick residue at 0 °C was added $CDCl_3$ (3 ml) and the solvent was again removed *in vacuo* to ensure the complete removal of CH_2Cl_2. The residue was dissolved in deuteriochloroform and was quickly transferred to a 10.00 (±0.04) ml volumetric flask. The molar concentration of the nitrone in the solution was determined by a ^1H n.m.r. technique. The n.m.r. spectra were recorded quickly after mixing a known volume of nitrone solution and a known quantity of ethyl vinyl ether or hex-1-ene. The ratio of the nitrone to alkene was determined using the integration of signals due to 2-H of nitrone and the olefinic protons. The molarity of nitrone was also determined using n.m.r. spectra of solutions containing a known amount of *p*-nitrobenzaldehyde. The average molarity of nitrone in the volumetric flask was found to be 0.462M with a precision of *ca.* 3%.

2-*Butylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**7b**).—To a nitrone solution [prepared as above from *N*-hydroxypiperidine (5 mmol)] in CH_2Cl_2 (5 ml) were added ethanol (5 ml) and hex-1-ene (5 ml) (ethanol was added to minimize dimerization). The solution was heated to 40 °C for 12 h. The mixture was taken up in CH_2Cl_2 (30 ml) and washed with water (10 ml). The organic layer was dried ($MgSO_4$), filtered, and rotovaped to give a yellow oil which on bulb-to-bulb distillation (125 °C at 1 mmHg) afforded (**7b**) (0.58 g, 63%) as an oil (Found: C, 71.9; H, 11.25; N, 7.8. $C_{11}H_{21}NO$ requires C, 72.1; H, 11.55; N, 7.6%); $\nu_{max.}$(neat) 2 924, 2 834, 1 472, 1 455, 1 383, 1 127, 1 012, 872, and 790 cm^{-1}; δ_H 0.90 (3 H m), 1.06—3.00 (16 H, m), 3.46 (1 H, m), and 4.06 (1 H, m).

2-*Ethoxyhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* (**7a**).—Following the same procedure as above the adduct was prepared by reacting excess of ethyl vinyl ether with nitrone (**2**). The crude product upon bulb-to-bulb distillation (70 °C at 0.4 mmHg) afforded the cycloadduct as an oil (67% yield), $\nu_{max.}$(neat) 2 956, 2 913, 1 448, 1 378, 1 353, 1 266, 1 205, 1 115, 1 090, 1 010, 991, 924, 869, and 859 cm^{-1}; δ_H 1.21 (3 H, t, *J* 7.2 Hz), 1.20—2.36 (8 H, complex), 2.58 (1 H, m), 3.16 (1 H, m), 3.46 (2 H, m), 3.82 (1 H, m), and 5.18 (1 H, m).

Kinetics of Cycloaddition Reaction.—Kinetic runs were studied by n.m.r. in the following way. A known volume of alkene was weighed in an n.m.r. tube which was then cooled in a salt–ice (−15 °C) bath. To the cold solution was added a known volume (1.00 ml; room temperature) of the nitrone solution. The n.m.r. tube was sealed immediately while the solution was still kept in the salt–ice bath. The mixture was properly mixed and inserted into the n.m.r. probe which was kept at constant temperature throughout the kinetic measurements. The ratio of the concentrations of the reactants and products was determined from time to time by integration of signals due to 2-H of the nitrone and the olefinic protons of the alkene. The amount of products formed was also determined in most cases. The second-order rate constant was determined by linear regression analysis of the data and at 26.0 °C it was reproducible within 5%. The initial concentrations of nitrone–methyl acrylate, nitrone–ethyl vinyl ether, and nitrone–hex-1-ene were kept at *ca.* 0.500—0.625M, 0.500—1.20M, and 0.500—1.15M, respectively. The additions were followed up to 40—80% chemical conversion.

Acknowledgements

Financial support provided by the University of Petroleum and Minerals, Dhahran, is gratefully acknowledged.

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Received 2*nd December* 1985; *Paper* 5/2102