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Effect of iminic nitrogen substituents on [4+2] versus [3+2] cycloaddition pathways in reactions of nitrosoalkenes with simple acyclic imines: an experimental and theoretical investigation

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Abstract—The results of experimental and theoretical investigations on the mechanism of competitive [3+2] versus [4+2] cycloaddition reactions of simple acyclic imines with nitrosoalkenes are reported. The effect of substituents on the iminic nitrogen in influencing the cycloaddition pathways has been meticulously explored.

α-Nitrosoalkenes are widely known as 4π components in cycloaddition reactions with a variety of polarized and unpolarized alkenes,[1a–c] allenes,[1d] dienes,[1e] enamines[1f–h] and enol ethers[1i] either via a concerted or a stepwise process involving a zwitterionic intermediate. Recently, the formation of an unusual [3+2] cycloadduct has also been observed in the reactions of α-nitrosostyrenes with a carbon–carbon double bond attached to a pyrimidinone ring.[2] In contrast, there are fewer reports of such reactions with substrates having carbon–nitrogen double bonds.[3] Mackay and co-workers reported an unusual [3+2] cycloaddition of α-nitrosoalkenes with the carbon–nitrogen double bond of oxazines and failed to observe any reaction with various other cyclic and acyclic models bearing a carbon–nitrogen double bond.[3] Since such a cycloaddition mode could not be generalized, it was concluded that the core requirements for such reactions to take place are: (i) an oxazine oxygen and (ii) an allene or alkene function allylic to this oxygen in a rigid bicyclic system.

Subsequent reports from our laboratories have shown a generalized and unusual [3+2] cycloaddition mode with the carbon–nitrogen double bond of polarized 1,3-diazabuta-1,3-dienes resulting in a useful access to synthetically and biologically significant heterocyclic *N*-oxides.[4] Further, the predominance of the products from such cycloadditions was explained on the basis of the preferred conformations of the nitrosoalkenes, in turn governed by the electronic nature of the substituents present on them.[3]

Recent reports by Tahdi and co-workers[5] regarding the role of substituents present on nitrosoalkenes in controlling their conformational preferences and in turn the nature of products formed via [3+2] and [4+2] cycloaddition pathways are not generalized.[6] In view of these contradictions and bearing in mind that the conformational preferences of 1,3-diazabuta-1,3-dienes play a pivotal role in determining the mode of cycloaddition followed in their reactions with ketenes,[6] it was felt that the nature of substituents on the iminic nitrogen of simple imines might be crucial in influencing the pathways followed and hence the distribution of the products formed in these reactions. Accordingly, the present communication describes experimental and theoretical investigations to examine the influence of substituents on iminic nitrogen on the mode of cycloadditions in the

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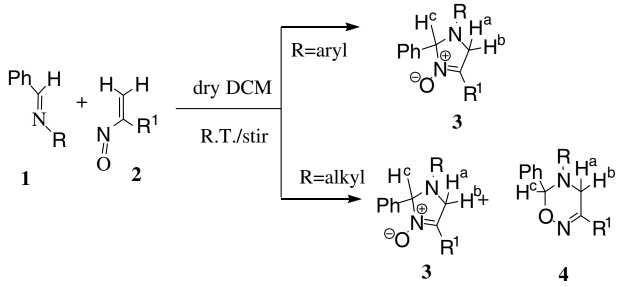
reactions of various *N*-alkyl/aryl-substituted imines (Schiff's bases) with nitrosoalkenes.

The acyclic aryl and alkyl imines **1** derived from condensation of alkyl/aryl amines and aldehydes reacted with nitrosoalkenes **2**, generated in situ from α-bromo oximes and sodium bicarbonate, in methylene chloride to give either nitrones **3** or a mixture of nitrones **3** and oxazines **4** in good yields (70–80%).[7] The reactions of *N*-aryl imines led to the exclusive formation of cyclic nitrones **3**. There was no evidence for the formation of oxazine **4** as co-product with **3**, even when the crude products were examined by high-resolution ^{1}H NMR spectroscopy. However, the reactions of *N*-alkyl imines with α-nitrosoalkenes resulted in the competitive formation of both [3+2] and [4+2] adducts, the latter being formed in higher proportions ~60:40 (Scheme 1).

The products **3a** and **4a** were characterized as 1-cyclohexyl-4-(4-nitrophenyl)-2-phenyl-2,5-dihydro-1*H*-imidazole-3-oxide and 5-cyclohexyl-3-(4-nitrophenyl)-6-phenyl-5,6-dihydro-4*H*-[1,2,5]oxadiazine on the basis of analytical and spectral data.[8] The mass spectrum of product **3a**, for example, analyzed for $C_{21}H_{23}N_3O_3$, exhibited an intense M-16 peak ($m/z = 349$) diagnostic of a nitrone,[3a] while the mass spectrum of **4a** exhibited a molecular ion peak at $m/z = 365$ for $C_{21}H_{23}N_3O_3$. In the ^{1}H NMR of **3a**, the methylene protons exhibited two doublets of doublets at δ 3.98 ($J = 14.7$ and 3.6 Hz, H^a) and 4.62 ($J = 14.7$ and 4.2 Hz, H^b) corresponding to a CH_2 of a nitrone, downfield from the position δ 3.62 typical of oxazines **4a**. A doublet of doublets ($J = 3.6$ and 4.2 Hz, H^c) corresponding to the CH of nitrone **3a** appeared at δ 5.72, while that for oxazine **4a** appeared as a singlet at δ 6.00. The ^{13}C NMR spectra were also in agreement with the nitrone and oxazine structures assigned above to **3a** and **4a**.

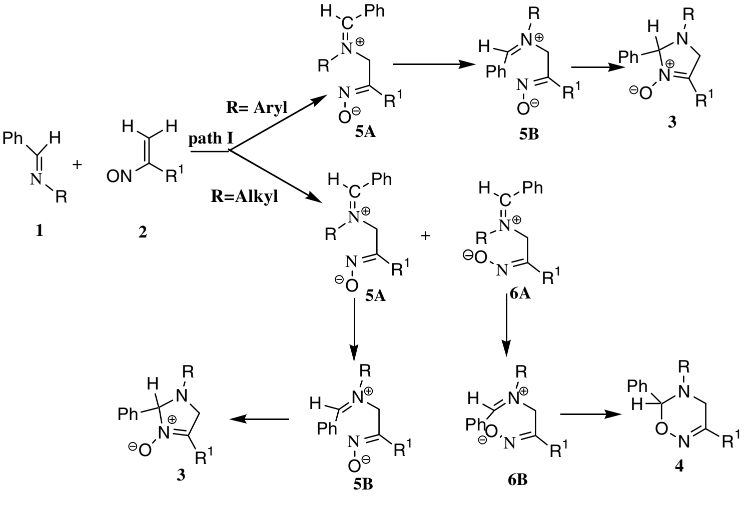


a. R = cyclohexyl; R^1 = $-C_6H_4-NO_2(p)$
b. R = benzyl, R^1 = $-C_6H_4-NO_2(p)$
c. R = phenyl, R^1 = $-C_6H_4-NO_2(p)$
d. R = cyclohexyl; R^1 = $-C_6H_5$
e. R = benzyl; R^1 = $-C_6H_5$
f. R = phenyl, R^1 = $-C_6H_5$
g. R = cyclohexyl, R^1 = $-C_6H_4-CH_3(p)$
h. R = benzyl, R^1 = $-C_6H_4-CH_3(p)$
i. R = phenyl, R^1 = $-C_6H_4-CH_3(p)$

Scheme 1.

The nitrones **3** and oxazines **4** are formed in competition and are not in equilibrium, these were separately shown to be stable to the reaction conditions, though rearrangements of oxazines to nitrones[9] and nitrones to oxazines[10] are well documented in the literature. The complete absence of oxazines in the reactions of aryl imines with nitrosoalkenes bearing an electron-withdrawing nitro group again contradicts the earlier proposal that the electronic nature of the substituents on nitrosoalkenes controls the preferred conformation of nitrosoalkenes and in turn, the nature of the products in the title reactions.[3a]

A plausible mechanism for the formation of nitrones and oxazines is illustrated in Scheme 2. The addition of nitrosoalkene to a C=N bond is less likely to proceed via a concerted single step as reported earlier.[1,11] The reaction appears to lead unusually to the resonance-stabilized zwitterionic intermediates **5A** and **6A**, which are formed from the *transoid* and *cisoid* conformations of the nitrosoalkenes. These two intermediates **5A** and **6A** are interconvertible into other intermediates **5B** and **6B**, respectively. However, interconversion between the zwitterionic intermediates **5** and **6** does not seem to be credible as suggested earlier,[11,3,4] since this requires rotation around a C=N–O bond, which becomes stronger after nucleophilic attack, that is changes from a partial double bond in the nitrosoalkene to a typical double



Scheme 2.

bond in the zwitterionic intermediate. Finally, the intermediates **5B** and **6B** cyclize to form the nitrones **3** and oxazines **4**, respectively. It seems that formation of the intermediate **6A** is discouraged in the case of aryl substituted imines because of the steric repulsions between the oxygen lone pairs and the π electron cloud on the aryl substituent. In the case of alkyl substituted imine; the formation of intermediates **5A** as well as **6A** is possible because of the reduced steric repulsion between the alkyl group and the nitrogen or oxygen of the nitrosoalkenes. The above mechanistic rationale is in agreement with the formation of both [4+2] and [3+2] cycloadducts in the case of alkyl imines and exclusively the [3+2] adduct in the case of aryl imines.

The experimental observations and the mechanistic rationale proposed above is further supported by theoretical studies performed at semi-empirical AM1 and ab initio[12] HF/6-31G* levels of computational analysis implemented in the Gaussian series of programs.[13] Gilchrist[1a] have proposed a concerted [4+2] cycloaddition mechanism for the formation of the six-membered ring. However, all attempts to locate a transition state for such a concerted process between $H_2C{=}NH$ and $H_2C{=}CH{-}N{=}O$ at AM1 and HF/6-31+G* levels led invariably to the zwitterionic intermediate. Complete optimizations carried out at HF/6-31+G* theory level on the reaction path involving $H_2C{=}NMe$ and the *cis*- and *trans*-conformers of $H_2C{=}CH{-}N{=}O$ showed that the initial nucleophilic attack occurs in such a way so as to form intermediates having the geometry as shown in **I** and **II**, respectively (Fig. 1). The intermediates **I** and **II** were found to be 17.6 and 27.6 kcal/mol higher in energy than the corresponding starting materials, respectively. The resultant final products are stable by −37.6 and −20.2 kcal/mol as compared to the starting materials (Fig. 2) indicating that the formation of a six-membered ring, in the subsequent ring closure step, is more favourable from kinetic as well as thermodynamic aspects.

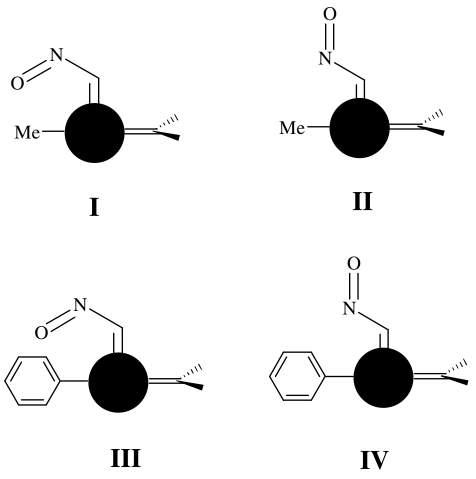


Figure 1. Schematic representation of the conformations of the intermediates on the reaction path between nitrosoalkenes and imines.

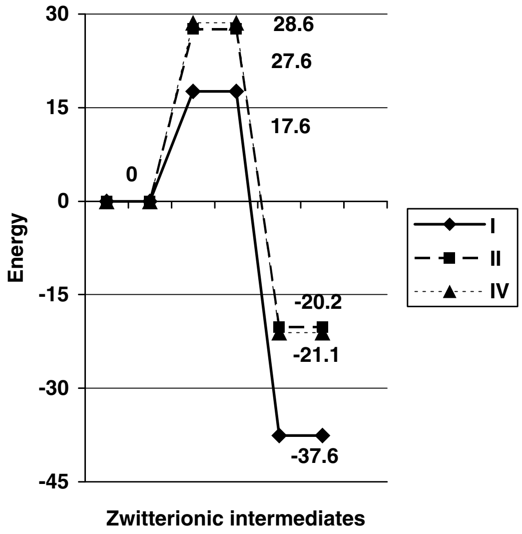


Figure 2. Potential energy surface showing the relative energy of zwitterionic intermediates on the reaction path between nitrosoalkene and imine. The path involving intermediate **I** leads to the formation of an oxazine, the path involving intermediates **II** and **IV** leads to the formation of nitrones. The path involving **III**, which should have led to an oxazine, could not be traced due to the instability of intermediate **III** on the PE surface.

Further, HF/6-31+G* calculations for the reaction path involving $H_2C{=}N{-}Ph$ and $H_2C{=}CH{-}N{=}O$ indicated that the formation of a zwitterionic intermediate is feasible for the *s-trans* arrangement of nitrosoethylene. However, such an intermediate could not be located for the *s-cis* arrangement. This may be due to the repulsive interactions operating between the approaching phenyl (π-electrons) and oxygen (non-bonding electrons) during the initial nucleophilic attack. Due to these repulsive forces, the formation of the corresponding zwitterionic intermediate is avoided. However, in the case of an *s-trans* arrangement of nitrosoethylene, the formation of intermediate **IV** is conceivable after a twist in the C–C–N–C angle, probably because of the decreased repulsive interactions. The relative energies of the intermediate **IV** and the nitrone are 28.6 and −21.1 kcal/mol with respect to the corresponding starting materials. Thus, the presence of a phenyl group on nitrogen does not allow the formation of zwitterionic intermediate **6**, thereby justifying the absence of the six-membered oxazine in the reactions of imines bearing aryl substituents. This rationale is further substantiated by the formation of nitrones and oxazines in the reactions of **1b** with nitrosoalkenes **2**, where the above referred electronic repulsions and steric interactions are supposedly decreased, the phenyl ring being one carbon away from the nitrogen of the imine due to the insertion of a methylene group.

Solvent effects, not taken into account here, might also change the chemoselectivity of the reaction. However, the solvent used experimentally is dichloromethane, which is a non-polar solvent and hence would not have any influence on the activation energies.

In conclusion, iminic nitrogen substituents have been found to play a crucial role in influencing the cycloaddition path followed in the reactions of various alkyl/aryl substituted imines with α-nitrosoalkenes. These cycloaddition reactions offer a practical access to a diversity of functional and synthetically flexible nitrogen-containing molecular assemblies (cyclic nitrones[14] and oxazines).

References and notes

1. (a) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53; (b) Lyapkalo, I. M.; Loffe, S. L. *Russ. Chem. Rev.* **1998**, *67*, 467–484; (c) Crystal, E. J. T.; Gilchrist, T. L.; Stretch, W. *J. Chem. Res. (S)* **1987**, *180*, (M) 1563, and references cited therein; (d) Zimmer, R.; Reissig, H. U. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1518; (e) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Chem. Commun.* **1976**, 581; (f) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 258; (g) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 249; (h) Gilchrist, T. L.; Lingham, D. A.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, 1089; (i) Gilchrist, T. L.; Iskander, G. M.; Yagoub, A. K. *J. Chem. Soc., Chem. Commun.* **1981**, 696.
2. Sharma, A. K.; Mahajan, M. P. *Heterocycles* **1995**, *40*, 787.
3. (a) Lai, E. C. K.; Mackay, D.; Taylor, N. J.; Watson, K. N. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1497; (b) Mackay, D.; Watson, K. N. *J. Chem. Soc., Chem. Commun.* **1982**, 775; (c) Mackay, D.; Papadopaelos, D.; Taylor, N. J. *J. Chem. Soc., Chem. Commun.* **1992**, 325–327; (d) Mackay, D.; McIntyre, D.; Wigle, I. D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1999.
4. (a) Sharma, A. K.; Mazumdar, S. N.; Mahajan, M. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3065–3070; (b) Sharma, A. K.; Hundal, G.; Obrai, S.; Mahajan, M. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 615–619; (c) Sharma, A. K.; Mazumdar, S. N.; Mahajan, M. P. *Tetrahedron Lett.* **1993**, *34*, 7961; (d) Bravo, P.; Gaudiano, G.; Panti, P. P.; Umani-Ronchi, A. *Tetrahedron* **1970**, *26*, 1315.
5. (a) Tahdi, A.; Lafquih-Titouani, S.; Soufiaoui, M.; Komiha, N.; Kabbaj, O. K.; Hegazi, S.; Mazzah, A.; Eddaif, A. *Tetrahedron* **2002**, *58*, 1507–1512; (b) Komiha, N.; Kabbaj, O. K.; Lafquih-Tiouani, S. *Internet Electron. J. Mol. Des.*, ISSN 1538–1546; 2004; (c) Sperling, D.; Mehlhorn, A.; Reibig, H. U.; Fabian, J. *Liebigs Ann.* **1996**, 1615–1621.
6. (a) Kumar, R. S.; Bharatam, P. V.; Mahajan, M. P. *Org. Lett.* **2000**, *18*, 2725–2728; (b) Marwaha, A.; Bharatam, P. V.; Mahajan, M. P. *THEOCHEM* **2003**, *640*, 1–12; (c) Marwaha, A.; Kumar, R. S.; Anand, A.; Mahajan, M. P. *ARKIVOC* **2002**, *part 7*, 106–115.
7. General procedure for the preparation of nitrones and oxazines: A solution of Schiff's base **1** (4 mmol) and α-bromooxime **2** (4.2 mmol) in dry CH_2Cl_2 was stirred at room temperature in the presence of anhydrous sodium bicarbonate (6 mmol) for 24–25 h. The deposited salt and the excess sodium bicarbonate were filtered off and washed with small portions (2 × 10 ml) of CH_2Cl_2. The combined filtrates were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The nitrones **3** and oxazines **4** were isolated and purified with the help of column chromatography on 60–120-mesh silica gel. The nitrones and oxazines were recrystallized from benzene–hexane (2:1) and EtOAc–hexane (1:5), respectively.
   % Yields: **3a**: 34%; **4a**: 51%; **3b**: 36%; **4b**: 54%; **3c**: 79%; **3d**: 35%; **4d**: 53%; **3e**: 37%; **4e**: 55%; **3f**: 82%; **3g**: 32%; **4g**: 48%; **3h**: 30%; **4h**: 50%; **3i**: 80%.
8. (a) 1-Cyclohexyl-4-(4-nitrophenyl)-2-phenyl-2,5-dihydro-1*H*-imidazole 3-oxide **3a**: mp 115–117 °C; yield: 34%; ^{1}H NMR (200 MHz, $CDCl_3$, Me_4Si): δ 1.18–1.95 (m, 10H, cyclohexyl); 2.65–2.66 (m, 1H, –CH–, cyclohexyl); 3.98 (dd, $J = 14.7$ and 3.6 Hz, 1H, H^a, $–CH_2–$); 4.62 (dd, $J = 14.7$ and 4.2 Hz, 1H, H^b, $–CH_2–$); 5.72 (dd, $J = 3.6$ and 4.2 Hz, 1H, H^c, methine); 7.43–7.61 (m, 5H, ArH); 8.27 (d, $J = 8$ Hz, 2H, ArH); 8.42 (d, $J = 8$ Hz, 2H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$, Me_4Si): 25.4; 25.7; 25.8; 31.1; 31.5; 38.9; 53.2 ($–CH_2$); 89.2 (–CH); 120.2; 123.6; 127.3; 127.8; 128.1; 129.7; 129.9; 134.3; 151.2; MS: $m/z = 365$ (M^+); 349 ($M^+–16$). Anal. Calcd for $C_{21}H_{23}O_3N_3$ requires: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.78; H, 6.22; N, 11.26.; (b) 5-Cyclohexyl-3-(4-nitrophenyl)-5,6-dihydro-4*H*-[1,2,5]-oxadiazine **4a**: mp 168–169 °C; yield: 51%. ^{1}H NMR (200 MHz, $CDCl_3$, Me_4Si): δ 1.21–2.05 (m, 10H, cyclohexyl); 2.85–2.87 (m, 1H, –CH–, cyclohexyl); 3.62 (s, 2H, $–CH_2–$, oxazine); 6.00 (s, 1H, –CH–, methine); 7.30–7.57 (m, 5H, ArH); 7.73 (d, $J = 8$ Hz, 2H, ArH); 8.19 (d, $J = 8$ Hz, 2H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$, Me_4Si): 25.5; 25.6; 25.7; 31.1; 31.4; 38.9; 61.1 ($–CH_2$); 89.4 (–CH); 123.6; 125.2; 126.5; 128.5; 138.0; 140.1; 148.2; 153.5; MS: $m/z = 365$ (M^+). Anal. Calcd for $C_{21}H_{23}O_3N_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.72; H, 6.35; N, 11.42.
9. Delpierre, G. R.; Lamchen, M. *Chem. Soc. Rev.* **1965**, 329.
10. Nakanishi, S.; Nantaku, J.; Otsuji, Y. *Chem. Lett.* **1983**, 341.
11. (a) Davis, D. E.; Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1275; (b) Smith, J. H.; Heidema, J. H.; Kaiser, E. T. *J. Am. Chem. Soc.* **1972**, *94*, 9276.
12. Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
13. Frisch, M. J.; Trucks, T.; Peterson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham M. A.; Zakrzawski, V. G.; Poresman, J. A.; Oritz, J. V.; Andres, J. L.; Replogle, E. S.; Gompetrs, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. L.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.;GAUSSIAN 94, Revision B.2., Guassian, Pittsburg, PA, 1995.
14. (a) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113–5123; (b) Goti, A.; Cicchi, S.; Cordero, F. M.; Fedi, V.; Brandi, A. *Molecules* **1999**, *4*, 1–12; (c) Murahashi, S. I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736, and references cited therein; (d) Dagoneau, C.; Tomassini, A.; Denis, J. N. *Vallie Synthesis* **2001**, 150–154.