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The first report of unusual flipping of the cycloadducts from 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydropyridine *N*-oxide to *N*-cinnamoyl piperidines

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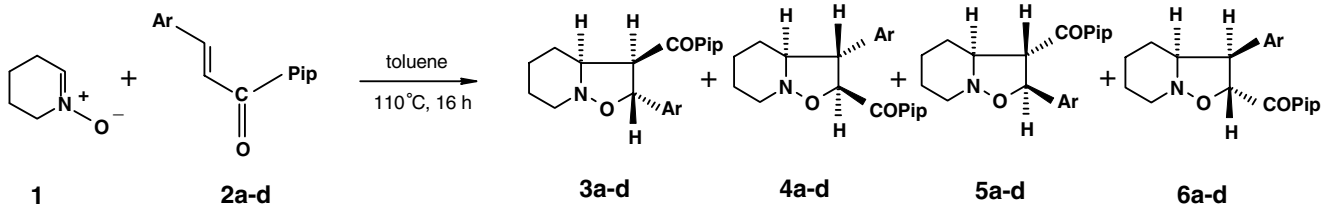
Abstract—A series of cycloadducts possessing unusual flipping modes have been isolated from the 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydropyridine *N*-oxide to piperidides of cinnamic acid and *para*-substituted cinnamic acids and these were analyzed by X-ray crystallography to reveal novel solid-state structures. The presence of two different flippomers arising due to flipping of the six/five bicyclic ring was confirmed both in solid state and in solution. This is the first observation of 1,3-dipolar cycloadducts having two different flippomers arising due to flipping of the isoxazolidine ring.

The 1,3-dipolar cycloaddition of nitrones to electron-deficient olefins is a reaction that has been of considerable use in organic chemistry.[1] Exploiting this strategy as the key step, a wide variety of natural products have been synthesized.[2–6] As a part of our investigations in this particular field,[7] we have recently reported[8] the $\pi^4s + \pi^2s$ cycloaddition reaction of 3,4-dehydromorpholine *N*-oxide with *N*-cinnamoyl piperidine **2a** and three of its *para*-substituted derivatives **2b–d**. Formation of the unexpected 2:1 cycloadducts was confirmed and mechanistically interpretated by an iminium–oxonium pathway[8] where O-4 (the ring oxygen) of the nitrone 3,4-dehydromorpholine *N*-oxide (derived from morpholine) plays a crucial role. To establish the proposed mechanism it was logical to extend this cycloaddition study to a cyclic nitrone where the ring oxygen of 3,4-dehydromorpholine *N*-oxide (i.e., O-4) was replaced by a methylene group, that is, 3,4,5,6-tetrahydropyridine *N*-oxide (**1**) was chosen for cycloaddition with the same set of dipolarophiles **2a–d**.

1,3-Dipolar cycloaddition involving **1** with several dipolarophiles (both cyclic and acyclic) has already been reported,[9] however, an unusual flipping of the ring



Scheme 1. For compounds **2–6**: Ar = Ph (**a**), C_6H_4–*p*Cl (**b**), C_6H_4–*p*OMe (**c**), C_6H_4–*p*NO_2 (**d**); Pip =  .

Keywords: Nitrones; Dipolar cycloaddition; Intermolecular; Isoxazolidines.
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junction of this particular type of cycloadducts was first observed during the present study in the reactions between **1** with **2a–d** (Scheme 1). This letter briefly presents the findings, which not only verify the iminium–oxonium pathway leading to the formation of novel 2:1 cycloadducts[8] but also reveals the unusual flipping of the ring junction of this particular type of cycloadducts which has been confirmed by detailed X-ray crystallographic analysis.

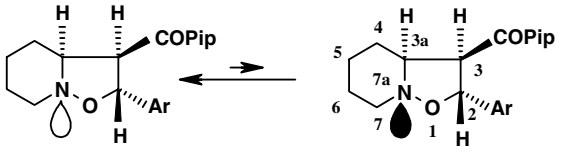
When equimolar amounts of **1** and each of **2a–d** were separately refluxed in anhydrous toluene for 16 h under a dry nitrogen atmosphere, followed by column chromatography over neutral alumina, compounds **3a–d**[10] were isolated as the major products (Scheme 1) along with other regio and stereoisomeric cycloadducts **4–6(a–d)**.

The ^{1}H NMR spectrum of **3a** was interesting as it showed that protons at or near the bicyclic (six/five) ring junction, that is, H-2, H-3, H-3a, H-4 and H-7 had two sets of chemical shifts. At first sight it might appear to be a mixture of two different compounds but two different flippomers were present in the NMR solution and not two different compounds, as was ascertained from extensive decoupling experiments. Irradiation of one of the relevant proton signals caused the disappearance of another signal, due to the same proton in the other isomer, in addition, to causing simplification to the proton signal(s) to which it was coupled. This disappearance of a signal on irradiation of another signal would not have been observed if two different compounds had been present, for example, irradiation of the H-3 proton signal at δ 3.59 caused the corresponding H-2 proton doublet at δ 5.81 to collapse to a singlet and the multiplet at δ 3.72 (H-3a) to simplify; concurrently the other signal due to the same proton at δ 3.42 disappeared. Similar observations of the second signal disappearing for the same proton were observed for H-2 and H-3a. Irradiation of the same set of H-2 and H-3a protons, appearing at δ 5.81 and δ 3.72, respectively, transformed the H-3 proton to a doublet.

Similar changes in coupling patterns were observed on consecutive irradiation of another set of signals (for the other flippomer) for the same non-aromatic protons at δ 5.63, δ 3.42 and δ 2.68 for H-2, H-3 and H-3a, respectively. The coupling behaviour of these protons was established from the COSY experiment. Two sets of protons (H-2, H-3, H-3a, H-4 and H-7) in one of the flippomers showed mutual coupling while the other set of the same protons exhibited corresponding couplings among themselves. From the long-range COSY experiment it was observed that the signals at δ 5.81 and δ 5.63 (for H-2 and H-2, respectively, where underlined signals refer to the minor flippomer) had a weak long-range coupling with the aromatic protons at δ 7.26–7.38. This confirmed that the C-2 proton was benzylic in nature and that the cycloadduct was the 2-phenyl-3-piperidinyloxo derivative of the hexahydroisoxazolo[2,3-*a*]pyridine ring system.

The ^{13}C NMR spectrum, including APT/DEPT-135^{0}, lent full support to the derived structure. As in the ^{1}H NMR, here also two sets of values were obtained for the carbon atoms at or near the bicyclic six/five ring junction (i.e., C-2, C-3, C-3a, C-4 and C-7). NMR values due to the presence of the minor flippomer are listed within square brackets.[10] From all these observations an equilibrium may exist between **I** and **II** (Scheme 2).

In order to establish the equilibrium, X-ray crystallographic studies were performed which confirmed the



Major (**I**, 76%) Minor (**II**, 24%)

Scheme 2.

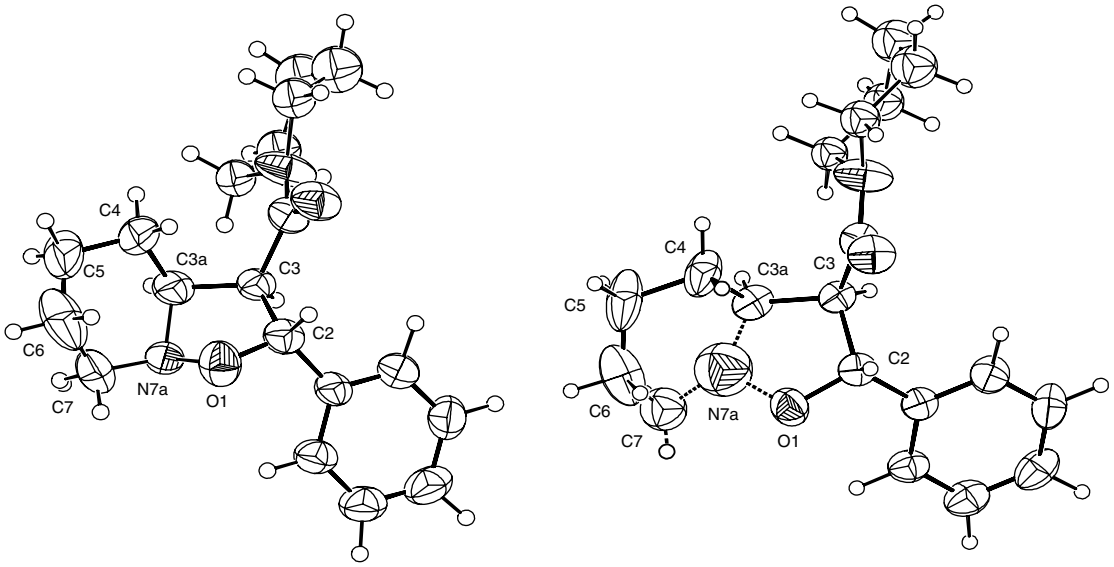


Figure 1. ORTEP views of **3a**-major flippomer (left) and minor flippomer (right).

existence of the equilibrium between structures **I** and **II** due to the N7a lone pair flipping (Fig. 1). The two structures were indeed identical excepting the spatial arrangement of the N7a lone pair which was *syn* with respect to H-3a in the case of the major flippomer (**I**, Scheme 2) and *anti* with that proton, that is, H-3a in the case of minor flippomer (**II**, Scheme 2). During the refinements, two chair conformations with 50:50 distributions were also clearly observed for the piperidinyl ring, suggesting two independent molecules in the noncentrosymmetric distribution of the structure factors.

Detailed NMR investigations for the compounds **4–6** have also been carried out[11a] but no indications of flipping as observed in **3** were obtained. Only one set of values was found for the protons at or near the bicyclic (six/five) ring junction of compounds **4–6**.

This denotes that for compounds **4–6** only one isomer is present for each of the compounds or two flippomers rapidly equilibrating on the NMR time scale, resulting in an averaged spectrum for each of compounds **4–6**. The NMR values of **4b**, **5a** and **6d** are listed.[11b–d] Moreover, the structures of **4b** and **5a** have been confirmed by X-ray crystallographic analyses[12] (Figs. 2 and 3, respectively).

In conclusion, the present investigation, (a) confirms that the presence of a ring oxygen in 3,4-dehydromorpholine *N*-oxide is responsible for the formation of unexpected (2:1) cycloadducts in the nitrone cycloaddition reaction and, (b) reveals the first example of unusual flipping of the bicyclic (six/five) isoxazolidine ring junction of a particular type of cycloadducts (**3**). An equilibrium was confirmed between two flippomers of **3** (**I** and **II**, Scheme 2, Fig. 1). The *syn*/*anti* flipping of the N7a lone pair in **3** could only occur if the conformational energy differences between **I** and **II** are low enough to permit both to co-exist either in solution or in the crystal state.

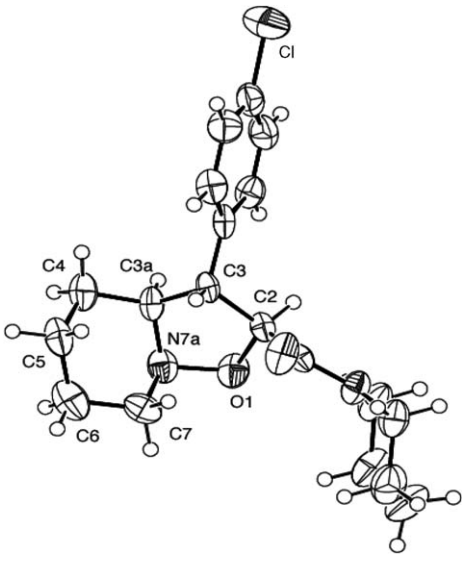


Figure 2. ORTEP projection of **4b**.

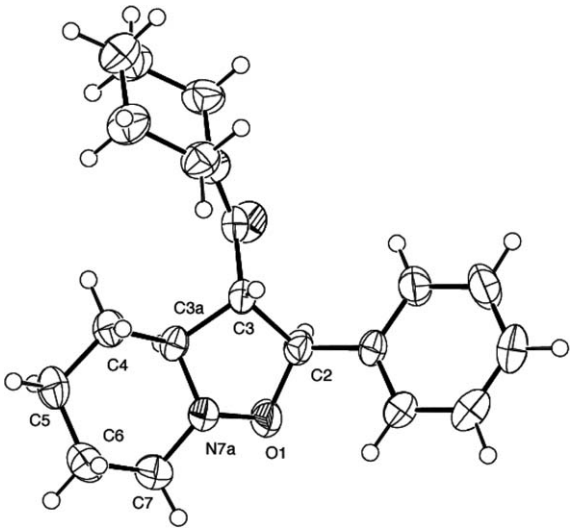


Figure 3. ORTEP projection of **5a**.

Acknowledgements

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10. Spectroscopic data for compound **3a**: (2*RS*,3*SR*,3a*SR*)-2,3,3a,4,5,6,7,8-octahydro-2-phenyl-3-(piperidin-ylcarbonyl)-isoxazolo[2,3-*a*]pyridine; mp 148 °C (50% ethyl acetate in benzene, yield 27%); IR (KBr) ν (cm^{-1}) 2882, 1630, 1120, 760, 700; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.28 (br m, 2H), 1.52–1.63 (m, 7H), 1.76 (m, 2H), 3.42 (m, 4H), 3.49 (br m, 1H), 3.52 (m, 1H), 3.59 (m, 2H), 3.72 (m, 1H), 5.81 (br m, 1H), 7.26–7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.3, 24.6, 24.8, 25.8, 26.7, 26.9, 43.3, 46.8, 54.3, 57.2, 71.8, 84.6, 126.3, 127.4, 128.3, 138.2, 166.2; [1.52–1.63 (m, 2H), 2.53 (m, 1H), 2.68 (m, 1H), 3.15 (m, 1H), 3.42 (m, 1H), 5.63 (br m, 1H); 27.7, 52.3, 49.6, 68.4, 80.7]. EIMS (*m*/*z*): 314 (M^+), 216, 131, 112, 100, 84, 77. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.49; H, 8.21; N, 8.73.
11. (a) Bandyopadhyay, D. Ph.D. Dissertation, Calcutta University, 2002; (b) Spectroscopic data for compound **4b**: (2*RS*,3*SR*,3a*RS*)-2,3,3a,4,5,6,7,8-octahydro-3-(*p*-chlorophenyl)-2-(piperidin-ylcarbonyl)-isoxazolo[2,3-*a*]pyridine; mp 142 °C (5% ethyl acetate in benzene, yield 22%); IR (KBr) ν (cm^{-1}) 1645, 1125, 1095, 835; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.18 (m, 2H), 1.52–1.60 (br m, 8H), 1.69 (m, 1H), 3.13 (m, 1H), 3.31 (m, 2H), 3.48 (m, 4H), 3.69 (m, 1H), 4.08 (dd, $J = 10.2$, 6.3 Hz, 1H), 4.59 (d, $J = 7.8$ Hz, 1H), 7.27 (br s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.4, 24.6, 24.8, 25.6, 26.5, 27.7, 43.8, 46.6, 54.8, 55.6, 74.9, 84.6, 128.9, 129.6, 132.9, 137.8, 168.2. EIMS (*m*/*z*): 348 (M^+), 250, 249, 236, 165, 138, 112, 84. Anal. Calcd for $C_{19}H_{25}N_2O_2Cl$: C, 65.42; H, 7.22; N, 8.03. Found: C, 65.28; H, 7.13; N, 7.94; (c) Spectroscopic data for compound **5a**: (2*RS*,3*SR*,3a*RS*)-2,3,3a,4,5,6,7,8-octahydro-2-phenyl-3-(piperidin-ylcarbonyl)-isoxazolo[2,3-*a*]-pyridine; mp 118 °C (5% ethyl acetate in benzene, yield 26%); IR (KBr) ν (cm^{-1}) 2932, 1630, 1118, 850, 762; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.21–1.34 (m, 2H), 1.44 (m, 1H), 1.46–1.62 (br m, 7H), 1.73 (m, 1H), 1.90 (m, 1H), 2.59 (td, $J = 11.9$, 2.8 Hz, 1H), 2.81 (td, $J = 10.3$, 2.1 Hz, 1H), 3.18 (m, 2H), 3.40 (dd, $J = 9.7$, 7.1 Hz, 1H), 3.50 (m, 1H), 3.55 (m, 1H), 3.68 (m, 1H), 5.23 (d, $J = 7.0$ Hz, 1H), 7.19–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.3, 24.4, 24.6, 25.8, 26.7, 28.1, 43.5, 46.8, 55.4, 58.1, 71.9, 81.3, 125.9, 127.4, 128.5, 143.2, 168.5. EIMS (*m*/*z*): 314 (M^+), 201, 130, 123, 112, 96, 84, 77. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.43; H, 8.25; N, 8.79; (d) Spectroscopic data for compound **6d**: (2*RS*,3*SR*,3a*SR*)-2,3,3a,4,5,6,7,8-octahydro-3-(*p*-nitrophenyl)-2-(piperidin-ylcarbonyl)-isoxazolo[2,3-*a*]-pyridine; mp 128 °C (50% ethyl acetate in benzene, yield 27%); IR (KBr) ν (cm^{-1}) 1645, 1515, 1340, 1105, 855; ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.83 (qd, $J = 12.3$, 3.6 Hz, 1H), 1.22 (m, 1H), 1.45 (m, 1H), 1.50–1.65 (m, 8H), 1.75 (m, 1H), 2.51 (td, $J = 10.8$, 2.7 Hz, 1H), 2.66 (ddd, $J = 11.4$, 6.9, 2.3 Hz, 1H), 3.48 (m, 1H), 3.50–3.64 (m, 4H), 4.38 (dd, $J = 6.9$, 3.5 Hz, 1H), 4.72 (d, $J = 3.5$ Hz, 1H), 7.62 (d, $J = 8.7$ Hz, 2H), 8.15 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 24.4, 24.7, 25.5, 26.2, 26.6, 43.6, 46.8, 53.6, 55.7, 70.5, 81.6, 123.3, 130.3, 147.0, 148.2, 165.9. EIMS (*m*/*z*): 359 (M^+), 260, 247, 246, 138, 130, 112, 102, 84. Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.31; H, 6.84; N, 11.53.
12. For all the three compounds viz., **3a**, **4b** and **5a**, crystal structure data were collected on a Phillips PW1100 four-circle diffractometer and refined using the SHELXL program. Wavelength for data recordings is 1.5418 Å (Cu-Kα) and temperature 298 K. Crystallographic data for all three compounds have been deposited with the Cambridge Crystallographic Data Centre as CCDC 236268 (**3a**), 236271 (**4b**) and 236270 (**5a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).