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X-ray Structural Analysis for the Prediction on the Nature of the Retro Diels–Alder Pathway: Concerted or Stepwise. Structural Studies on Nitrosobenzene Cycloadducts

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Crystal structures of nitrosobenzene cycloadducts **5**–**7** reveal structural effects consistent with the early stages of the retro Diels–Alder fragmentation. There is a clear differentiation between the structure parameters of cycloadduct **5**, which reacts by a concerted synchronous pathway and that of cycloadduct **6**, which must react by a two-step pathway. Based on these data, cycloadduct **7** is predicted to react by a highly asynchronous or two-step pathway.

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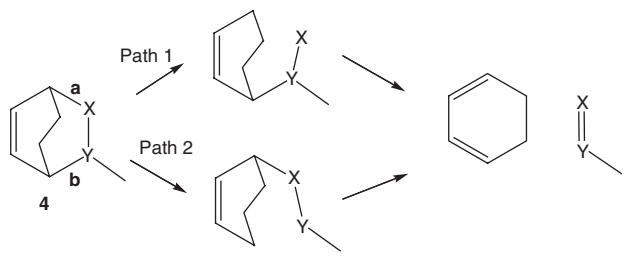
Introduction

According to the structure–correlation principle (SCP),[1,2] structural changes that occur to a molecule during a chemical reaction can manifest in the ground state structure of the reactant as deformations of bond distances and angles from their 'normal values' along the reaction coordinate. This principle applies provided the geometry of the molecule in question is similar to the transition state geometry for the reaction. The SCP is illustrated by the cycloadduct **1** in which the two bonds (**a** and **b**), which are broken during the retro Diels–Alder reaction (mean 1.579(2) Å) and are significantly longer than those corresponding bonds in the saturated analogue **2** (mean 1.550(2) Å), which cannot undergo this reaction (Scheme 1).[3]

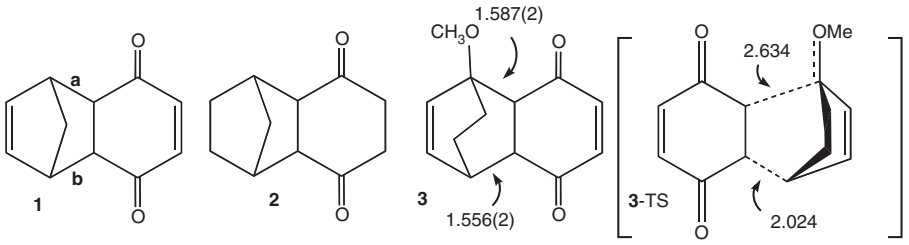
A systematic study on a range of cycloadducts which react by a concerted mechanism[4] has established that: (i) symmetrical cycloadducts show similar degrees of lengthening of bonds **a** and **b**, while the degree of lengthening is related to the reactivity towards the retro Diels–Alder reaction, and (ii) in substituted cycloadducts (e.g. **3**) differences in the degree of lengthening of the bonds, which break in this reaction are reflected in asymmetry in the corresponding distances in the calculated transition state for the reaction (e.g. **3**-TS).

Structural effects arising in cycloadducts (**4**), which undergo fragmentation by a stepwise mechanism (Scheme 2) will be dependant on the order of the bond breaking events. For example, if the reaction proceeds by path 1, then bond **a** may be lengthened in the ground state structure of **4** but bond **b** should be 'normal', whereas if the reaction occurs by path 2 then bond **b** will be lengthened and bond **a** will be 'normal'. Thus, crystal structures of such adducts may allow differentiation between a concerted and stepwise pathway, and in the latter case the order of bond breaking might be predicted.

To test this proposal we determined the crystal structures of the nitrosobenzene cycloadducts with cyclohexadiene (**5**),[5] cycloheptatriene (**6**),[6] and 1-methoxycyclohexadiene (**7**). The cycloadduct **5** is formed by a normal concerted $[4\pi + 2\pi]$ cycloaddition, and hence the reverse reaction will also be concerted. However, adduct **6** is the product of a $[6\pi + 2\pi]$ cycloaddition and fragmentation must occur stepwise to avoid



Scheme 2. Possible stepwise pathways for unimolecular fragmentation.



Scheme 1.

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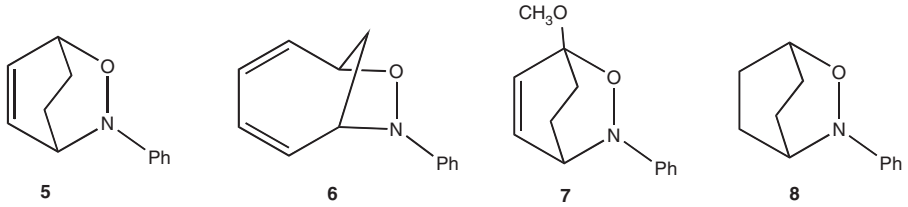
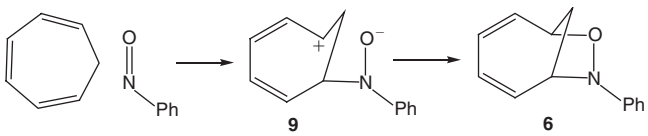


Scheme 3.

Table 1. Selected structural parameters for compounds 5–8

Compound	C-N [Å]	Δ [Å]	C-O [Å]	Δ [Å]
5	1.503(2)	0.018(2)	1.473(2)	0.023(2)
6	1.482(2)	−0.003(2)	1.485(2)	0.035(2)
7[A]	1.488(2)	0.003(2)	1.493(2)	0.043(2)
8	1.485(2)		1.450(2)	

[A] Compound **8** crystallizes with four molecules in the asymmetric unit. There is no significant variation between the C-O and C-N bond distances, therefore the value given represents the average from these four molecules.



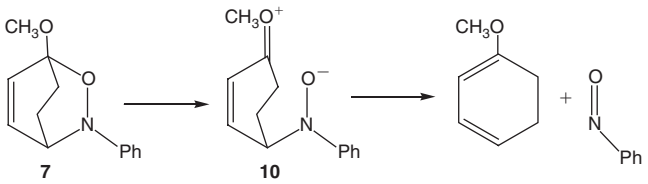
Scheme 4. Proposed mechanism for the nitrosobenzene-cycloheptatriene cycloaddition.

the antiaromatic transtion state.[7] Adduct **7** was chosen as it may react by either a highly asymmetric concerted or a stepwise pathway. In addition to these, the structure of the reduced derivative **8**, which was prepared by diimide reduction of **5**, was determined to provide appropriate standard C-O and C-N bond distances for comparison.

Results and Discussion

The structures of compounds **5**–**8** (Scheme 3) were determined at low temperature to minimize the unwanted effects of thermal libration. Data of satisfactory quality for this analysis were obtained with selected structure parameters presented in Table 1.

The C-N and C-O bonds in cycloadduct **5** are both significantly lengthened compared with the standard values provided by the saturated analogue **8**. This is consistent with an adduct whose fragments react by a concerted mechanism. In contrast, for cycloadduct **6**, for which a stepwise reaction is demanded, the C-O bond is lengthened whereas the C-N bond is essentially 'normal', suggesting a stepwise fragmentation where C-O bond cleavage is followed by C-N bond cleavage (Scheme 4). The mechanistic interpretation based on the structural data is supported by experimental evidence; thus cycloaddition of nitrosobenzene to cycloheptatriene is shown to occur in a stepwise fashion, via the zwitterionic intermediate **9**. This is based on the insensitivity of the cycloaddition to radical scavengers, and on a Hammett analysis on the rates of reaction of various substituted nitrosobenzene derivitives with cycloheptatriene.[8] Thus, based on the principle of microscopic reversibility, the reverse reaction must involve C-O bond breaking as the first step followed by C-N bond breaking.



Scheme 5. Proposed mechanism for the retro Diels–Alder reaction of adduct **7**.

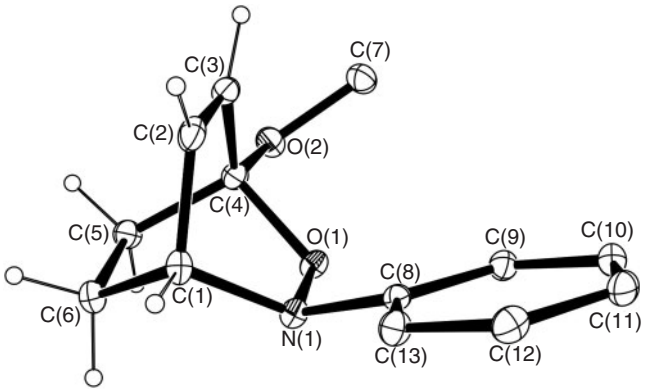


Fig. 1. Thermal ellipsoid plot of cycloadduct **7**. Ellipsoids are at the 20% probability level.

In the structure of cycloadduct **7** the C-N bond is 'normal' while the C-O bond is significantly lengthened, suggesting that this molecule may also undergo the retro Diels–Alder reaction by a stepwise mechanism, probably involving the zwitterionic intermediate **10** (Scheme 5). This intermediate arises by heterolytic C-O bond breaking, which is facilitated by involvement of the methoxy-oxygen lone pair of electrons, followed by C-N bond breaking in the second step.

Also consistent with the proposed mechanism in Scheme 3 is the marked shortening of the C-OCH_3 bond distance (0.033 Å), which is 1.376(2) Å compared with the standard C-OCH_3 distance of 1.409 Å obtained from analysis of the search fragment R_3C-OCH_3 (367 hits, R factor <5%) from the Cambridge Crystallographic Database.[9] Shortening of the C-OCH_3 bond and the extra bond lengthening of the C-O bond in the structure of **7** compared with **5** are consistent with the donation of non-bonded electrons on the exocyclic oxygen into the C-O(NPh) antibonding orbital. The molecular structure of **7** presented in Fig. 1, shows that the conformation of the methoxy substituent satisfies the stereoelectronic requirements associated with this n_O-$\sigma^*_{C\text{-}O}$ interaction, which is the basis of the generalized anomeric effect.[10]

Conclusion

Crystal structure analysis of nitrosobenzene cycloadducts **5**–**7** show structural effects consistent with the early stages of fragmentation. In the case of compound **5**, which is predicted to undergo a thermally allowed concerted retro Diels–Alder reaction, both the C-O and C-N bonds were significantly lengthened compared with standard values. In contrast only the C-O bond was lengthened in the structures of compounds **6** and **7**. We therefore predict that these molecules fragment by a two-step process involving C-O bond cleavage, followed by C-N bond breaking.

Experimental

(1) Crystallography

Intensity data for **6**–**8** were collected with an Oxford Diffraction Sapphire CCD diffractometer using Cu-K_α radiation (graphite crystal monochromator $\lambda = 1.54184$ Å). Intensity data for **5** were collected with a Bruker SMART Apex CCD detector using Mo-K_α radiation (graphite crystal monochromator $\lambda = 0.71073$ Å). The temperature during data collection was maintained at 130.0(1) K.

Crystal data for **5**. $C_{12}H_{13}NO$, $M = 187.23$, $T = 130.0(2)$ K, $\lambda = 0.71073$ Å, monoclinic, space group $P2_1/c$, $a = 9.515(1)$, $b = 12.206(2)$, $c = 8.616(1)$ Å, $\beta = 104.546(2)°$, V 968.6(2) Å^3, $Z = 4$, $D_c = 1.284$ mg M^{-3}, μ(Mo-K_α) 0.082 mm^{-1}, $F(000) = 400$, crystal size $0.5 \times 0.35 \times 0.30$ mm. 5982 reflections measured, 2189 independent reflections ($R_{int} = 0.019$) the final R was 0.0428, [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1125 (all data).

Crystal data for **6**. $C_{13}H_{13}NO$, $M = 199.24$, $T = 130.0(2)$ K, $\lambda = 1.54184$ Å, orthorhombic, space group Pbca, $a = 11.5795(3)$, $b = 9.1698(2)$, $c = 19.4705(4)$ Å, V 2067.41(8) Å^3, $Z = 8$, $D_c = 1.280$ mg M^{-3}, μ(Cu-K_α) 0.640 mm^{-1}, $F(000) = 848$, crystal size $0.57 \times 0.35 \times 0.04$ mm. 5503 reflections measured, 1850 independent reflections ($R_{int} = 0.034$) the final R was 0.0420, [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1190 (all data).

Crystal data for **7**. $C_{13}H_{15}NO_2$, $M = 217.26$, $T = 130.0(2)$ K, $\lambda = 1.54184$ Å, monoclinic, space group $P2_1/c$, $a = 18.5752(2)$, $b = 17.4530(1)$, $c = 15.0817(1)$ Å, $\beta = 113.937(1)°$, V 4468.85(6) Å^3, $Z = 16$, $D_c = 1.292$ mg M^{-3}, μ(Cu-K_α) 0.702 mm^{-1}, $F(000) = 1856$, crystal size $0.4 \times 0.4 \times 0.20$ mm. 20653 reflections measured, 8053 independent reflections ($R_{int} = 0.034$) the final R was 0.052, [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1507 (all data).

Crystal data for **8**. $C_{12}H_{15}NO$, $M = 189.25$, $T = 130.0(2)$ K, $\lambda = 1.54184$ Å, monoclinic, space group $P2_1/c$, $a = 9.5075(2)$, $b = 11.4893(2)$, $c = 9.2650(2)$ Å, $\beta = 104.842(3)°$, V 978.29(3) Å^3, $Z = 4$, $D_c = 1.285$ mg M^{-3}, μ(Cu-K_α) 0.640 mm^{-1}, $F(000) = 408$, crystal size $0.28 \times 0.16 \times 0.11$ mm. 4525 reflections measured, 1902 independent reflections ($R_{int} = 0.037$) the final R was 0.0476, [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.1262 (all data).

(2) Synthesis. General Synthetic Details and Procedures are Reported Elsewhere[11]

*3-Phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**5**)*

1,3-cyclohexadiene (0.45 mL, 4.67 mL) was added to a solution of nitrosobenzene (0.5 g, 4.67 mmol) in chloroform (10 mL) and stirred at 25°C for 2 h. The solvent was removed under reduced pressure producing a white solid, which was recrystallized from dichloromethane to give **5** clear block-shaped crystals (0.87 g, >99%) mp 65–66°C (lit.[12] 65–66°C). ^{1}H NMR ($CDCl_3$): $\delta = 7.23$–7.19 (2H, m), 7.02–7.00 (2H, m), 6.94–6.91 (1H, m), 6.60–6.57 (1H, m), 6.16–6.13 (1H, m), 4.72–4.70 (1H, m), 4.44–4.42 (1H, m), 2.30–2.24 (2H, m), 1.43–1.37 (2H, m). ^{13}C NMR ($CDCl_3$): $\delta = 152.3$, 131.6, 129.9, 128.3, 122.0, 117.4, 69.1, 56.5, 24.0, 21.3.

*(2Z,4Z)-7-Phenyl-8-oxa-7-azabicyclo[4.2.1] nona-2,4-diene (**6**)*

Cycloheptatriene (0.24 mL, 2.33 mmol) was added to a solution of nitrosobenzene (0.25 g, 2.33 mmol) in chloroform (7 mL) at 0°C and stirred for 3 h, while monitored by TLC. The solution was stirred for an additional 16 h at room temperature. The solvent was removed under reduced pressure giving the crude product, which was separated by a dry flash column (petroleum spirit/diethyl ether) and recrystallized from pentane giving **6** as a white solid (0.16 g, 35%) mp 47–48°C (lit.[13] 41–42°C). ^{1}H NMR ($CDCl_3$): $\delta = 7.28$–7.24 (2H, m), 7.06–7.03 (2H, m), 6.99–6.96 (1H, m), 6.21–6.12 (2H, m), 6.07–5.99 (2H, m), 4.89–4.86 (1H, m), 4.28–4.25 (1H, m), 2.39–2.34 (1H, m), 2.30–2.28 (1H, m). ^{13}C NMR ($CDCl_3$): $\delta = 151.9$, 133.8, 132.1, 128.9, 128.7, 127.7, 122.6, 115.4, 72.5, 64.0, 31.1.

*1-Methoxy-3-phenyl-2-oxa-3-azabicyclo[2.2.2] oct-5-ene (**7**)*

A solution of nitrosobenzene (0.25 g, 2.33 mmol) in chloroform (5 mL) was cooled to 0°C and to this 65% 1-methoxy-1, 2-cyclohexadiene (0.639 mL, 3.50 mmol) was added. The solution was stirred below 0°C for 2 h under nitrogen and then warmed to 25°C and stirred for an additional 5 h. The solvent was removed at a low temperature under reduced pressure giving a yellow solid, which was recrystallized from toluene at low temperature (−18°C) (0.5 g, 99%) mp 67–68°C. HRMS (ESI) (m/z) calc for $[C_{13}H_{15}NO_2 + H]^+$ 218.1176, found 218.1176. ^{1}H NMR ($CDCl_3$): $\delta = 7.24$–7.20 (2H, m), 7.04–7.02 (2H, m), 6.95–6.91 (1H, m), 6.52 (1H, d, $J = 8.99$ Hz), 6.22–6.20 (1H, dd, $J = 8.7$, 5.0 Hz), 4.47–4.44 (1H, m), 3.66 (3H, s), 2.43–2.38 (1H, m), 2.22–2.17 (1H, m), 1.70–1.63 (1H, m), 1.58–1.53 (1H, m). ^{13}C NMR ($CDCl_3$): $\delta = 152.2$, 131.4, 131.3, 128.4, 121.9, 116.7, 101.8, 56.5, 52.1, 28.7, 22.7.

*3-Phenyl-2-oxa-3-azabicyclo[2.2.2]octane (**8**)*

A solution of adduct **5** (0.39 g, 2.098 mmol) in ethanol (8 mL) was chilled to 0°C. Hydrazine hydrate (0.75 mL) was added along with 1% cupric sulfate pentahydrate with vigorous stirring. 30% hydrogen peroxide (0.38 mL) was slowly added and the resulting solution stirred for 3 h at 0°C. NMR showed ~50% conversion to **8**, so the reaction was continued with twice the amount of each reactant, however further conversion was not achieved. The reduction product **8** was separated from the starting material **5** via a dry flash column impregnated with silver nitrate (0.02 g, 5%) mp 48–49°C (from pentane). HRMS (ESI) (m/z) calc for $[C_{12}H_{15}NO + H]^+$ 190.1226, found 190.1227. ^{1}H NMR ($CDCl_3$): $\delta = 7.28$–7.25 (2H, m), 7.11–7.10 (2H, dd, $J = 7.99$, 1.0 Hz), 6.92–6.89 (1H, dd, $J = 7.5$, 1.0 Hz), 4.18–4.17 (1H, m), 3.78–3.76 (1H, m), 2.19–2.11 (4H, m), 1.76–1.62 (4H, m). ^{13}C NMR ($CDCl_3$): $\delta = 152.1$, 128.7, 120.8, 115.7, 69.8, 52.6, 25.2, 22.7.

Supporting Information

Crystallographic information files have been deposited with the Cambridge Crystallographic Data Centre and assigned the deposit codes 715311–715314 respectively. These can

be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

References

[1] H. B. Buergi, J. D. Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153. doi:10.1021/AR00089A002

[2] H. H. Burgi, *Acta Crystallogr.* **1998**, *A54*, 873.

[3] B. R. Pool, J. M. White, *Org. Lett.* **2000**, *2*, 3505. doi:10.1021/OL006553W

[4] D. Birney, T. K. Lim, J. Peng, B. R. Pool, J. M. White, *J. Am. Chem. Soc.* **2002**, *124*, 5091. doi:10.1021/JA025634F

[5] D. Zhao, M. Johansson, J.-E. Baeckvall, *Eur. J. Org. Chem.* **2007**, 4431. doi:10.1002/EJOC.200700368

[6] G. Kresze, G. Schulz, *Tetrahedron* **1961**, *12*, 7. doi:10.1016/0040-4020(61)80093-8

[7] I. Fleming, *Frontier Orbitals and Organic Chemical Reactions* **1976** (John Wiley and Sons: Chichester).

[8] S. Itô, S.-I. Narita, K. Endo, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3517. doi:10.1246/BCSJ.46.3517

[9] F. H. Allen, S. Bellard, M. D. Brice, B. A. Cartwright, A. Doubleday, H. Higgs, T. Hummelink, T. Hummelink-Peters, O. Kennard, W. D. S. Motherwell, J. R. Rogers, D. G. Watson, *Acta Crystallogr.* **1979**, *B35*, 2331.

[10] A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen* **1983** (Kirby: New York, NY).

[11] Y. W. Goh, S. M. Danczak, T. K. Lim, J. M. White, *J. Org. Chem.* **2007**, *72*, 2929. doi:10.1021/JO0625610

[12] Y. A. Arbuzov, T. A. Mastryukova, *Izvestiya Akademii, Nauk SSSR, Seriya Khimicheskaya* **1952**, 665.

[13] G. Kresze, G. Schulz, *Tetrahedron* **1961**, *12*, 7. doi:10.1016/0040-4020(61)80093-8