Mechanistic Impact of Oxime Formation Accompanying 1,3-Dipolar Cycloadditions of Nitrile Oxides

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Received January 25, 1989

Benzonitrile oxide (1a) reacts with 1,1,2,2,3,3-hexamethyl-4,5-bis(methylene)cyclopentane (5) to give a mixture of the 1,3-dipolar cycloaddition product 8 and the oxime 9. This reaction is 26 times slower than the corresponding reaction of 1a with 1,2-bis(methylene)cyclopentane (15), which exclusively yields the 2-isoxazoline 19. With the assumption that the oxime 9 is generated by a stepwise process, one can estimate that the barrier for the concerted cycloaddition of 1a with 15 is approximately 2 kcal/mol lower than the barrier for the formation of an intermediate.

A. Introduction

Grünanger's observation that nitrile oxides 1 and aryl-acylenes 2 yield the oximes 4 in addition to the normal [3 + 2] cycloadducts 3 has played an important role in the discussion on the mechanism of 1,3-dipolar cycloadditions. While a common intermediate for the formation of 3 and 4 has been mainly discussed, different pathways for the formation of 3 and 4 have later been suggested (Scheme I).

Examples for the formation of oximes in reactions of nitrile oxides with CC double-bonded dipolarophiles are very rare. Benzonitrile oxide and furan gave 1% of an oxime in addition to the regular cycloadducts, and only in reactions of trifluoroacetonitrile oxide with conjugated olefins, such as styrenes, indenes, and 1,3-dienes, were larger amounts of oximes produced. The latter reaction was interpreted in terms of a competition between a concerted cycloaddition and a two-step substitution through electrophilic attack of the nitrile oxide (Scheme II).

Since the generation of intermediate diradicals or zwitterions from nitrile oxides and dipolarophiles appears to be feasible in view of these results, we attempted to obtain further knowledge on these intermediates by employing 1,1,2,2,3,3-hexamethyl-4,5-bis(methylene)cyclopentane (5) as a mechanistic probe. As the diene 5 has previously been shown to possess increased 1,4- and reduced 1,2-reactivity, we had speculated that the intermediacy of 7a might give rise to the formation of the [4 + 3] cycloadduct 6 (Scheme III).

B. Results and Discussion

1. Products from Benzonitrile Oxide and Diene 5. When benzonitrile oxide (1a) was generated from benzo-

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Scheme I

Scheme II

Scheme III

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[Diagram of Scheme I, II, and III]
The Z configuration at the trisubstituted CC double bond of 9 is indicated by the fact that the vinylic proton H_a experiences a similar shielding from 9 (δ 6.43) to 10 (δ 6.09) as from 5 (δ 5.30) to 8 (δ 5.04 or 5.07). If 9 and 10 had the opposite configuration at the double bond, the vinylic proton should experience a downfield shift of approximately 0.3 ppm as observed for H_b from 5 (δ 4.75) to 8 (δ 5.04 or 5.07). The bisadduct 11 shows three methyl carbons in the 13C NMR spectrum, indicating C_6 symmetry since for the stereoisomer with C_6 symmetry, four signals would be expected. An accidental coincidence of two carbon signals in the stereoisomer of 11 is improbable, since all six methyl signals of 8 are separated from each other by at least 0.7 ppm.

Both 8 and 9 were treated with benzonitrile oxide (1a) under the original reaction conditions in order to ascertain that 10 is a sequential product of 9, not of 8. While 9 reacted with 1a instantaneously to give 10, the reaction of 8 with 1a gave a low yield of 11 as well as the dimer of 1a.

The isoxazoline 8 is not affected when treated with triethylamine in hexane (10 h, 25 °C) or trifluoroacetic acid in acetonitrile (10 h, 25 °C). No change in the NMR spectrum was observed when neat 8 was heated at 70 °C for 12 h or when a solution of 8 in toluene was heated at 98 °C for 13 h.

2. Reaction Mechanism. Though the expected [4 + 3] cycloaddition of 1a with 5 did not take place, another unusual reaction was observed. Compounds 9 and 10 are the first oximes that have been produced from benzonitrile oxide (1a) and a nonaromatic CC double-bonded dipolarophile. Therefore, this reaction system appeared to be suited for acquiring more information on the mechanistic significance of oxime formation accompanying the 1,3-dipolar cycloadditions of nitrile oxides.

Influence of Solvent Polarity. In reactions of nitrile oxides with arylacetylenes, the oxime/isoxazol ratio was only slightly affected by a variation of solvent polarity, and the formation of oximes through zwitterionic intermediates has been excluded. The situation has been different for reactions of nitrile oxides with CC double-bonded dipolarophiles. Oxime formation through zwitterionic intermediates has been discussed for the reaction of benzonitrile oxide with furan and postulated for the reactions of tri-

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an intermediate from equal height, if not lower than in the case of assume that the approach of a phenyl-substituted sp-hybridized carbon to one of the diene termini is not hindered therefore, allow differentiation of these possibilities (Figure 3). Since the concerted reaction of cycloadditions. Since the concerted reaction of oxime rate-determining step in a (Figure 1), product determination occurs in the rate-determining step in explanation b (Figure 2). Though explanation b (Figure 2) offers a satisfactory explanation for the different reaction rates of 5 and 15 as well as for the different product composition, a blend of explanations a and b is also conceivable. A change of mechanism, i.e., concerted reaction of 15 and stepwise reaction of 5, even appears to be quite attractive, since with this assumption all products obtained from 1a and 5 could be rationalized by the intermediacy of diradicals. On the basis of Figure 2 (right) the barrier for the formation of the intermediate 7 can be calculated to be 0.3 kcal/mol higher than the barrier for the concerted formation of 8. This number is an upper limit, however, since 8 may also arise from cyclization of 7 (Figure 1, right). The small reactivity difference between 15 and 5 indicates that the reaction of 1a with 15 (which is regarded as a "normal" diene) does not profit highly from concertedness (energy of concert = 2 kcal/mol).

C. Conclusion

If an intermediate diradical (7) accounts for the formation of the oxime 9, closely similar activation energies for the concerted and stepwise 1,3-dipolar cycloadditions of benzonitrile oxide (1a) with 1,3-dienes can be derived. Though 7 is a reasonable intermediate to explain the formation of 9, a concerted process for oxime formation cannot rigorously be excluded, particularly since 6, an expected cyclization product of the tentative intermediate 7 could not be detected (cf. ref 8b). If a mechanism for oxime formation can be found, which avoids the inter-

Table I. Competition Experiments for Determining Relative Reactivities of 5, 12, 13, and 15 toward Benzonitrile Oxide (1a)

<table>
<thead>
<tr>
<th>dipolarophiles (mg, mmol)</th>
<th>NEt₃ (mg, mmol)</th>
<th>product ratio (molar)</th>
<th>rel addtn ratesa</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (91.6, 0.513), 13 (56.4, 0.521)</td>
<td>14.9, 0.096</td>
<td>10.9, 0.108</td>
<td>8:17 = 1:4.36 k(5):k(13) = 1:3.49 (NMR)</td>
</tr>
<tr>
<td>13 (56.3, 0.520), 12 (62.6, 0.505)</td>
<td>15.1, 0.097</td>
<td>10.9, 0.108</td>
<td>17:16 = 1:2.53 k(13):k(12) = 1:2.73 (NMR)</td>
</tr>
<tr>
<td>5 (89.2, 0.500), 12 (61.9, 0.498)</td>
<td>15.8, 0.102</td>
<td>10.9, 0.108</td>
<td>8:16 = 1:1.17 k(5):k(12) = 1:19.89 (NMR)</td>
</tr>
<tr>
<td>12 (45.5, 0.437), 15 (41.5, 0.441)</td>
<td>13.6, 0.087</td>
<td>10.9, 0.108</td>
<td>16:19 = 1:2.85 k(12):k(15) = 1:2.73 (GC)</td>
</tr>
</tbody>
</table>

*Calculated according to ref 18 with the assumption that 8 and 9 are formed in 77:23 ratio (see above); the formation of the 2:1 products 10 and 11 is negligible under these conditions.

(b) The isoxazolines 8 and 19 are formed by concerted cycloadditions. Since the concerted reaction of 1a with 5 is retarded by steric hindrance, the formation of the oxime 9 can compete (Figure 1).

Assume that the approach of a phenyl-substituted sp-hybridized carbon to one of the diene termini is not hindered by the methyl groups. The barrier for the formation of an intermediate from 5 can therefore be expected to be of equal height, if not lower than in the case of 15 (Figure 1).

(kcal/mol)

| Scheme V |
|--------------------------|-----------------|-----------------------|------------------|
| Ph-CH=C=CH₂ | 1a | [Scheme V] |
| 12 | 1 | 16 |
| 13 | 1a | 17 |
| + traces of regioisomer |
| 14 | 1a | 18 |
| 15 | 1a | 19 |


mediacy of 7, the above estimates for the energy of concert of the 1,3-dipolar cycloaddition had to be augmented correspondingly.

Experimental Section

General. IR spectra were recorded on a Shimadzu IR-435 spectrometer. NMR spectra were taken on a Varian XL 200 spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on a 70-2500 VG spectrometer and the microanalyses were carried out by Ilse Beetz, Microanalyticals Laboratorium, D-8640 Kronach. Melting points are uncorrected. NMR spectra were taken on a Shimadzu GC 9A gas chromatograph equipped with FID.

Substrates. Benzonitrile oxide (1a) was generated in situ from benzoylhydroxamoyl chloride and triethylamine as described in ref 4b. The dipolarophiles 12 and 14 are commercially available, and 5 was prepared as described previously.7 Diene 13 has previously been prepared with a second isomer from 3-methyl-2-cyclohexene-1-one and magnesium iodide and successive dehydroboration.8

We obtained pure 13 in 56% yield from 3-methyl-2-cyclohexene-1-one (Aldrich), methyltriphenylphosphonium bromide, and sodium amide (Instant Ylide, Fluka) in THF following the general procedure by Schlösser.16 1,2-Bis(methylene)cyclopentane (15) was prepared in 12% overall yield from cyclopentanone by using the five-step synthesis described in ref 17.

Benzonitrile Oxide (1a) and Diene 5. A solution of triethylamine (3.35 mL, 2.43 g, 24 mmol) in 50 mL of dry ether was added dropwise at ambient temperature to a stirred solution of 5 (1.68 g, 9.42 mmol) and benzoylhydroxamoyl chloride (3.40 g, 21.8 mmol) in 50 mL of dry ether. Stirring was continued for 12 h, and triethylammonium hydrochloride was removed by filtration and washed with a few milliliters of dry ether. The combined filtrates were concentrated under reduced pressure and finally kept at 0.1 mbar/20 °C for 1 h to give 4.72 g of a crude product. Separation by MPLC (RP 18, CH₂OH) gave six fractions (increasing retention times): 3,4-diphenyl-1,2,5-oxadiazole 2-oxide (dimer of benzonitrile oxide) (1.04 g, 10 (442 mg, 11.3%) 9 (186 mg, 6.6%), 8 (1.53 g, 54.6%), 11 (114 mg, 2.9%), and traces of nonidentified products, probably formed by attack of 1a at the nitroso group of the monoxide.
described before to give 160 mg of crude 19, which was purified by MPLC (RP 18, CH₂OH/H₂O = 9:1). Yield: 119 mg (82%) of 19 and traces (20 mg) of a bisadduct, which has not been purified.

6-Methylene-3-phenyl-1,2-oxazaspiro[4.4]non-2-ene (19): mp 42-43 °C (pentane); IR (neat) 2946, 1444, 1357, 915, 757, 690 cm⁻¹; 'H NMR (CDCl₃) δ 6.16-3.72 (m, 8 H), δ 7.66-7.71 (m, 2 H); ¹³C NMR (CDCl₃) δ 222.12 (t), 129.14 (d), 128.52 (d), 128.66 (d), 129.86 (d), 129.98 (s), 153.43 (s), 155.91 (s); mass spectrum (70 eV), m/z (relative intensity) 213 (M⁺, 36), 212 (18), 196 (8), 185 (6), 184 (8), 171 (100), 104 (9), 103 (7), 95 (9), 94 (21), 93 (8), 91 (11), 79 (34), 77 (34); high resolution mass spectrum, m/z calcd for C₁₄H₁₅NO 213.1593, found 213.1519. Anal. Calcd for C₁₄H₁₅NO: C, 78.84; H, 7.09; N, 6.35. Found: C, 78.84; H, 6.35; N, 6.35.

Solvent Dependence of the Product Ratio from 1a and 5. The reaction was carried out with equimolar amounts of 1a and 5 at ambient temperature in different solvents as described for ether (above).¹⁹ The crude product mixture was analyzed by ¹H NMR using the singlets at δ 5.04 and 5.07 for 8, the singlets at δ 5.58 and 6.43 for 9, and the singlet at δ 6.09 for 10. The small amounts of 11 have been neglected.

Relative Reactivities of Dipolarophiles toward Benzenitrile Oxide (1a). A mixture of two dipolarophiles and benzyldroxamoyl chloride were dissolved in 4 mL of CCl₄. Triethylamine was added, and the mixture was stirred at 20.5 °C for 8 h. The mixture was filtered to remove triethylenonium hydrochloride, and the filtrate was concentrated under reduced pressure to give a mixture of products, which was analyzed by ¹H NMR or GC.

The ¹H NMR analyses were based on the relative intensities of the following signals: 8, δ 5.04 and 5.07 (2 s, 2 H); 16, δ 7.50, (dd, 1 H); 17, δ 5.51, (6, 1 H). The GC separation was carried out on a 50-m SE 30 fused-silica capillary column (id 0.2 mm) at 270 °C. Compounds 8, 16, and 19 had retention times of 7.66, 5.87, and 4.72 min, respectively. For the evaluation of the product ratios, area factors of 0.5934 (8), 1.000 (16), and 0.6446 (19) were used.

Acknowledgment. We thank Mr. W. Hellebrandt for experimental assistance, Dr. E. Bäuml for discussions of the spectra, and the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

Stepwise [4 + 2]- and [4 + 4]-Cycloadditions of 1,1,2,2,3,3-HexamethyI-4,5-bis(methylene)cyclopentane

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Received March 23, 1989

The thermal dimerization of the title compound 1 yields the [4 + 2]-cyclodimer 3 and the [4 + 4]-cyclodimer 4 in a ratio of approximately 3.5:1. Comparison of activation enthalpies (ΔH°* (3) = 80.1 kJ/mol, ΔH°* (4) = 76.6 kJ/mol) and activation entropies (ΔS°* (3) = -143.1 J/mol K, ΔS°* (4) = -183.3 J/mol K) indicates both cycloadditions proceed by analogous mechanisms. A study of the pressure dependence (0.5-9.3 kbar) yields activation volumes in the same order of magnitude for both dimers (ΔV* = (15 to 16) cm³/mol), indicative of two parallel stepwise processes. A selective cycloaddimerization of 1 to give the [4 + 2]-cyclodimer 3 is achieved by acid catalysis.

Dimerizations of 1,3-dienes have attracted great attention in the mechanistic discussion of Diels–Alder reactions¹ since the regular [4 + 2]-cyclodimers are often accompanied by certain amounts of 1,2-divinylcyclobutanes and 1,5-cyclooctadienes.¹⁻³ The question of whether the diene pathway, which accounts for the formation of the four- and eight-membered ring compounds, also represents the dominant route to the Diels–Alder products has been intensively studied, and evidence for concerted and stepwise Diels–Alder reactions has been presented.¹ Since in most cases the studies have been carried out with acyclic dienes, the analysis of the results is complicated by the conformational freedom of the dienes.

A conformationally rigid diene fragment with sterically shielded 2- and 3-positions is incorporated in the bis(methylene)cyclopentane.¹⁴ Since this compound has been found to give a higher amount of 1,4-adducts than other dienes in several cycloadditions,⁵ it appeared to be

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0022-3633/89/1945-5016$01.50/0 © 1989 American Chemical Society