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Hetero Diels-Alder Adduct Formation between Nitrosobenzene and Tetra-methyl Purpurogallin and its *retro*-Diels-Alder Reaction

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É descrita uma síntese eficiente de um aduto de Diels-Alder da tetrametilpurpurogalina (TMPG) e o nitrosobenzeno (NOB). A cinética da decomposição térmica do aduto, que segue um mecanismo de *retro*-Diels-Alder foi estudada usando espectroscopia de ¹H-RMN.

An efficient synthesis of a Diels-Alder adduct between purpurogallin tetramethyl ether (TMPG) and nitrosobenzene (NOB) is reported. The thermal decomposition kinetics of the adduct, which follows a *retro*-Diels-Alder mechanism, was studied using ¹H-NMR spectroscopy.

Keywords: Hetero Diels-Alder, tetra-methyl purpurogallin, nitrosobenzene

Introduction

The renewed interest in both natural and semisynthetic endoperoxides and NO-containing products, both of which present interesting medicinal applications¹⁻⁵, led us to reconsider the preparation of these structures through Diels-Alder reactions. Heteroatomic functional arrangements can result in dienophiles which react to produce heterocyclic Diels-Alder adducts^{6,7}. Some di-heteroatomic systems, such as O=O, O=N and N=N, also show this behavior, with the formation of di-heteroatomic cyclic structures^{6,8-11}. Nitroso compounds, in particular, are known to give oxazine type adducts¹²⁻¹⁵.

Adequately substituted tropolones and benzotropolones behave as dienes in Diels-Alder reactions, both with homo- and heteroaromatic (Figure 1. **I** from TMPG and **II** from eucarvone) dienophiles^{8,9,10,14}.

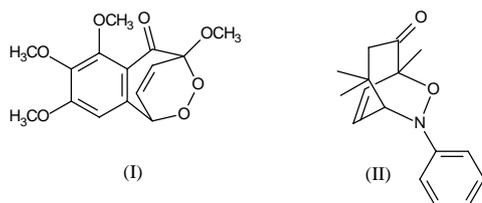


Figure 1.

Peroxo TMPG (**I**) is thermally unstable, and breakage of the peroxide bond results in a rearranged product^{8,9}. In the case of NO bond the thermal behavior is different, giving way to a facile *retro* Diels-Alder reaction with quantitative recovery of both diene and dienophile. Adducts from thebaine acting as diene and nitrosoarenes as dienophiles show different degrees of dissociation, depending on the electronic characteristics of the substituents placed *para*- to the nitroso group in the nitrosoarenes¹⁵.

We here describe the preparation of the tetramethyl purpurogallin and nitrosobenzene Diels-Alder adduct, together with the determination of the rates of the *retro*-Diels-Alder reaction.

Results and Discussion

The adduct was obtained both in polar (methanol, diethyl ether) and non-polar solvents (dichloromethane, toluene, hexane). In polar solvents the reaction was not complete giving rise to mixtures of unreacted starting products and the adduct. Using hexane the adduct could be isolated in good yields and purified.

The structure of the TMPG-NOB Diels-Alder adduct (Figure 2) was characterized by ¹H NMR, ¹³C NMR and confirmed by X-Ray diffractometry¹⁶. Of the two possible orientations of the N-O bridge, only **III** was observed.

The thermal decomposition of the adduct proceeds through a *retro*-Diels-Alder mechanism as it is shown by

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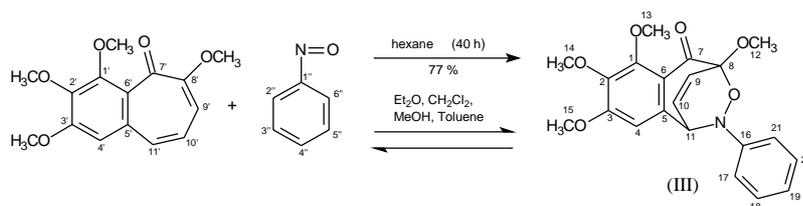


Figure 2.

^1H NMR experiments, in which the coexistence of the three compounds involved in the reaction could be detected at the equilibrium point. When using an initial adduct concentration of 10 mg/mL the dissociation of the adduct was 60 % at 30°C, 78 % at 40°C and 86 % at 50°C.

To establish the kinetic parameters for the *retro*-Diels-Alder we studied the intensity variations in the ^1H NMR signals for specific protons (H-9 and H-9'), both of the adduct and starting materials. The experiments were carried out in CDCl_3 solution at 30° and 50° with an initial adduct concentration (Ci) of 10 mg/mL, and at 40 °C with (Ci) = 5, 10, and 15 mL.

Kinetic law at 40° C and direct rate constant (k_1) were determined using the differential method, studying the system at the start of the reaction¹⁷.

Table 1.

Adduct initial concentration (Ci) (mol L ⁻¹)	Initial rate (Vo) (mol L ⁻¹ min ⁻¹)
1.3055×10^{-2}	0.0001
2.611×10^{-2}	0.0002
3.916×10^{-2}	0.0003

$$\text{Reaction order} = \alpha = 1; R^2 = 1$$

$$V_0 = k_1[\text{Adduct}]$$

Constants were obtained from the equilibrium concentrations (eq. [1]), and the inverse rate constant k_{-1} was established by combining equations (1) and (2).

$$K_{\text{eq}} = [\text{TMPG}][\text{NOB}]/[\text{TMPG-NOB}] \quad (1)$$

$$K_{\text{eq}} = k_1/k_{-1} \quad (2)$$

The values for ΔG° , ΔH° and ΔS° were obtained from equations (3) and (4)¹⁸.

$$\Delta G^\circ = -RT \ln K_{\text{eq}} \quad (3)$$

Table 2.

T (°C)	K_{eq} (mol L ⁻¹)	k_1 (min ⁻¹); R^2	k_{-1} (mol L ⁻¹ min ⁻¹)	ΔG° (KJ mol ⁻¹)	ΔS° (u.e.)
30	2.28×10^{-2}	2.4×10^{-3} 0.9878	1.05×10^{-1}	2.3	37.6
40	5.02×10^{-2}	8.2×10^{-3} 0.9992	1.63×10^{-1}	1.9	37.7
50	9.29×10^{-2}	2.7×10^{-3} 0.9983	2.93×10^{-1}	1.5	37.6

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (4)$$

$$\Delta H^\circ = 13.7 \text{ K J mol}^{-1}; R^2 = 0.9972$$

Activation energy (Ea) was calculated using Arrhenius equation:

$$k_1 = A e^{-E_a/RT}$$

$$E_a = 23.6 \text{ K J mol}^{-1}; R^2 = 0.9999$$

Conclusions

The Diels-Alder reaction of TMPG and NOB in hexane resulted in the formation of the TMPG-NOB adduct as a crystalline solid. The structure could be established by spectroscopic methods and X-ray diffraction.

The kinetic and thermodynamic characteristics of the decomposition reaction at three temperatures were studied. Rate law, rate constant of the direct and inverse reaction at 40°C and the activation energy of the reaction were determined. The concentration of each species in equilibrium was established by observation of the ^1H NMR signals for specific protons.

The equilibrium in the *retro*-Diels-Alder reaction of TMPG-NOB was characterized by the determination of the thermodynamic constants ΔG° , ΔH° and ΔS° . The ΔG° value of approximately 2 kcal/mol is low, which is borne out by the facile formation and decomposition of the adduct where the direction of the reaction controlled simply by displacing the product from solution or eliminating one of the reactants from the mixture. The ΔH° value for the reaction (approximately 14 kcal/mol) indicates that while the adduct is stable once formed, it can be decomposed with a small energy outlay, for both of the liberated moieties recover their condition of free aromatic systems. While there is a strict control of the orientation of the reactants leading to the adduct, ΔS° is not influenced by temperature.

These results indicate that there is the possibility of modulating the rates of the Diels-Alder and *retro*-Diels-Alder reactions by controlling the aromaticity of starting materials. A series of compounds and derivatives capable of liberating NO containing moieties has been planned to further study their stability, decomposition patterns and pharmacological properties.

Experimental

General

NMR Spectra were measured in a Bruker Avance 400 DPX.

Kinetic studies were measured by ^1H NMR at 400 MHz using CDCl_3 (Aldrich 99.8% pure) as solvent.

IR spectra were measured in a FT-IR DR-8031 Shimadzu spectrophotometer in KBr pellets.

UV spectra were measured in a Unicam SP 800 ultraviolet spectrophotometer.

MS were measured in a Shimadzu GC-MS QP 1100 EX. Sample ionization was carried out by electron impact (20 and 70 eV).

Solvents were distilled in glass prior to use.

Nitrosobenzene

Nitrosobenzene (m.p. 68 °C) was prepared immediately prior to use following Vogel¹⁹.

Purpurogallin

Purpurogallin (m.p. 265-267 decomp.) was prepared following Bartrop¹⁹.

Tri-O-methyl purpurogallin

An aqueous solution of sodium hydroxide (28 g, 0.70 mol in 200 mL) was added to a mixture of purpurogallin (45 g, 0.20 mol), crushed ice (100 g) and dimethylsulfate (60 mL) with continuous stirring. The mixture was stirred overnight. The solid precipitate was collected, washed with water and recrystallized from ethanol to yield tri-O-methyl purpurogallin (24 g, 45 %, m.p. 169-171 °C)²⁰. ^1H -NMR (CDCl_3): δ 7.17 (d, J 11.2 Hz, H-11'), 6.67 (s, H-4'), 6.67 (dd, J 9.3 and 11.2 Hz, H-10'), 6.60 (d, J 9.3 Hz, H-9'). ^{13}C -RMN (CDCl_3): δ 186.34, 159.77, 158.67, 157.28, 137.62, 136.52, 134.82, 123.96, 112.74, 106.07, 61.11, 56.99, 56.49. MS (IE; 70 eV, 25 °C) m/z 262 (100 %), 247 (30 %), 233 (22 %), 219 (32 %), 201 (15 %), 191 (19 %), 173 (19 %), 147 (15 %), 131 (9 %), 105 (23 %), 89 (13 %), 77 (14 %), 63 (11 %), 51 (13 %).

Tetra-O-methyl purpurogallin

Tri-O-methyl purpurogallin (5 g, 0.02 mol) and aqueous potassium hydroxide (32.5 g, 0.58 mol in 50 mL) were shaken until an homogeneous mixture was obtained. Dimethylsulfate (10 mL) was added in one portion, and the mixture warmed over a free flame until a reaction ensued. The flame was then removed, and after the first violent reaction had subsided, the mixture was boiled for a further 30 minutes. The reaction mixture was cooled to room temperature, the solid collected and washed with water. The solid was then dried and extracted with a large volume of diethyl ether. The ether extract was dried (MgSO_4), and the solvent removed to yield tetra-O-methyl purpurogallin (45 g, 86 %, m.p. 87-88 °C). Recrystallization from methanol yields the pure compound, m.p. 92-93 °C²⁰. IR (KBr): $\nu_{\text{max}}/\text{cm}^{-1}$ = 2943.7, 1647.4, 1620.4, 1587.6, 1572.2, 1529.7, 1489.2, 1466.1, 1450.0, 1394.7, 1350.3, 1279.0, 1252.0, 1215.3, 1178.6, 1095.7, 1043.6, 1014.7, 981.9, 951.5, 870.0, 808.3, 787.1, 771.6, 748.5, 719.5, 648.2. ^1H -NMR (CDCl_3): δ 6.90 (d, J 11.7 Hz, H-11') 6.75 (s, H-4'), 6.51 (dd, J 11.7 and 8.7 Hz, H-10'), 6.15 (d, J 8.7 Hz, H-9'). ^{13}C -RMN (CDCl_3): δ 185.11, 159.21, 155.57, 153.34, 143.95, 133.06, 129.27, 126.01, 123.69, 107.17, 105.25, 62.95, 61.37, 56.36, 56.35. MS (IE; 70 eV, 25 °C): m/z 276 (100 %), 261 (19 %), 248 (29 %), 244 (31 %), 233 (22 %), 218 (62 %), 205 (20 %), 190 (16 %), 173 (13 %), 161 (15 %), 147 (13 %), 131 (21 %), 119 (17 %), 115 (13 %), 89 (12 %), 76 (17 %).

Tetra-O-methyl purpurogallin-nitrosobenzene adduct

Tetra-O-methyl purpurogallin (1.11 g, 4.02 mmol) and nitrosobenzene (0.52 g, 4.9 mmol) were dissolved in hexane (50 mL). The solution was left standing at room temperature, in the absence of light, for 40 hours. The white crystals obtained were filtered and recrystallized from methanol to yield tetra-O-methyl purpurogallin-nitrosobenzene adduct (1.18 g, 77 %), m.p. 114-115 °C. The filtrate was concentrated under vacuum and a further crop of crystals was obtained and recrystallized from methanol (160 mg, 10 %). IR (KBr): $\nu_{\text{max}}/\text{cm}^{-1}$ 3003.5, 2982.3, 2943.7, 1693.7, 1589.5, 1491.2, 1456.4, 1402.4, 1356.1, 1325.3, 1282.8, 1257.7, 1215.3, 1197.9, 1134.3, 1107.3, 1088.0, 1049.4, 1032.0, 987.7, 954.9, 918.2, 898.9, 877.7, 841.1, 806.3, 763.9, 694.5, 655.9. ^1H -NMR (CDCl_3): δ 7.21 (dd, J 7.8 and 7.3 Hz, H-18 and H-20), 7.09 (d, J 7.8 Hz, H-17 and H-21), 6.93 (d, J 7.3 Hz, H-19), 6.62 (s, H-4), 6.55 (dd, J 9.2 and 6.7 Hz, H-10), 6.12 (d, J 9.2 Hz, H-9), 5.18 (d, J 6.7 Hz, H-11), 3.87 (s, H-12), 3.84 (s, H-13), 3.79 (s, H-14), 3.63 (s, H-15). ^{13}C -NMR (CDCl_3): δ 190.2, (7); 157.9, (3); 156.7, (1); 150.9, (16); 144.2, (2); 136.7, (10); 135.8, (5);

129.3, (18, 20); 127.7, (9); 123.4, 19); 120.5, (6); 118.3, (17, 21); 109.4, (4); 102.7, (8); 69.5, (11); 62.2, (13); 61.4, (14); 56.6, (15); 53.3, (12). MS (IE; 70 eV, 25°C): m/z = 276 (83 %), 261 (17 %), 248 (32 %), 233 (24 %), 218 (65 %) 205 (20 %), 190 (15 %), 173 (11 %), 161 (14 %), 147 (9 %), 131 (7 %), 115 (10 %), 107 (62 %), 77 (100 %), 51 (52 %). Found: C: 65.8 %; H: 5.8 %; N: 3.7 %; Requires: C: 65.8 %; H: 5.5 %; N: 3.7 %. IR ν_{\max} (CH₂Cl₂) 1696, 1586 cm⁻¹; ν_{\max} (nujol) 1700, 1585 cm⁻¹. UV λ_{\max} (methanol) 245, 296 nm ($\epsilon = 26,500$ and $10,500$, respectively).

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