ACCELERATION OF DIELS-ALDER REACTIONS BY REMOTE METHYL GROUPS

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Abstract. The hexamethyl substituted bismethylenecyclopentane 1a is 4 to 7 times more reactive towards the acetylenic dienophiles 2 and 3 than the nonmethylated 1,2-bismethylenecyclopentane 1b. This unusual consequence of branching is explained in terms of steric and electronic effects.

Substituent effects of alkyl groups depend on the degree of branching. While the electronic effects of branching are commonly small in the condensed phase, significant steric effects may be encountered. Branching usually accelerates reactions, in which bonds are broken in the rate determining step, e.g. homolytic or heterolytic CC and CX bond fissions. On the other hand, bond forming reactions, e.g. cycloadditions or additions of radicals to alkenes, often experience considerable retardations with increasing bulk of the alkyl substituents. We now report the unusual observation that a Diels-Alder reaction is accelerated as the bulkiness of one of the cycloaddends is increased.

Scheme 1

\[
\begin{align*}
1,1,2,2,3,3\text{-Hexamethyl-4,5-bis(methylene)cyclopentane} 1a, & \text{ an s-cis fixed 1,3-diene has been shown to undergo some unprecedented 1,4-additions,} & \text{since its 1,2-reactivity is reduced by the bulky substituents attached to the 2- and 3-position of the diene fragment. In order to use 1a as a mechanistic probe for the study of cycloaddition reactions, we needed information about the influence of the methyl groups on the 1,4-reactivity of 1a and we have, therefore, compared the reactivity of 1a and 1b towards the dienophiles 2-4.}
\end{align*}
\]
While the acetylenic dicarboxylate 2 reacted smoothly with the dienes 1a and 1b at room temperature, the cycloaddition of 1a,b with the methyl ester of phenylpropionic acid was very slow, even at 60°C. As expected, the corresponding acid chloride 3 was considerably more reactive, and at room temperature gave cycloadducts, which were solvolyzed in methanol to afford 6a and 6b. The cycloadditions of 4 were sluggish at room temperature, but proceeded quantitatively in toluene within a few hours at 60 or 80°C.

Competition experiments revealed that the acetylenic dienophiles 2 and 3, in contrast to the ethylenic dienophile 4, react noticeably faster with the highly substituted diene 1a than with the nonmethylated homolog 1b (right column of Scheme 1). How can k2/k3 ratios greater than 1 be explained? Force field calculations reveal that the reaction of 1a with acetylene is 0.4 kcal/mol more exothermic than the corresponding reaction of the nonmethylated compound 1b. The strain associated with the vicinity of 3 quaternary carbon centres in 1a is somewhat released when the C-1/C-2 bond becomes shortened during the cycloaddition.

If the difference of the reaction enthalpies is represented correctly by the molecular mechanics calculations, a k2/k3 value of 2 might be due to steric effects, if the geometrical reorganisation were complete in the transition state. Since Diels-Alder reactions are assumed to proceed through early transition states, the weight of the steric effect should be even smaller, and electronic contributions have to be considered. The ionization potential of 1a (IPa(I) = 8.4 eV) was found to be 0.3 eV lower than that of the nonmethylated compound 1b (IPA(I) = 8.73 eV). Since all these reactions can be assumed to be controlled by the HOMO(diene)-LUMO(dienophile) interactions, the higher reactivity of 1a can be explained by the reduced HOMO-LUMO gap. We, therefore, suggest that a combination of steric and electronic effects accounts for the reactivity preference of 1a over 1b towards acetylenic dienophiles.

According to force field calculations (MMX), the Diels-Alder reaction of ethylene with 1a is also slightly more exothermic than the corresponding reaction with 1b (ΔH = 0.6 kcal/mol). Since the frontier orbital argument applies in the same way as above, the inverse reactivity ratio of 1a and 1b towards fumarate 4 must be due to steric repulsions in the transition state 8a.

EXPERIMENTAL.

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 70-250E VG spectrometer and the microanalyses were carried out by Ilse Beetz, Microanalytisches Laboratorium, D-8640
3,4-Bis(methoxycarbonyl)-7,7,8,9,9-hexamethyl-bicyclo[4.3.0]nona-1(6),3-diene (5a). Compounds 1a (0.152 g, 0.852 mmol) and 2 (0.115 g, 0.809 mmol) were mixed in absence of a solvent. An exothermic reaction took place, and the 1H NMR spectrum taken after 5 h showed quantitative formation of 5a, which was recrystallized from methanol. Mp 78-79°C. - IR (KBr): 2971, 2939, 2909, 2863, 1727, 1437, 1300, 1271, 1228, 1060 cm\(^{-1}\). - 1H NMR (CDCl\(_3\)) \(\delta\) 0.81 (s, 6 H), 0.92 (s, 12 H), 2.92 (s, 4 H), 3.80 (s, 6 H). - 13C NMR (CDCl\(_3\)) \(\delta\) 21.45 (q), 23.63 (q, double int.), 25.75 (t), 47.03 (s), 52.25 (q), 133.59 (s), 133.87 (s), 168.96 (s). - MS (70 eV) \(m/z\) = 320 (M\(^+\), 19), 305 (31), 289 (20), 288 (28), 273 (100), 204 (73), 177 (15), 139 (59), 41 (14). - Anal. Calcd for C\(_{19}\)H\(_{30}\)O\(_4\) (320.4): C, 71.22; H, 8.81. Found: C, 70.90; H, 8.84.

3,4-Bis(methoxycarbonyl)-bicyclo[4.3.0]nona-1(6),3-diene (5b). Compounds 1b (0.790 g, 2.17 mmol) and fumarate 4 (0.511 g, 3.55 mmol) were dissolved in toluene (2 mL) and heated in a nitrogen atmosphere at 80°C for 6 h. The 1H NMR spectrum taken after evaporation of excess diene and toluene indicated the quantitative formation of 7a, which was recrystallized from methanol: Mp 56-57°C. - IR (KBr): 2908, 2867, 2827, 1725, 1438, 1329, 1288, 1226, 1192, 1167, 1145, 1045 cm\(^{-1}\). - 1H NMR (CDCl\(_3\)) \(\delta\) 0.89 (s, 6 H), 0.89 (s, 6 H), 1.73 - 2.36 (m, 4 H), 2.81 - 3.05 (m, 2 H), 3.71 (s, 6 H). - 13C NMR (CDCl\(_3\)) \(\delta\) 21.49 (q), 23.38 (q), 23.88 (q), 23.95 (q), 24.97 (t), 42.32 (d), 46.95 (s), 48.94 (s, double intensity), 51.87 (q), 132.61 (s), 175.59 (s). - MS (70 eV) \(m/z\) = 338 (M\(^+\), 67), 323 (100), 307 (13), 306 (8), 305 (12), 291 (75), 263 (53), 261 (26), 254 (77), 245 (43), 222 (91), 195 (83). - Anal. Calcd for C\(_{13}\)H\(_{20}\)O\(_2\) (338.5): C, 81.61; H, 6.83. Found: C, 81.77; H, 8.88. Traces of an isomer of 6a (probably double bond migration) were detected in the mother liquors of 5a.

3-Methoxycarbonyl-7,7,8,9,9-hexamethyl-4-phenyl-bicyclo[4.3.0]nona-1(6),3-diene (6a). Diene 1a (0.218 g, 1.22 mmol) and 3 (0.103 g, 0.626 mmol) were combined and kept for 3 d at ambient temperature. The mixture was dissolved in 2 mL of dry ether and added dropwise to the stirred suspension of NaHC\(_4\) (0.12 g) in methanol (3 mL). After 1 h, the solvents were evaporated under reduced pressure, and the dry residue was extracted with two 5-mL portions of ether. For this purpose, ether was added, stirred with a spatula, put into an ultrasonic bath for 1 min, and filtered. The ether was evaporated and the residue was recrystallized from methanol to give 0.173 g (82%) of colorless crystals with mp 116-117°C. - IR (KBr): 2968, 2939, 2904, 2861, 1711, 1698, 1442, 1431, 1373, 1306, 1247, 1054, 766, 701 cm\(^{-1}\). - 1H NMR (CDCl\(_3\)) \(\delta\) 0.78 (s, 6 H), 0.89 (s, 6 H), 1.65 - 2.15 (m, -2 H), 2.2 - 2.6 (m, -4 H), 3.07 (br. s, 4 H), 3.45 (s, 3 H), 7.05 - 7.45 (m, 5 H). - 13C NMR (CDC\(_3\)) \(\delta\) 21.80 (t), 29.82 (t), 34.93 (t), 35.04 (t), 35.51 (t), 51.31 (q), 125.61 (s), 126.51 (d), 127.10 (d), 127.11 (d), 130.88 (s), 131.51 (s), 142.87 (s), 143.76 (s), 1724, 1437, 1373, 1365, 1318, 1296, 1228, 1187, 1167, 1147, 1041 cm\(^{-1}\). - MS (70 eV) \(m/z\) = 338 (M\(^+\), 67), 323 (100), 307 (13), 306 (8), 305 (12), 291 (75), 263 (53), 261 (26), 254 (77), 245 (43), 222 (91), 195 (83). - Anal. Calcd for C\(_{13}\)H\(_{20}\)O\(_2\) (338.5): C, 81.61; H, 6.83. Found: C, 81.77; H, 8.88.
Competition Experiments. The dienes 1a and 1b were dissolved in ether or toluene, and one of the dienophiles 2, 3, or 4 was added. After completion of the cycloaddition (times see Table), the cycloadduct ratio was determined by GC (Fused silica capillary column SE 30, length 50 m, i.d. 0.2 mm, N₂ carrier, 270°C column temperature), and the competition constants were evaluated using the formula \( k_d/k_b = \frac{\log(1-\text{[DP]_a})}{(1+R)} \), with \([\text{DP}]_o = \text{initial dienophile concentration and } R = \text{molar ratio of the cycloadducts from 1a and 1b.}\)

Table. Determination of the Relative Reactivities of 1a and 1b towards the Dienophiles 2-4.

<table>
<thead>
<tr>
<th>Dienophile (mg)</th>
<th>1a (mg)</th>
<th>1b (mg)</th>
<th>Reaction conditions</th>
<th>Cycloadducts (Molar ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (13.8)</td>
<td>64.2</td>
<td>37.8</td>
<td>0.38 mL Et₂O, 26 h, 20°C</td>
<td>5a:5b = 5.62, 6.98</td>
</tr>
<tr>
<td>2 (18.5)</td>
<td>274</td>
<td>39.9</td>
<td>0.75 mL Et₂O, 26 h, 20°C</td>
<td>5a:5b = 22.7, 6.49</td>
</tr>
<tr>
<td>3 (15.4)</td>
<td>82.3</td>
<td>38.8</td>
<td>0.25 mL Et₂O, 14 h, 20°C</td>
<td>6a:6b = 4.45, 4.26</td>
</tr>
<tr>
<td>3 (13.8)</td>
<td>40.3</td>
<td>40.1</td>
<td>0.25 mL Et₂O, 14 h, 20°C</td>
<td>6a:6b = 1.93, 4.11</td>
</tr>
<tr>
<td>4 (40.4)</td>
<td>264</td>
<td>137</td>
<td>1.5 mL toluene, 5 h, 60°C</td>
<td>7a:7b = 0.113, 0.102</td>
</tr>
<tr>
<td>4 (42.9)</td>
<td>247</td>
<td>53.4</td>
<td>0.75 mL toluene, 5 h, 60°C</td>
<td>7a:7b = 0.350, 0.116</td>
</tr>
</tbody>
</table>

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References

1) Present address: Institute of Fundamental Chemistry, Technical University of Szczecin, Poland.
10) MMX version by Gilbert, K.E. and Gajewski, J.J., based on MM2 (Allinger-QCPE 395) and MMP1 Pi (Allinger-QCPE 318) modified by K. Steliou.
11) We thank Prof. R. Gleiter, Heidelberg, for determining the photoelectron spectrum of 1a.