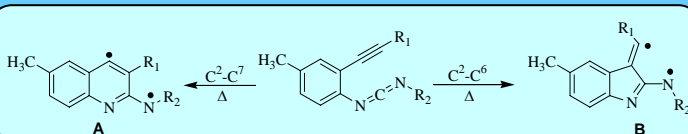




Mechanistic Studies of the Thermal C²-C⁶ Cyclization of Enyne-Carbodiimides

Introduction:

The cyclization of enyne-carbodiimides,¹ C²-C⁶ or C²-C⁷ depending on the substituent at the alkyne termini, has a wide range of applications, e.g. for the synthesis of 5-aza analogues of ellipticine, an alkaloid and potent antitumor antibiotics, and also for the production of pharmaceutically active indolo[2,3-*b*]quinoline.



Our Goal:

To highlight the mechanism of the C²-C⁶ cyclization of enyne-carbodiimides by studying the electronic effects of the substituent, at the alkyne termini or at the carbodiimide termini, on the cyclization.

Thermal Cyclization

Onset Temperatures and kinetic data of enyne-carbodiimide cyclizations were obtained from solid state reactions (DSC) using Eyring equation.

| Entry | R ¹ | R ² | T _{onset} [°C] | E _a [kcal mol ⁻¹] | k ₁₂₀ [10 ⁻³ s ⁻¹] |
|----------------|--|--|-------------------------|--|--|
| 1 | Ph | Ph | 97 | 27.7 | 2.60 |
| 2 | 4-NO ₂ C ₆ H ₄ | Ph | 126 | 29.4 | 0.33 |
| 3 | 4-CNC ₆ H ₄ | Ph | 110 | 28.6 | 0.98 |
| 4 | 4-MeOC ₆ H ₄ | Ph | 73 | 27.2 | 7.71 |
| 5 ^a | 4-Me ₂ NC ₆ H ₄ | Ph | 35 | 21.6 | 9.66 x 10 ³ |
| 6 | Ph | 4-NO ₂ C ₆ H ₄ | 115 | 28.4 | 1.29 |
| 7 | Ph | 4-CNC ₆ H ₄ | 111 | 27.9 | 2.56 |
| 8 | Ph | 4-MeOC ₆ H ₄ | 64 | 25.7 | 43.0 |
| 9 ^a | Ph | 4-Me ₂ NC ₆ H ₄ | 18 | 20.8 | 2.37 x 10 ⁴ |

[a] DSC data were obtained without purification.

Electronic Effects

| | | | | | |
|--------------------|------------------------|-------|-------|-------|-----------------|
| Y = H, X = | NMe ₂ | OMe | H | CN | NO ₂ |
| k _{rel} = | 3.72 x 10 ³ | 2.96 | 1.00 | 0.38 | 0.13 |
| E _a = | 21.57 | 27.24 | 27.72 | 28.68 | 29.49 |
| X = H, Y = | NMe ₂ | OMe | H | CN | NO ₂ |
| k _{rel} = | 9.12 x 10 ³ | 16.5 | 1.00 | 0.98 | 0.50 |
| E _a = | 20.82 | 25.69 | 27.72 | 27.89 | 28.42 |

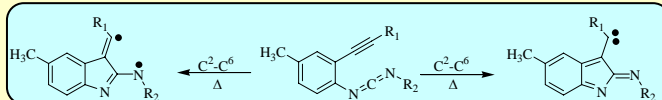
*Activation energies are in kcal mol⁻¹.

Electron donating groups accelerate the rate of cyclization, in contrast electron withdrawing groups impede it.

Acknowledgments:

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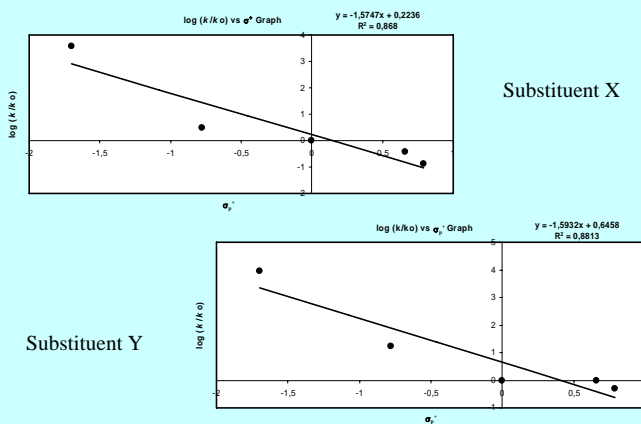
Possible Mechanisms



Enyne-carbodiimides cyclize through either a biradical or a carbene intermediate.

Hammett Correlation

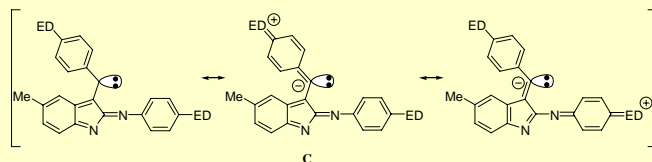
► To get an idea about the character of the transition state, qualitative correlation was done with the Hammett σ -values.



The best correlation was received with σ_{p+} values, showing that electron donating group stabilize the transition state but electron withdrawing group destabilize it.²

Proposed mechanism

These kinetic studies and Hammett correlations support a carbenoid intermediate **C**, stabilized by electron donating groups.



Conclusion:

The C²-C⁶ cyclization proceeds via singlet carbene intermediate, which is stabilized by electron donating groups but destabilized by electron withdrawing groups.

References:

- 1) a) Schmittel, M.; Steffen, J.-P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2371-2373. b) Schmittel, M.; Steffen, J.-P.; Wencesla Ángel, M. A.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1562-1564. c) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M.; Strittmatter, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1960 - 1963; *Angew. Chem.* **1998**, *110*, 2067 - 2070. 2) Engels, B.; Hanrath, M. *J. Am. Chem. Soc.* **1998**, *120*, 6356 - 6361.