Two Novel Thermal Biradical Cyclizations in Theory and Experiment: New Synthetic Routes to 6*H*-Indolo[2,3-*b*]quinolines and 2-Aminoquinolines from Enyne-Carbodiimides**

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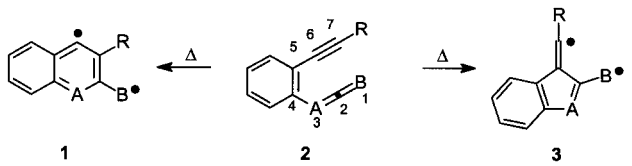
In memory of Reimund Stadler

We have recently become interested in controlling the regioselectivity of biradical cyclizations as a function of substituents. As a result, the novel thermal biradical C^2-C^6 cyclization[1] of enyne-allenes **2b** → **3b** was established when aryl substituents (R = Ph) are attached at the alkyne terminus. This cyclization behavior contrasts the regiochemistry of the well-known Myers–Saito (C^2-C^7) cycloaromatization[2] **2a** → **1a** (Scheme 1). The biradical intermediate **3b** has several



Scheme 1. Biradical intermediates of the thermal C^2-C^7 (**1**) and C^2-C^6 cyclization (**3**) of **2**.

options—depending on R′ and R″—for efficient intramolecular follow-up reactions (to formal [4+2][3] and [2+2] cycloadducts[4] and ene products[5]), which makes it a versatile intermediate for the construction of various ring systems.[6]

A similar switch in the regioselectivity of biradical cyclizations has been demonstrated with heteroanalogous enyne-allenes, such as enyne-ketenes[7] and enyne-ketenimines **2c**,**d**,[8] that undergo C^2-C^7 and C^2-C^6 cyclizations as a function of substituents at the alkyne terminus. Herein, we report that theoretical and experimental evidence points to the occurrence of equivalent biradical cyclizations in enyne-carbodiimides **2e**,**f**, which makes them versatile precursors to interesting heterocyclic systems.

To study the influence of substituents at the alkyne terminus on the cyclization behavior of the enyne-carbodiimides we have carried out quantum-chemical calculations. A correct description of biradical intermediates needs a multireference approach.[9] However, because the biradical nature of the wavefunction develops only beyond the transition state (TS)—that is, in the density functional theory (DFT) calculations $[S^2] = 0$ was found for all TSs—the influence of substituents on the activation energy ($\Delta E^{\neq}$) of both processes can be obtained from DFT calculations.[1b] Consequently, activation energies were determined with the density functional approach in combination with a 6-31G* AO basis set, while a multireference configuration interaction (MR-CI) approach was used for the computation of the reaction energies (ΔE^{r}).[10, 11]

The theoretical results summarized in Table 1 suggest—as for enyne-allenes[1b] and enyne-ketenimines[8]—a switch in the regioselectivity of the enyne-carbodiimide cyclization as a function of group R at the alkyne terminus. For R = R′ = H our calculations predict an activation barrier ($\Delta E^{\neq}$) of 31 kcal mol^{-1} for the C^2-C^7 cyclization of **2e** to **1e**, which is much lower than that for the C^2-C^6 cyclization to **3e** ($\Delta E^{\neq}$ = 39 kcal mol^{-1}). However, if R = H is replaced by R = Ph (R′ = H) the activation barrier is increased to 37 kcal mol^{-1} for the C^2-C^7 cyclization **2f** → **1f**, whereas it is decisively lowered for the C^2-C^6 cyclization of **2f** to **3f** ($\Delta E^{\neq}$ = 32 kcal mol^{-1}). As such the calculations propose that the reaction switch is even more pronounced than with the corresponding enyne-allenes.[1b]

Table 1. Summary of the calculated data. While the energies of the reactants are given in Hartree, the energies computed for the other structures are presented relative to that of the reactants in kcal mol^{-1}. The energies of the TSs are in boldface. Distances *R* are given in Å.

Substituent	**e**: R = H	**f**: R = Ph
reactant **2** (R′ = H)[a,b]	− 455.976797	− 687.047232
reactant **2** (R′ = H)[a,c]	− 454.538468	–
C^2-C^7 cyclization		
$R_{C^2-C^7} = 2.0$[b]	26	30
$R_{C^2-C^7} = 1.8$[b]	**31**	**37**
$R_{C^2-C^7} = 1.66$[b]	26	32
$R_{C^2-C^7} = 1.43$ (**1**, R′ = H)[c,d]	24	22[e]
C^2-C^6 cyclization		
$R_{C^2-C^6} = 2.0$[b]	28	25
$R_{C^2-C^6} = 1.8$[b]	**39**	**32**
$R_{C^2-C^6} = 1.68$[b]	36	31
$R_{C^2-C^6} = 1.53$ (**3**, R′ = H)[c,d]	33	22[e]

[a] $R_{C^2-C^7} = 3.41$ Å, $R_{C^2-C^6} = 2.97$ Å. [b] DFT(B3LYP) in combination with a 6-31G* basis set. [c] MR-CI+Q in combination with a double zeta polarization (DZP) basis set. [d] Biradical intermediate. [e] Reference [11].

However, the MR-CI calculations indicate that both biradical cyclizations of enyne-carbodiimides are strongly endothermic (Table 1), which is in contrast to the situation with enyne-allenes[1b] and enyne-ketenimines.[8] Since both intermediates **1e**,**f** and **3e**,**f** constitute (σ,π)-biradical intermediates such as **1a**–**d** and **3a**–**d**, the reason for the difference in reaction energies is not yet clear. Hence, from the above calculations it is not obvious whether the cyclization will be operating under kinetic control despite the fast follow-up reactions of **1e**,**f** and **3e**,**f** ($k > 10^6$ s^{-1}).[12]

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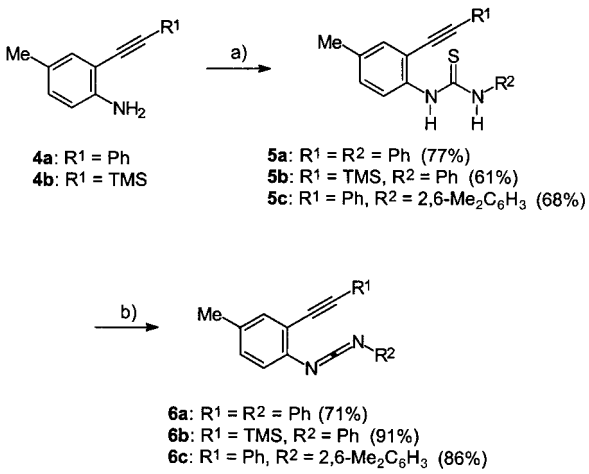
[**] Thermal and Electron Transfer Induced Reactions of Enediynes and Enyne-Allenes, part 13. We gratefully acknowledge the financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 12: reference [8].

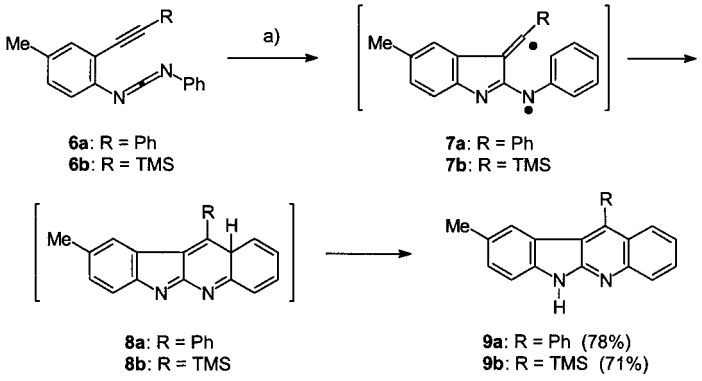
  1433-7851/98/3717-2371 $ 17.50+.50/0

To probe the reaction switch experimentally enyne-carbodiimides **6a–c** were prepared from **4a,b** via thioureas **5a–c**[13] by a procedure described by Fell and Coppola[14] (Scheme 2). Compounds **6a–c**, which were fully characterized by standard spectroscopic means, constitute the first isolated members of this new class of heteroanalogues of enyne-allenes.[15]



Scheme 2. Synthesis of enyne-carbodiimides **6a–c**. a) **5a**: R^2NCS, EtOH, RT, 6 d, 35 °C, 10 min; **5b**: DMAP, acetone, 50 °C, 4.5 d; **5c**: acetone, reflux, 16 h; b) CH_3SO_2Cl, DMAP, NEt_3, CH_2Cl_2, 0 °C, 5 min.

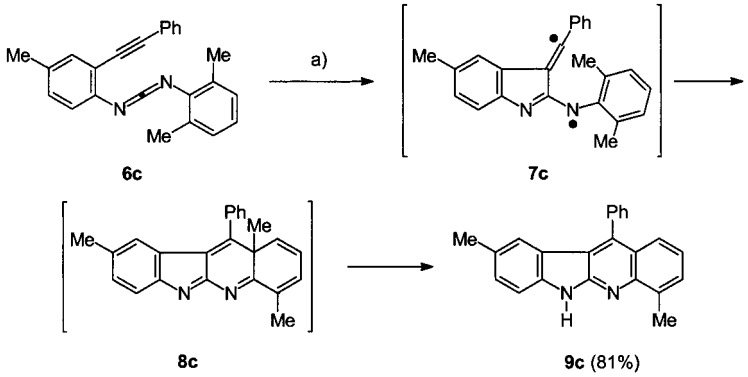
The thermal behavior of **6a,b** was investigated with differential scanning calorimetry (DSC). The enyne-carbodiimides exhibited an overall exothermic reaction, with the heat evolvement starting at 97 °C (**6a**) and 166 °C (**6b**). Thermolysis of **6** (in toluene at reflux temperature) and **6b** (in mesitylene at reflux temperature) led to the formation of the 6*H*-indolo[2,3-*b*]quinolines **9a** and **9b** in 78 and 71 % yield, respectively (Scheme 3). Hence, the thermal reaction of **6a**, **b** proceeds analogously to the cyclization of phenyl- or trimethylsilyl-substituted enyne-allenes,[4a, 6b, 12a] and it is tempting to rationalize the formation of **9a** and **9b** by an initial biradical cyclization via **7a**, **b** followed by intramolecular cyclization to **8a**, **b** and subsequent tautomerization.



Scheme 3. Synthesis of 6*H*-indolo[2,3-*b*]quinolines **9a**, **b**. a) **9a**: 1,4-cyclohexadiene, toluene, reflux, 6 h; **9b**: 1,4-cyclohexadiene, mesitylene, reflux, 18 h.

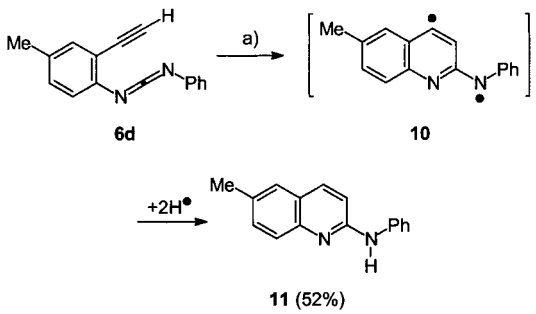
Nevertheless, formation of **9** cannot be regarded as a rigorous proof for the occurrence of a biradical cyclization via **7**, since it could have been formed in a concerted Diels–Alder reaction **6** → **8**.[15, 16]

To rigorously test for a biradical intermediate the phenyl ring at the carbodiimide terminus in **6a** was replaced by a 2,6-dimethylphenyl group, because it is well established that in concerted Diels–Alder reactions *ortho*-alkyl substituents are prohibitive owing to steric hindrance.[15b, 17] Despite the presence of the *ortho*-methylated phenyl group the thermal reaction of **6c** afforded as the only product the 6*H*-indolo[2,3-*b*]quinoline **9c** (81 %) at only slightly higher temperature (DSC: 118 °C for **6c**) than for the cyclization of **6a** (DSC: 97 °C). Certainly, such a behavior is in compliance with a rate-determining biradical cyclization to intermediate **7c** (Scheme 4), but not with a concerted Diels–Alder cycloaddition. Just as **7a**, **b**, biradical **7c** closes to the formal Diels–Alder cycloadduct **8c**, which subsequently looses a methyl group after protonation at the nitrogen atom in a S_N2-type reaction.[8]



Scheme 4. Thermolysis of enyne-carbodiimide **6c**. a) 1,4-cyclohexadiene, toluene, reflux, 2 h.

After we had established a $C^2–C^6$ biradical cyclization in enyne-carbodiimides **6a–c**, we synthesized **6d** with a hydrogen atom at the alkyne terminus to experimentally check for the predicted $C^2–C^7$ biradical cyclization **2e** → **1e**. Compound **6d** was prepared along the same route as **6a–c** via the corresponding thiourea and fully characterized. Thermolysis of **6d** in toluene (1,4-cyclohexadiene as hydrogen donor) at 90–100 °C (DSC: 90 °C) afforded **11** in 52 % yield (Scheme 5),



Scheme 5. $C^2–C^7$ cycloaromatization of enyne-carbodiimide **6d**. a) 1,4-cyclohexadiene, toluene, 90–100 °C, 20 h.

  1433-7851/98/3717-2372 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 17

but no C^2-C^6 cyclization product (detection limit 5%). The 2-aminoquinoline **11** is clearly derived from biradical **10** through hydrogen abstraction, which is indicative of a novel C^2-C^7 biradical cyclization in enyne-carbodiimides.

In conclusion, we have provided theoretical and experimental evidence for two novel biradical cyclizations triggered thermally from enyne-carbodiimides. The C^2-C^6 cyclization pathway via an azafulvene amine biradical is operative with aryl and trimethylsilyl groups at the alkyne terminus, and opens the way to a convenient synthesis of substituted 6*H*-indolo[2,3-*b*]quinolines with interesting pharmacological activity.[18] Conversely, the presence of a hydrogen atom at the alkyne terminus leads to the C^2-C^7 cyclization. The fact that a clean switch between C^2-C^6 and C^2-C^7 cyclizations can now be effected in enyne-allenes, enyne-ketenes, enyne-ketenimines, and enyne-carbodiimides points to a rather general, hitherto little known motif to control the regioselectivity of biradical cyclizations.

Received: March 23, 1998 [Z11625IE]
German version: *Angew. Chem.* **1998**, *110*, 2531 – 2533

Keywords: carbodiimides · cycloaromatizations · diradicals · enynes · quantum chemical calculations

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[10] To compute the biradical intermediates an individually selecting MR-CI approach was used: a) M. Hanrath, B. Engels, *Chem. Phys.* **1997**, *225*, 197 – 202. The reference space consisted of up to 15 configurations. This led to total MR-CI configuration spaces of more than 500×10^6 configuration state functions (CSFs), whereby the secular equations actually solved were in the order of 5×10^6—8×10^6 CSFs. The influence of the neglected CSFs was estimated by the Buenker – Peyerimhoff extrapolation: b) R. J. Buenker, S. D. Peyerimhoff, *Theor. Chim. Acta* **1975**, *39*, 217 – 228; c) R. J. Buenker, S. D. Peyerimhoff, W. Butscher, *Mol. Phys.* **1978**, *35*, 771 – 791; d) R. J. Buenker, R. A. Phillips, *J. Mol. Struct.* **1985**, *123*, 291 – 300, and references therein. The influence of higher excitations was estimated by the normalized form of the usual Davidson correction: e) J. E. Del Bene, E. A. Stahlberg, I. Shaviatt, *Int. J. Quantum Chem. Symp.* **1990**, *24*, 455 – 466. In these calculations (in the following abbreviated as MR-CI + Q) all 34 valence electrons were correlated. The calculations were performed with the DIESEL-MR-CI program package: f) B. Engels, M. Hanrath: DIESEL-MR-CI (*d*irect *i*nternal *e*xternal separated individually *sel*ecting MR-CI) program package, Universität Bonn, Germany, **1997**. To determine the TSs the energy for fixed C^2-C^7 and C^2-C^6 distances, which represent the reaction coordinates for the C^2-C^7 and C^2-C^6 cyclizations, respectively, was computed. In these calculations all other geometrical parameters were optimized. These calculations were performed with the Gaussian94 program package[10g] and the Turbo-Mol program:[10h, i] g) M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Pittsburgh, PA, **1995**; h) R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165 – 169; i) O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346 – 354.

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Synthesis of Hyperbranched Aminopolysaccharides

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Dendritic polymers such as dendrimers and hyperbranched polymers have a highly branched backbone and exhibit very different properties compared to their linear analogues. Dendrimers, which have a perfect branched and exact monodisperse structure, are prepared by either divergent or convergent methods.[1] However, their preparation normally

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  1433-7851/98/3717-2373 $ 17.50+.50/0