Polar Effects in the Transition State of the Bergman Cyclization

Michael Schmittel* and Susanne Kiau
Institut für Organische Chemie der Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany

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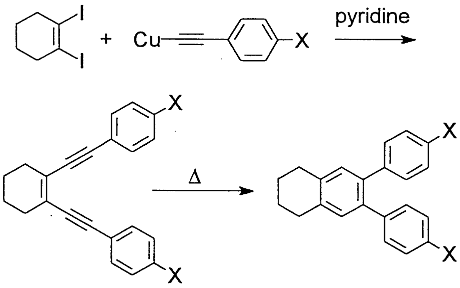
From the kinetic data of enediynes **1a-c** it is concluded that electron withdrawing substituents are lowering the free activation energy in the Bergman cycloaromatization by decreasing the repulsion of the in-plane π-orbitals.

Since the recent discovery of a new series of antitumor antibiotics, namely calicheamicin, dynemicin, esperamicin and kedarcidin, whose mode of biological action is ultimately linked to the cycloaromatization of an enediyne core inducing a double-stranded DNA cleavage by hydrogen abstraction, the various possibilities of triggering the Bergman cyclization have received considerable attention in the literature.[1] While several investigations have delineated the importance of strain and distance control in determining the activation barrier,[2] very little work has aimed for studying electronic influences. In the context of our work to initiate the Bergman cyclization through electron transfer pathways,[3] we have become interested to study the electronic influence in aryl substituted enediyne systems on the cyclization kinetics.

As model compounds we have chosen **1a-c** that carry the polar substituents in the *para* position of the phenyl groups thus far remote from the enediyne core to avoid ground state effects on the cyclization kinetics. **1a-c** were readily synthesized from 1,2-diiodocyclohexene through a tandem coupling with the corresponding copper arylacetylides.

Scheme 1. Synthesis and thermolysis of the model systems **1a-c**.



1a	43%	(X = OCH_3)	**2a**	25%
1b	56%	(X = H)	**2b**	80%
1c	54%	(X = NO_2)	**2c**	15%

The Bergman cyclization products **2a-c** were obtained by heating the enediynes with 1,4-cyclohexadiene as a hydrogen donor in diphenylether under nitrogen in sealed tubes at temperatures above 240 °C. They were isolated through a series of preparative chromatographies and characterized by standard spectroscopic techniques.

After probing several solvents, concentrations and hydrogen donors to optimize the yields of the Bergman cyclization, finally the following conditions were used for the kinetic study: a 0.01 M solution of enediynes **1a-c** in diphenylether with 1,4-cyclohexadiene as hydrogen donor (2000 mol %).[4] All kinetic traces showed a clean first-order behavior with respect to the enediynes for at least 2.5 half-times.[5]

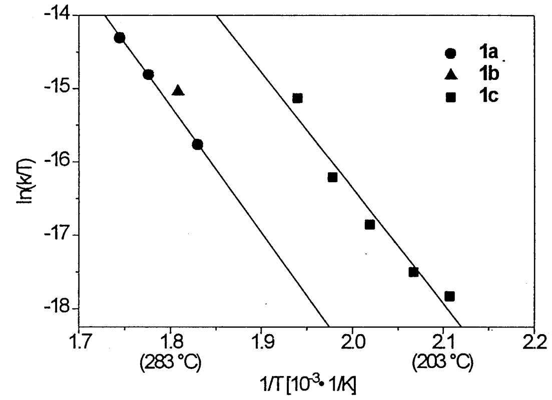


Figure 1. Eyring plots and rate constants for the cycloaromatization of enediynes **1a-c**.

Kinetic data and the activation parameters of **1a-c** are provided in Figure 1 and table 1. In comparison with kinetic data of the parent system, hex-3-ene-1,5-diyne ($\Delta H^{\neq}$ = 117.9 kJ • mol^{-1}, $\Delta S^{\neq}$ = - 44.3 J• mol^{-1} K^{-1}),[6] **1a-c** show higher $\Delta H^{\neq}$ due to transition state destabilization[7] by the aromatic groups and a more negative $\Delta S^{\neq}$ since rotational degrees of freedom are restricted for the two aromatic rings in the transition state.

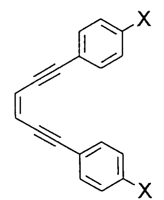
Importantly, however, by changing from electron releasing to electron withdrawing substituents at the phenyl groups in **1a-c** the activation enthalpy of the cycloaromatization is lowered by about 12 kJ • mol^{-1} without significant change in the activation entropy. This change in rate is remarkable considering the remote position of the *para* substituents.

Table 1. Activation parameters for the cycloaromatization of enediynes **1a-c**

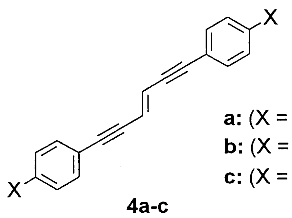
Ene-diyne	$\Delta H^{\neq}$ (kJ•mol^{-1})	$\Delta S^{\neq}$ (J•K^{-1}mol^{-1})	T (°C) for $t_{1/2}$ = 71 min	$\Delta G^{\neq}$ (at 280.2°C) (kJ•mol^{-1})
1a	+ 143.2	- 66	285.9	180.0
1b	--	--	280.2	178.5
1c	+ 131.0	- 72	249.6	170.6

In order to interpret the substituent effect on the cycloaromatization kinetics it is important to evaluate whether ground state effects in the aryl substituted enediynes or steric effects in the transition state do exert an influence on the cyclization rate. As a measure of ground state effects induced by *para* substituents we have determined the differences of the standard heats of formation between the *cis* substituted enediynes **3a-c** and the corresponding *trans* isomers **4a-c** by AM1 calculations.[8] Importantly, no significant substituent effect can be derived from the data $\Delta\Delta H_f°$ (**3** - **4**) given in table 2.

Similarly, the differences of the standard heats of formation between the *ortho* (**5a-c**) and *para* substituted systems **6a-c** can be used to describe differential steric effects in the product of the Bergman cyclization. These values, to some extent, should

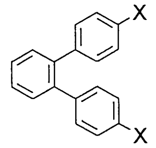


3a-c

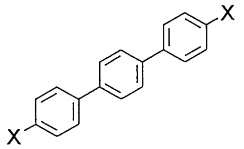


4a-c

a: (X = OCH3)
b: (X = H)
c: (X = NO2)



5a-c



6a-c

Table 2. Difference of standard heat of formation $\Delta\Delta H_f^\circ$ between *cis* and *trans* enediynes, and *ortho* and *para* substituted benzenes

	$\Delta\Delta H_f^\circ$ (**3-4**)[a] (kJ • mol^{-1})	$\Delta\Delta H_f^\circ$ (**5-6**)[b] (kJ • mol^{-1})	ΔH_r (**1**+ $H_2 \rightarrow$ **2**) (kJ • mol^{-1})
a: X=OCH$_3$	2.42	15.84	-352.50
b: X=H	1.50	14.50	-353.17
c: X=NO$_2$	2.63	16.34	-358.11

[a] $\Delta\Delta H_f^\circ$ (**3-4**) = ΔH_f°(**3**) $-\Delta H_f^\circ$(**4**), [b] $\Delta\Delta H_f^\circ$ (**5-6**) = ΔH_f°(**5**) - ΔH_f°(**6**).

allow extrapolation of the differential steric crowding in the biradical and transition state as well, since the C-C bond distance in **5a-c** is even smaller than the one calculated for the transition state (ca. 2.0 Å).[2,9,10] However, $\Delta\Delta H_f^\circ$ (**5-6**) does not change significantly when the *para* substituents are altered indicating that differential steric interactions can be neglected. In addition, neither with $\Delta\Delta H_f^\circ$ (**3-4**) nor with $\Delta\Delta H_f^\circ$ (**5-6**) the same trend is observed as in the cyclization rate of **1a-c**.

The above considerations propose that the found acceleration of the Bergman cyclization in **1c** > **1b** > **1a** is due to an electronic stabilization of the transition state, since steric effects in our systems are highly unlikely to interfere in the transition state and since ground state effects could be eliminated as well. Hence, our experimental results now confirm for the first time the conclusion drawn by Koga and Morokuma[11] on the basis of CASSCF calculations that electron withdrawing substituents do exert an accelerating effect on the Bergman cyclization by decreasing the repulsion of the in-plane π-orbitals. Interestingly, some very recent high level calculations[9,10] that predict correctly the experimental activation data provided by Roth and Hopf[6] do not comment on electronic influences on the transition state.

It should be noted, that experimental data concerning electronic effects on the kinetics of the Bergman cyclization are rare. Maier[12] and Semmelhack[13] have tentatively explained substituent effects on the cyclization rate with polar effects but did not consider a correction for ground-state effects.

Moreover, an interesting corollary of our kinetic-thermochemical analysis can be visualized when we correlate the measured free activation energy with the calculated reaction enthalpy ΔH_r (**1** + $H_2 \rightarrow$ **2**). Although at this point, since only few data are available, conclusions can only be preliminary, the very good linear correlation (R = 0.998) in Figure 2 ($\Delta G^{\neq}$ = 1.65 ΔH°_r (**1** +$H_2 \rightarrow$**2**) + 760.4 kJ • mol^{-1}) and the slope thereof propose that electronic effects in the product are not only reflected but even increased in the transition state.

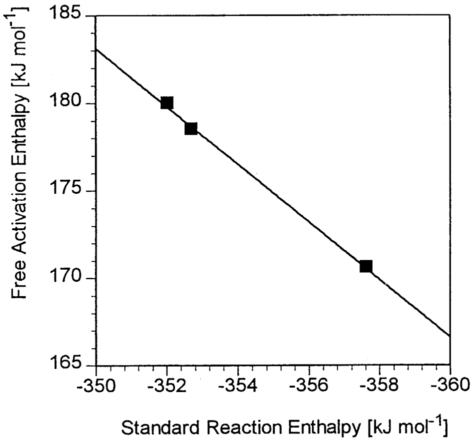


Figure 2. Correlation of $\Delta G^{\neq}$ (280.2°C) with ΔH_r (**1** + $H_2 \rightarrow$ **2**).

This finding suggests to use electronic substituent effects more extensively in order to influence the activation barrier of the Bergman cyclization for example by protonation or oxidation of an attached group.

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References and Notes

1 Review: K. C. Nicolaou and W.-M. Dai, *Ang. Chem.*, **103**, 1453 (1991).
2 J. P. Snyder, *J. Am. Chem. Soc.*, **111**, 7630 (1989).
3 M. Schmittel and C. Wöhrle, *Tetrahedron Lett.*, **34**, 8431 (1993).
4 Ampoules containing 0.1 ml of the enediyne solution were heated in a tin or oil bath for defined times. The decrease of enediyne with time was followed by GLC or HPLC. For a selected temperature we have established that the rate constant of decomposition of **1c** corresponded to the rate constant of formation of **2c**. Lower concentrations of enediynes weren't used to avoid analytical problems.
5 Importantly, the rate constant of the Bergman cyclization of **1b** proved to be roughly independent from the hydrogen donor as demonstrated in a kinetic study at 280 °C using 1,4-cyclohexadiene (k = 1.6•10^{-4} s^{-1}) and mesitylene (k = 1.1•10^{-4} s^{-1}), respectively.
6 W. R. Roth and H. Hopf, *Chem. Ber.*, **127**, 1765 (1994).
7 Since aryl substitution of acetylenes is known to entail *ground state* destabilization of about 8 kJ • mol^{-1} [S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969)] **1a-c** are destabilized versus 1,2-diethinylcyclohexene by about 16 kJ • mol^{-1}.
8 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985); Program: T. Clark, VAMP 4.5, Universität Erlangen-Nürnberg (1991).
9 R. Lindh and B.J. Persson, *J. Am. Chem. Soc.*, **116**, 4963 (1994).
10 E. Kraka and D. Cremer, *J. Am. Chem. Soc.*, **116**, 4929 (1994).
11 N. Koga and K. Morokuma, *J. Am. Chem. Soc.*, **113**, 1907 (1991).
12 M. E. Maier and B. Greiner, *Liebigs Ann.*, 855 (1992).
13 M. F. Semmelhack, T. Neu, and F. Foubelo, *J. Org. Chem.*, **59**, 5038 (1994).