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Solvent Dependent Bergman Cyclization of 2,3-Diethynylquinoxaline

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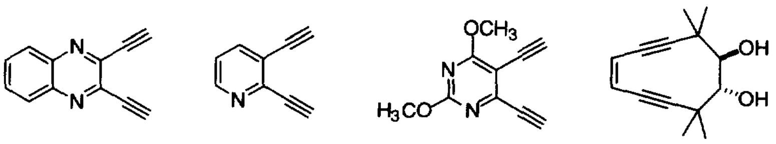
Abstract: Kinetics of thermocyclization of 2,3-diethynylquinoxaline have been studied in various solvents. The cyclization rates observed were surprisingly solvent dependent. The half-lives varied from 361 in CH_3CN to 16 min in THF. The half-life data show a good correlation with the solvents' spectroscopic $E_T(30)$ values and dielectric constants.

The Bergman cyclization was not extensively investigated until the structures of naturally occurring enediynes, which have anticancer antibiotic activities, were unveiled.[1] In the natural products, a 3-ene-1,5-diyne moiety undergoes cycloaromatization generating diradicals which capture hydrogens from the DNA backbone, causing DNA cleavage and ultimately, cell death.[2] The activity of enediynes toward Bergman cyclization have generally been explained in three ways; 1) the distance between termini of diynes (the so-called cd distance),[3] 2) strain energy,[4] and 3) electronic effects.[5] The first two have been thoroughly studied and are well understood. However, the electronic effects remain more nebulous.

Recently, we have synthesized heteroarenediynes (**1-3**) in an effort to further establish the role of electronic effects on Bergman cyclization.[6] These studies have shown that electron deficient heteroarenes are significant factor in lowering the activation energy of cyclization. In an extension of our previous work, we have performed kinetic studies of the thermal cyclization of **1** in various solvents in order to determine any further effects are driven by solvation. To our surprise, the cyclization was found to be remarkably solvent dependent with half-lives of **1** ranging from 361 to 16 min for the solvents examined. This result is more interesting since it was reported that the cyclization of **4** is solvent independent, the rate being the same in both C_6D_6 and d_8-THF.[7]

Figure 1



1 **2** **3** **4**

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In the general experimental procedure, a stock solution of **1** (6.0 mM),[6] naphthalene (7.4 mM), and 1,4-cyclohexadiene (CHD; 60 mM) in the solvents listed in Table 1 were prepared and transferred into melting point capillary tubes which were later vacuum-sealed. The tubes were heated in a oil bath at 168 °C and the reaction was followed as a function of time by HPLC.[8] The results are summarized in Table 1.

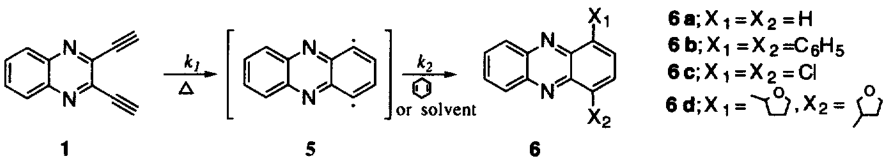
Table 1. Kinetic Data of Thermal Cyclization of **1** in Various Solvents at 168 °C.[10]

Solvent	Rate constant (k_{obs})	Correlation coefficient	half life ($\tau_{1/2}$; min)	Yield (%)[a, b, c]	Dielectric [11] Constant(ε)	$E_T(30)$[12] (kcal/mol)
Acetonitrile	3.3 × 10 -5	0.986	361	**6a**(7)	36.64	45.6
Methanol	3.7 × 10 -5	0.994	312	**6a**(2)	33.00	55.4
Benzene	1.2 × 10 -4	0.990	96	**6a**(12), **6b**(58)	2.38	36.0
Dioxane	1.9 × 10 -4	0.990	60	**6a**(15)	2.21	36.0
CCl_4[13]	2.6 × 10 -4	0.994	44	**6c**(81)	2.23	39.0
THF	7.1 × 10 -4	0.989	16	**6a**(36), **6d**(9)	7.52	37.4

[a] Bulk cyclization was performed under the same condition as the kinetics.
[b] Solvent adducts gave expected spectral data.
[c] Isolated yields

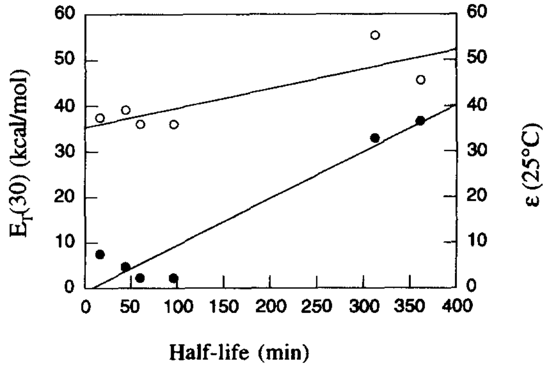
Proof of the cyclization during kinetics was established by co-injection of kinetic samples with authentic phenazine (**6a**). Furthermore, the bulk cyclization of **1** in each solvent was performed in the presence and absence of CHD, allowing CHD or the solvent to act as the radical trap. Each reaction gave phenazine and solvent adducts as shown in Scheme 1. The exclusion of CHD from bulk cyclizations did not have a significant impact on the reaction products or their yields. The yields in the absence of CHD were ±3 % from those in its presence and reported in Table 1.

Scheme 1. The thermocyclization of **1**.



1 **5** **6**

Kinetic data for all solvents was first-order, as expected.[9] The solvent effect gave half-lives ranging from 361 to 16 min. In acetonitrile and methanol, the cyclizations were slowest, with half-lives of 361 min and 312 min, respectively. The cyclization rates were modest in benzene ($\tau_{1/2}$ = 96 min) and dioxane ($\tau_{1/2}$ = 60 min), and astonishingly fast in THF ($\tau_{1/2}$ = 16 min). We attempted to correlate these half-lives with dipole moment, dielectric constant (ε), and $E_T(30)$ values. Both ε and $E_T(30)$ showed linear correlations with coefficients 0.96326 and 0.84065 respectively (Plot 1). Even though ε showed better overall correlation, it seems that $E_T(30)$ values correlate better with less polar solvents and ε does with polar solvents. There was no relation between half-life and solvent dipole moment. These results can be explained if ground state of **1** is more polar than its transition state so that polar solvents stabilize the ground state better than the transition state. This increases the activation energy of Bergman cyclization in polar solvents, and *vice versa* in less polar solvents.



Plot 1. Linear correlation between Half–lives *vs.* Solvent. ○ corresponds $E_T(30)$ *vs.* $\tau_{1/2}$ with correlation coefficient (R=0.84065) and • represents ε *vs.* $\tau_{1/2}$ (R=0.96326)

The kinetic results suggest that bulk solvent properties are playing the dominant role in determining the rate. Hydrogen bonding does not seem to play a significant role in this system. Solvents without hydrogen bonding capabilities gave half-lives slower than those found in methanol (CH_3CN) and also faster than methanol (all others). Furthermore, trace amounts of water or alcohol present in unpurified THF and benzene, respectively, showed negligible differences in the observed half-lives compared to those in the purified solvents.

It is also interesting that the product yield varied with solvent. Generally, less polar solvents gave better yields of identifiable Bergman cyclization products. Even though CCl_4 gave best yield (81 %) as the dichloride adduct, good yields were also obtained in benzene (69 %) and THF (45 %). On the other hand, acetonitrile and methanol gave only 7 % and 2 %, respectively, along significant amounts of intractable dark solids which accounted for the majority of the mass balance. In most solvents the proton adduct, phenazine, was major product. Benzene was the exception in which the solvent adduct (**6b**) was predominant (58% yield).

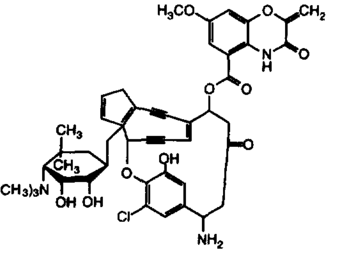


Figure 2. The C-1027 Chromophore

The only example of an enediyne reported in the literature which shows such a significant solvent dependent thermal cyclization is the C-1027 chromophore (Figure 2).[15] Yoshida tested the reactivity of the C–1027 chromophore in ethanol, ethyl acetate, DMSO, and DMF as well as the solvents listed in table 1. The C–1027 chromophore also showed the shortest half-life in THF and some of the other data also parallels our results.

In conclusion, the thermocyclization of heteroarenediyne **1** shows a remarkable solvent dependence. Its half-lives varied from 361 to 16 min over a range of solvents and showed a reasonably linear correlation with solvent dielectric constants and $E_T(30)$ values. The data showed that non-polar solvents give shorter half-lives and better yields of isolatable of Bergman cyclization products. It is not yet clear how general this solvent effect is. If this phenomenon is relatively general, it can be used as a synthetic tool to either suppress cyclization or activate cyclization in the presence of competing thermal reactions or to improve the yields of tandem Bergman cyclizations.[16] Our work in this area will be reported elsewhere.

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