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Linear free energy relationships in the Bergman cyclization of 4-substituted-1,2-diethynylbenzenes

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Abstract

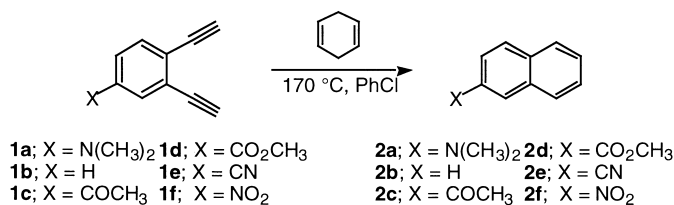
A series of 4-substituted-1,2-diethynylbenzenes were prepared (**1a–f**) and subjected to Bergman cyclization. Bulk cyclization proceeded to produce the corresponding 2-substituted naphthalenes (**2a–f**) in good yields (59–78%). Kinetic experiments show a linear free energy relationship between the cyclization rate and the Hammett σ_m substituent coefficient and the Swain–Lupton field and resonance parameters. © 2000 Elsevier Science Ltd. All rights reserved.

Ever since the discovery of the naturally occurring enediyne anticancer antibiotics in the mid 1980s, interest in the Bergman cyclization reaction has been rejuvenated.¹ Numerous studies have explored ways to activate cyclization in analogues of the natural products. Evidence has resulted in the recognition of two primary contributing factors which effect cyclization. First is the strain energy. As the triple bond termini are drawn closer together, the strain energy of the molecule is increased, facilitating cyclization. This can be accomplished in structurally simple enediynes by incorporating the enediyne into a 10-membered ring, lowering the cyclization onset temperature.² The second factor is an electronic effect. This effect can be seen through manipulation of several different variables, such as solvent,³ incorporation of the double bond into an aromatic ring,⁴ or the use of electron-withdrawing or -releasing groups.⁵

Recently, we have been involved in the investigation of enediynes where the double bond is incorporated into an electron-deficient heterocycle.⁶ Our data strongly supports the notion that when the double bond is electron-deficient, Bergman cyclization is accelerated. Based on these results, we wished to determine if a linear free energy relationship exists for the Bergman cyclization of 4-substituted-1,2-diethynyl benzenes (Scheme 1).

The Bergman cyclization is unusual in that it generates a neutral σ,σ -diradical intermediate. Since currently no parameters are available for diradical forming reactions of this type, an

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Scheme 1.

important issue is to establish which parameters or combinations of parameters, if any, are appropriate to describe this relationship. The various types of Hammett parameters are usually involved with charges or radicals which are associated with π -systems. The fact that the radicals are orthogonal to the π -system, although they are in benzylic positions brought into question whether any of the currently available Hammett-type parameters could be used to draw reasonable linear free energy relationships in this case.

Table 1 shows the Hammett parameters used in this study. The standard σ_m and σ_p values were examined, in spite of the fact that they are generally used for polar reactions.⁷ The σ_{jj} and σ_{mb} parameters were developed specifically to deal with radical systems.⁸ The constants F and R are for field and resonance contributions, respectively, for the Swain–Lupton model.⁹

Table 1
Hammett-type parameters for compounds used in this study^a

Substituent	σ_m	σ_p	σ_{jj}	σ_{mb}	F	R
N(CH ₃) ₂	-0.1600	-0.8300	1.0000	-0.9600	0.1500	-0.9800
H	0.0000	0.0000	0.0000	0.0000	0.0300	0.0000
CO ₂ CH ₃	0.3700	0.4500	0.3300	0.4800	0.3400	0.1100
COCH ₃	0.3800	0.5000	0.5400	0.5600	0.3300	0.1700
CN	0.5600	0.6600	0.4200	0.8600	0.5100	0.1500
NO ₂	0.7100	0.7800	0.3600	0.8600	0.6500	0.1300

^a σ_m , σ_p , F and R from ref 7; σ_{jj} and σ_{mb} from ref 8;

Compounds **1a–f** were synthesized using palladium coupling strategies from the corresponding 4-substituted dihalobenzenes.¹⁰ In order to be certain the kinetics being measured were related to Bergman cyclization, bulk cyclization of each material was performed under conditions nearly identical to those used for the kinetics runs. The yields of isolated Bergman cyclized products (**2a,c–f**) ranged from 58–78% and are summarized in Table 2. The cyclization yield of **2b** was not determined since the cyclization of this compound has been carefully studied previously.¹¹

Kinetics were measured at 170°C using chlorobenzene as the solvent and 100 equiv. 1,4-cyclohexadiene (1,4-CHD) as the radical trap.¹² Each sample was measured over a minimum of two half-lives. The kinetics were measured as a function of the disappearance of starting material under the pseudo-first order conditions using anthracene as an internal standard. The kinetic data are summarized in Table 2. In each case the data gave an excellent linear correlation ($R \geq 0.990$). As expected, the nitro compound (**1f**) had the shortest half-life (4.3 min) and the aniline derivative

Table 2
Kinetic data^a and bulk cyclization yields^b for the thermal cyclization of **1a–f**

Compound, Substituent	k, sec ⁻¹ (x 10 ⁻²)	$\tau_{1/2}$, min	corr ^c	Yield, %
1a , X = N(CH ₃) ₂	1.93	15.6	0.9977	63
1b , X = H	2.54	11.8	0.9900	-- ¹¹
1c , X = CO ₂ CH ₃	5.08	5.9	0.9949	78
1d , X = COCH ₃	4.66	6.5	0.9986	65
1e , X = CN	5.78	5.2	0.9915	60
1f , X = NO ₂	7.03	4.3	0.9987	59

^aT = 170 °C; [enediynes] = 6 mM; [1,4-CHD] = 600 mM; [anthracene] = 6 mM.

^bT = 170 °C; [enediynes] = 6 mM; [1,4-CHD] = 600 mM.

^cCorrelation coefficient from plot of ln([enediynes]_t/[enediynes]_{t=0}) vs. time.

(**1a**) had the longest half-life (15.6 min). The only apparently anomalous data came from ketone **1d** and ester **1c**. Although comparison of the parameters examined in this study show the electron-withdrawing potential of the ketone and ester are similar, in each case the ketone is the more electron-withdrawing of the two. However, the kinetics clearly show that while the half-lives of **1c** and **1d** were the closest of any two compounds, ketone **1d**, with a half life of 6.5 min cyclized slightly more slowly than ester **1c**, whose half-life was 5.9 min.

Individual Hammett plots were constructed for the σ_m , σ_p , σ_{jj} and σ_{mb} parameters. The coefficients for the field and resonance parameters of the Swain–Lupton model were determined using a two parameter regression algorithm.¹³ The results are summarized in Table 3. The best correlation was achieved using the Hammett σ_m value. This gave a Hammett constant of 0.654. None of the other parameters gave nearly the same correlation. In addition, since the H value for each parameter is 0.0, with the exception of *F*, where the value is 0.3, the intercept of the Hammett plot is expected to be 0.0. Again, the Hammett plot using σ_m has the intercept closest to its expected value. The Hammett constants and intercepts for σ_p , and σ_{mb} are quite similar, but still not as good as those for σ_m . The Swain–Lupton model gave a relationship of $0.662F + 0.227R$, with correlation comparable to σ_m .

Table 3
Slope (ρ), intercept and correlation from Hammett plots of **1a–f** versus various parameters

	σ_m	σ_p	σ_{jj}	σ_{mb}	<i>F</i> ^d	<i>R</i> ^d
Corr	0.992	0.958	0.307	0.954	0.994	0.994
ρ	0.654	0.350	-0.204	0.300	0.662	0.227
intercept	0.002	0.116	0.298	0.117		

^dcalculated from a dual parameter algorithm using Psi Plot.¹³

The results from the Hammett study indicate a linear free energy relationship between the rate of Bergman cyclization and the Hammett σ_m value as well as appropriate contributions from the field and resonance effects. The value of ρ from σ_m (0.654) is reasonable since the reaction goes

through uncharged transition states and intermediates. Also, the larger field parameter (0.662) versus the resonance parameter (0.227) from the Swain–Lupton model is reasonable since the developing diradical is orthogonal to the π -system. These results give a clearer insight into the factors which provide electronic control over the Bergman cyclization, and may provide a valuable design tool in the development of enediyne based drugs.

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12. **General procedure for kinetic studies:** A solution was made by dissolving the enediyne, methyl-3,4-diethynybenzoate (**1c**; 2.88 mg, 0.012 mmol), 1,4-cyclohexadiene (1.1 mL, 1.2 mmol, 100 equiv.) and an anthrathene internal standard (3.1 mg, 0.012 mmol) in chlorobenzene in a 2 mL volumetric flask. In each of 10 capillary melting point tubes was placed 40 μ L of the solution. The tubes were cooled to -78°C and degassed under high vacuum and sealed at same dead volume heights. Each tube was placed in an oil bath maintained at 170°C and removed at proper time intervals to obtain a suitable half-life for our studies. The content of each tube was analyzed by analytical HPLC (water:acetonitrile, isocratic 30:70) at 315 nm. The percent starting material remaining was plotted versus time and the resulting curve was fitted to a single exponential decay rate equation using the KaleidaGraph program on a Macintosh PC.
13. Psi Plot version 6.0. Poly Science International, Salt Lake City, UT, 1999.