Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 5392–5396
Bioorganic & Medicinal Chemistry Letters

Photoisomerization as a trigger for Bergman cyclization: Synthesis and reactivity of azoenediynes

Moumita Kar, Amit Basak* and Manish Bhattacharjee

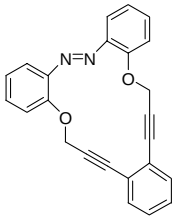
Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

Received 8 June 2005; revised 27 August 2005; accepted 2 September 2005

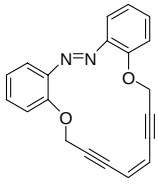
Abstract—Cyclic enediynes **1a** and **2a** containing stable *E*-azo moiety (azoenediynes) have been synthesized. These compounds upon irradiation with long wavelength UV isomerize to the *Z*-compounds **1b** and **2b**, which can be thermally reisomerized to the *Z* compounds. Reactivity studies toward BC using DSC predictably indicate higher reactivity for the *Z*-isomers. Our studies may provide a novel way to modulate the reactivity of enediynes under thermal or photochemical conditions.

Modulation of reactivity toward Bergman cyclization (BC) is an important aspect of research in enediynes.[1] From a chemists' standpoint, there could be various possibilities by which such modulations can be done. Incorporation of strain,[2] changing the hybridization,[3] complexation with metal ions,[4] pH,[5] light[6] or thiol-based deprotection[7] are some of the methods widely employed for enediyne activation. pH-based activation has become an extremely attractive strategy as one can utilize the intrinsic acidity of cancer cells. Pioneering work has been carried out in several laboratories.[5] In the area of triggering by metal ion complexation, Konig et al.[8] in a pioneering work reported that for a bipyridyl containing enediyne, the decrease in the distance between the acetylenic carbons undergoing covalent connection (c, d-distance) upon complexation with mercury (II) brings about a remarkable increase in its activity toward BC. We envisioned that similar conformational changes might be achieved if a group capable of switching between *E* and *Z* configurations is incorporated in an enediyne moiety. Azo compounds are well known to exist in two isomeric forms *Z* and *E*. Their reversible isomerization, induced by light or heat, has been exploited for photoresponsive host molecules,[9] polymers[10], and liquid crystals.[11] Very recently, a light driven hairpin formation in a peptide backbone has been achieved using azo functionality.[12] Consideration of all these led us to design two azo-based enediyne systems **1a** and **2a**. These molecules exist in the thermally stable *E*-configuration. Their photoisomerization to the *Z*-isomer and subsequent reactivity changes have been studied. These along with their synthesis and characterization are reported in this paper.

The synthesis of both the molecules involves bis-N alkylation of 2,2′-azo bis phenol with the corresponding dibromo enediynes **3** and **4** (Schemes 1 and 2).[13] While the aromatic fused



1a

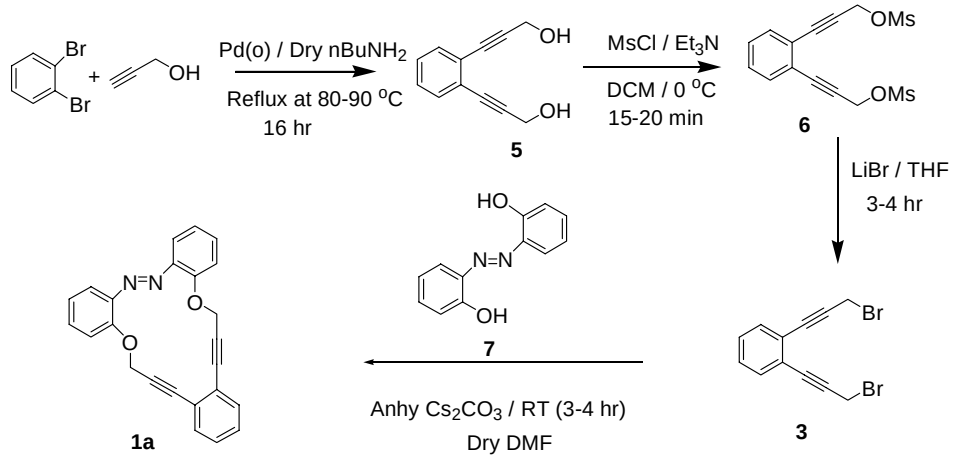


2a

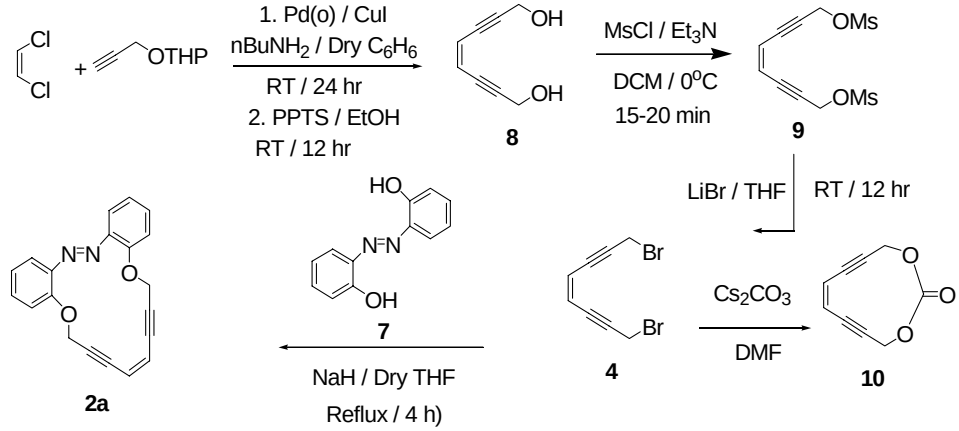
compound **1a** could be prepared using Cs_2CO_3 in DMF at room temperature and could be isolated pure by Si-gel chromatography as a red solid, the non-benzenoid compound could not be obtained under similar condition possibly because of the formation of a cyclic carbonate[14] (**10**) from the dibromo enediyne **4**. Thus, the alkylation condition had to be modified and the target molecule **2a** was finally obtained, also as a red solid, using NaH as base. Incidentally, the dibromides **3** and **4** were prepared from the dimesylates **6** and **9**, which were obtained from the diols **5** and **8**, respectively. The latter compounds (**5/8**) were prepared by a Pd

Keywords: Photoisomerization; Azoenediyne; Triggering; Bergman cyclization; Coupling.
* Corresponding author. Tel.: +91 3222 2833 00; fax: +91 3222 2822 52; e-mail: absk@chem.iitkgp.ernet.in

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.09.005



Scheme 1. Synthesis of aryl-fused enediyne **1a**.



Scheme 2. Synthesis of aryl-fused enediynes **2a**.

(0)-catalyzed Sonogashira coupling.[15] Both the azoenediynes were fully characterized by NMR and mass spectroscopy. For compound **1a**, ^{1}H NMR showed characteristic singlet for the methylene proton at δ 5.02, while the aromatic protons could be correctly assigned. For **2a**, the ene-hydrogens appeared at δ 5.9, while the methylenes resonated as a singlet at δ 5.04. From MM2 calculations using Spartan,[16] it was revealed that there is significant reduction of c, d-distance (the distance between the reacting acetylenic carbons) if the *E*-azo functionality isomerizes to the *Z* form (data shown in Table 1).

Having successfully synthesized the azoenediynes in the thermally stable E configuration, the UV spectra (Fig. 1) of both **1a** and **2a** were recorded before carrying out any photoisomerization. The molecules exhibited characteristic bands in three regions 220–260 nm (σ–σ^*), 300–350 (π–π^*), and 438–445 nm (n–π^*). The wavelength of π–π^* absorption region was selected as the irradiation wavelength.

The photoisomerization of the *E* to *Z* azoenediynes **1a** and **2a** was then studied (Scheme 3). Thus, their solutions in methanol (0.005 M) were separately irradiated with high pressure Hg lamp for 7 h. The color of the solution, which was initially red, changed to yellowish orange with time. The solvent was removed under cold condition (~15 °C) and ^{1}H NMR was recorded on the residue. The singlet for the methylene protons for the *E*-isomer **1a** decreased in intensity, while a new peak appeared at δ 4.7, which was assigned to the *Z* isomer. The ratio of the *Z* to *E* isomer was found to be 4:1. The NMR solution upon heating to 60 °C for 4 h showed complete disappearance of the *Z* isomer and reisomerization to the *E*-isomer took place. For **2a**, the methylene and the ene-hydrogens for the *Z*-isomer appeared at δ 4.71 and 5.85, respectively. Here again the thermal reisomerization from *Z* to *E* was observed. The kinetics of thermal reisomerization of *Z* to *E* in both the cases was studied. The reaction followed first order kinetics (NMR spectra shown in Fig. 2). The rate of conversion from *Z*-azo to *E*-azo was 1.4 times faster for the aryl fused enediyne (Table 1). This indicates that differential strain between the *Z* and *E* forms for **1a/1b** is more than that in **2a/2b**, which is also reflected in their difference of onset temperatures for BC.

The reactivity toward BC of these enediynes was then studied by Differential Scanning Calorimetry (DSC).[17]

Table 1. Results of MM2 calculations

Compound	c, d-distance (Å)	Minimized energy (kcal/mol)
1a	4.161	108.81
1b	3.846	121.93
2a	3.938	87.57
2b	3.861	101.80

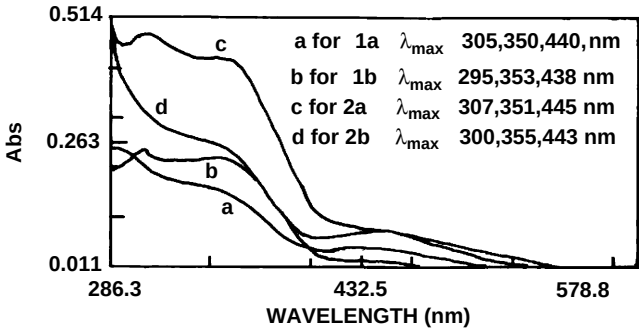


Figure 1. Absorption spectra of the various enediynes in the range of 300–500 nm.

The rate of heat supply was made faster for the *Z*-isomer so that the DSC could be recorded in a short time before significant isomerization can take place. The various onset temperatures for BC, shown in Table 2, clearly show higher reactivity for the *Z*-isomer as compared to the *E*-isomer (Fig. 3).[18]

In conclusion, we have synthesized two novel photoswitchable azo enediynes. The reactivity of these can be modulated by photochemical isomerization. Current studies are aimed toward synthesizing azoenediynes with a smaller ring size so that the photoisomerization can lead to a molecule capable of undergoing BC under ambient conditions.

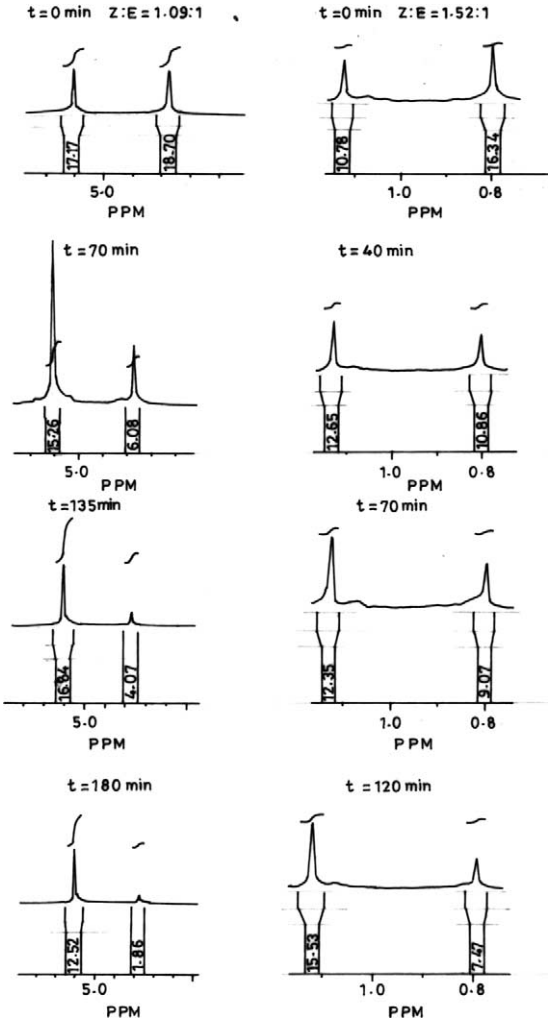
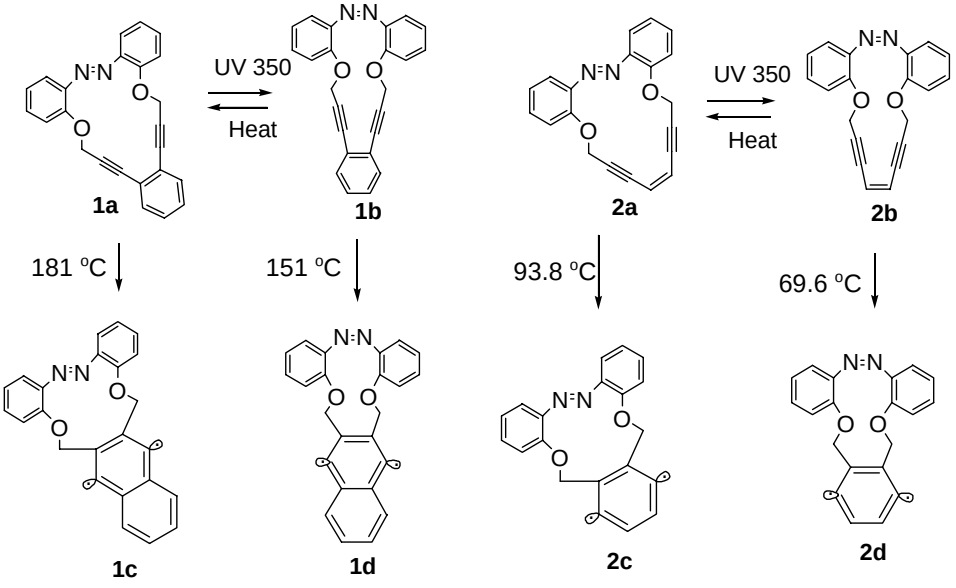


Figure 2. ^{1}H NMR at different time points for **1a** and **2a**.



Scheme 3. Photoisomerization of E-enediynes to Z-enediynes and respective thermal reactivities.

Table 2. Results of DSC and kinetics of *Z* to *E* conversion

Compound	Onset temperature for *E*-azo enediynes (T_E, °C)	Onset temperature For *Z*-azo enediynes (T_Z, °C)	ΔT ($T_E - T_Z$)	Rate constants for *Z* to *E* thermal isomerization (min^{-1})
1a	181		30	7.3×10^{-2}
1b		151		
2a	93.8		23.9	5.3×10^{-2}
2b		69.6		

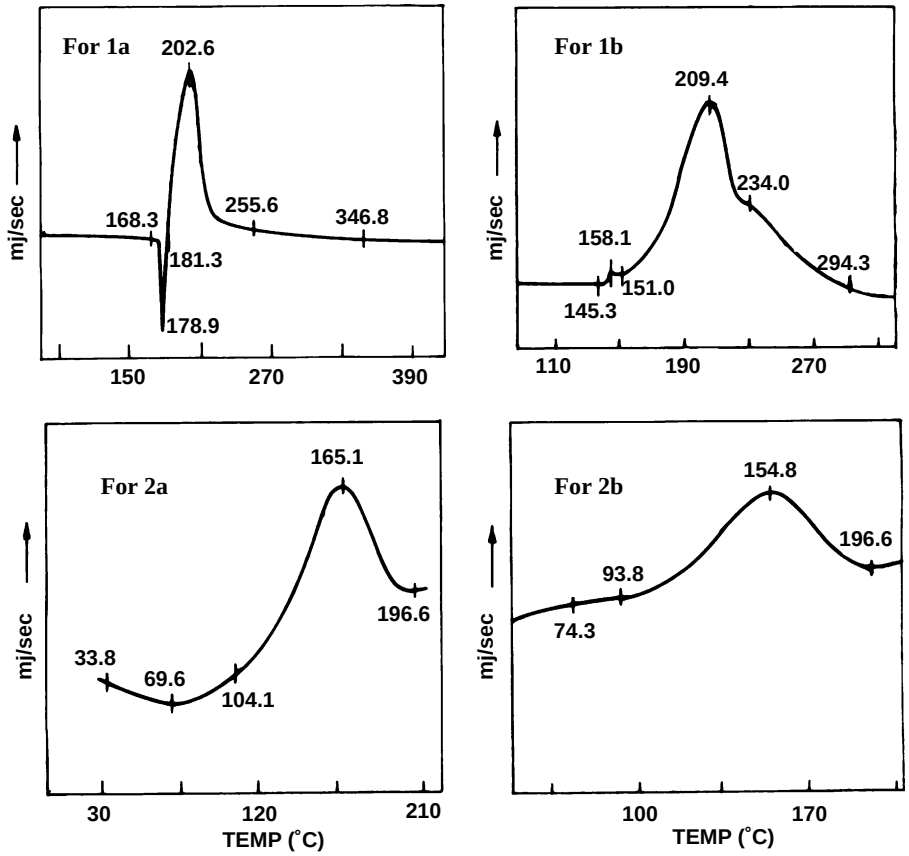


Figure 3. DSC curves of various enediynes **1a/1b** and **2a/2b**.

For **1a** δ_H (200 MHz $CDCl_3$) 7.80 (2H, d, $J = 1.66$ Hz aromatic-H) 7.44–7.34 (4H, m, aromatic-H), 7.26 (2H, q, $J = 3.2$, aromatic-H), 7.11 (2H, t, $J = 3.9$, aromatic-H), 7.06 (2H, d, $J = 8.31$, aromatic-H), 5.11 (4H, s, $2 \times CH_2$); δ_C (50 MHz, $CDCl_3$) 152.11 (quaternary C), 142.98 (quaternary C), 131.47 (CH), 131.23 (CH), 128.05 (quaternary C), 124.95 (CH), 124.01 (CH), 121.66 (CH), 114.14 (CH), 87.62 (acetylenic-C), 85.56 (acetylenic-C) 58.33 (CH_2); Mass (ES^+) *m/z* 365.16 (MH^+), 387.15 (MNa^+).

For **1b** δ_H (200 MHz, $CDCl_3$) 7.45–7.15 (6H, complex m, aromatic-H), 7.0 (2H, d, $J = 8.2$ Hz, aromatic-H), 6.85 (4H, m, aromatic-H), 4.79 (4H, s, $2 \times CH_2$).

For **2a** δ_H (200 MHz, $CDCl_3$) 7.78 (2H, d, $J = 1.82$ Hz, aromatic-H), 7.37 (2H, t, J = 1.43 Hz, aromatic-H), 7.11 (2H, t, $J = 1.16$ Hz, aromatic-H), 7.017 (2H, d, $J = 0.917$, aromatic-H), 5.86 (2H, s, ethylenic-H), 5.04 (4H, s, $2 \times CH_2$); δ_C (50 MHz, $CDCl_3$) 152.40 (quaternary C), 143.01 (quaternary C), 131.55 (CH), 123.66 (CH), 121.73 (CH), 119.52 (CH), 114.31 (ethylenic C), 91.426 (acetylenic C), 84.73 (acetylenic C), 58.49 (CH_2); Mass (ES^+) *m/z* 315.09 (MH^+), 337.07 (MNa^+).

For **2b** δ_H (200 MHz, $CDCl_3$) 7.29 (3H, m, aromatic-H), 7.20 (2H, m, aromatic-H), 7.03 (2H, m, aromatic-H), 7.01–6.8 (1H, m, aromatic-H), 5.84 (2H, s, ethylenic-H), 4.71 (4H, s, $2 \times CH_2$).

Acknowledgments

M.K. thanks Council of Scientific and Industrial Research (Govt. of India) for a Junior research fellowship. A.B. thanks Department of Science and Technology (Govt. of India) for financial support.

References and notes

1. (a) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995, p 203; (b) Maier, M. E. *Synletters* **1995**, 13; (c) Dai, W. M.; Nicolaou, K. C. *Angew Chem. Int. Ed. Engl.* **1991**, *30*, 1387; (d) Lhermite, H.; Grierson, D. *Contemp. Org. Synth.* **1996**, *3*, 93; (e) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453.
2. (a) Nicolaou, K. C.; Sorensen, E. J.; Discordia, R.; Hwang, C.-K.; Minto, R. E.; Bharucha, K. N.; Bergman, R. G. *Angew Chem. Int. Ed. Engl.* **1994**, *33*, 1044; (b) Banfi, L.; Guanti, G. *Angew Chem. Int. Ed. Engl.* **1995**, *34*, 2393; (c) Basak, A.; Khamrai, U. K.; Mallick, U. K. *J. Chem. Soc. Chem. Commun.* **1996**, 749.
3. (a) Magnus, P.; Fairhurst, R. A. *J. Chem. Soc. Chem. Commun.* **1994**, 1541; (b) Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367; (c) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Patterna, T.; Butta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.
4. (a) Basak, A.; Mandal, S.; Bag, S. S. *Chem. Rev.* **2003**, *103*, 4077; (b) Rawat, D. S.; Benites, P. J.; Incarvito, C. D.; Rheingold, A. L.; Zaleski, J. M. *Inorg. Chem.* **2001**, *40*, 1846; (c) Coalter, N.; Concolino, T. E.; Streib, W. E.; Hughes, C. G.; Rheingold, A. L.; Zaleski, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 3112; (d) Benites, P. B.; Rawat, D. S.; Zaleski, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7208; (e) Konig, B.; Rutters, H. *Tetrahedron Lett.* **1994**, *35*, 350; (f) Warner, B. P.; Miller, S. P.; Broee, R. D.; Buchwald, S. L. *Science* **1995**, *269*, 814.
5. (a) David, W. M.; Kerwin, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 1464; (b) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2000**, *122*, 8245; (c) Hoffner, J.; Schottelius, J. M.; Feichtinger, D.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 376; Alabugin, I. V.; Manoharan, M.; Kovalenko, S. V. *Org. Lett.* **2002**, *4*, 1119; Alabugin, I. V.; Manoharan, M. *J. Phys. Chem. A* **2003**, *107*, 3363; Basak, A.; Kar, M.; Mandal, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2061.
6. Basak, A.; Mandal, S.; Das, A. K.; Bertolasi, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 873; Schmittel, M.; Kiau, S. *Chem. Lett.* **1995**, 953.
7. (a) Basak, A.; Roy, S. K.; Mandal, S. *Angew Chem. Int. Ed.* **2005**; (b) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464; (c) Golik, J.; Clardy, J.; Dubay, G.; Groenwold, G.; Kawaguchi, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462; (d) De Voss, J. J.; Townsend, C. A.; Ding, W.-D.; Morton, G. O.; Ellestad, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9669; (e) De Voss, J. J.; Hangeland, J. J.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 4554; (f) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888; (g) Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908.
8. Konig, B.; Hollnagel, H.; Ahrens, B.; Jones, P. G. *Angew Chem. Int. Ed. Engl.* **1995**, *34*, 2538.
9. Shinkai, S.; Minami, T.; Kasano, Y.; Manabe, O. *J. Am. Chem. Soc.* **1983**, *105*, 1851; Vogtle, F. In *Supramolecular Chemistry An Introduction*; Wiley: Chichester, UK, 1989, Chapter 7.
10. Delaire, J. A.; Nakatani, K. *Chem. Rev.* **2000**, *100*, 1817.
11. Ichimura, K. *Chem. Rev.* **2000**, *100*, 1847.
12. Aemissegger, A.; Krautler, V.; van Gunstaren, W. F.; Hilvert, D. *J. Am. Chem. Soc.* **2005**, *127*, 2929.
13. (a) Bhattacharyya, S.; Pink, M.; Baik, Mu. H.; Zaleski, J. M. *Angew Chemie Int. Ed.* **2005**, *44*, 592; (b) Basak, A.; Bag, S. S.; Majumder, P. A.; Das, A. K.; Bertolasi, V. *J. Org. Chem.* **2004**, *69*, 6927; (c) Koenig, B.; Leue, S.; Horn, C.; Caudan, A.; Desvergne, J.-P.; Bouas-Laurent, H. *Liebigs Annalen* **1996**, 1231; (d) Hopf, H.; Jones, P. G.; Bubenitschek, P.; Werner, C. *Angew Chemie Int. Ed.* **1995**, *34*, 2367; (e) Koenig, B.; Fricke, T.; Dix, I.; Jones, P. G. *J. Chem. Res. Synop.* **1997**, 68; (f) Koenig, B.; Pitsch, W.; Thondorf, I. *J. Org. Chem.* **1996**, *61*, 4258.
14. Nuss, J. M.; Murphy, M. M. *Tetrahedron Lett.* **1994**, *35*, 37.
15. (a) Sonogashira, K.; Tohoda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467; (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627; (c) Crout, D. H. G.; Gaudet, V. S. B.; Laumen, K.; Schneider, M. *J. Chem. Soc. Chem. Commun.* **1986**, 808; Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831.
16. Spartan MM2 software presented to us on a limited day trial basis.
17. Konig, B.; Schofield, E.; Bubenitschek, P.; Jones, P. G. *J. Org. Chem.* **1994**, *59*, 7142.
18. This was in conformity to our theoretical predictions. It may be pointed out that the solution-phase kinetics for BC widely differs from the solid state reactivity. The rate of isomerization from *Z* to *E* is too fast in solution which prevented us from comparing the solution -phase reactivity of the two isomers. In the solid phase the rate of such isomerization was much slower, which allowed us to measure the onset temperature for BC for pure *Z* isomers by increasing the rate of heat supply. DSC measurement to follow the isomerization of *Z* to *E*-isomer of 2,2′-diallyloxy azobenzene expectedly showed a small exothermic peak starting at a high temperature of 143 °C. Thus, the exothermic peak associated with high heat change (possible for BC followed by polymerization) as seen in the DSC for the *cis*-azo compounds can be predicted to be due to BC.