Photoisomerization as a modulator of the DNA-cleaving efficiency of novel azo bispropargyl sulfones

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Novel azobenzene based bispropargyl sulfones have been prepared in the thermally stable E-form; irradiation with a high-pressure Hg lamp converted them to the Z-isomer which showed higher DNA-cleaving efficiency.

Bispropargyl sulfones have recently emerged as a new class of DNA-cleaving agents. They exert their activity via isomerization to the allenic sulfone, which subsequently alkylates the DNA bases, thus allowing a Maxam–Gilbert type cleavage to take place. An alternative pathway, though usually not followed, is the formation of diradicals from the bisallenic sulfone via Garratt–Braverman rearrangement and subsequent oxidative DNA damage. It is important to note that diradical formation can take place only if the sulfone gets isomerized to the bisallen, which in many cases may not be possible for stereoelectronic reasons.

Since monoallenic sulfones show their DNA cleavage activity via an alkylation pathway, they may be inferior in terms of their DNA-cleaving efficiency when compared to the bisallenic sulfones (as the latter can have dual mechanisms for cleavage, namely mono or bis-alkylation, as well as oxidative damage through diradicals). Modulation of the reactivity of bispropargyl sulfones has not drawn much attention, unlike the enediyne counterpart. The only triggering device that is used is the variation of pH, which is kept in the alkaline range. Dai et al. has recently exploited photoelectron transfer to enhance the DNA cleaving potency of monopropargyl sulfones. Recently, we have shown how a photochemical E to Z isomerization can activate azoenediynes towards Bergman cyclization (BC). We were curious to know what happens to the reactivity of azo bispropargyl sulfone systems upon such E–Z photoisomerization. Our curiosity arises from the fact that the kinetics of BC are dependent upon the distance between the terminal acetylenic carbons which presumably is less in Z-azo enediynes. In a similar argument, the reactivity of the Z-azo bispropargyl sulfones may be higher, as the allenic carbons (formed by isomerization) should come closer, compared to the corresponding E-system, and are thus geared towards Garratt–Braverman cyclization. Thus, we would like to address the following points: does the configuration of the azo moiety (E or Z) affect the rate of isomerization to the monoallen and subsequently to the bisallen? Does it induce any change in DNA-cleaving efficiency and also any change in the DNA-cleaving mechanism? All these possibilities are summarized in Scheme 1.

In order to have an answer, we synthesized the E-azobenzene sulfones 1 and 2 (Fig. 1). These have been successfully photoisomerized to the Z-sulfones 3 and 4. The reactivity of these isomers in presence of a base (triethylamine) as well as their DNA-cleaving ability under alkaline pH revealed interesting results, which are described in this Communication.

The starting material for the synthesis of both the sulfones was the commercially available 2,2′-bishydroxy azobenzene (5). This was bisalkylated with butyne-1,4-diol mono tosylate (7) in the presence of K2CO3 and DMF. The resulting diol 8, isolated in 70% yield, was converted to the dimesylate 9 and the cyclic sulfide 10 was obtained when the dimesylate was treated with Na2S, preabsorbed in alumina (neutral) in CH2Cl2. The sulfide was then oxidized with mCPBA to the sulfone 1 which was isolated as a
yellow solid after purification by chromatography (Scheme 2). The formation of the sulfone was confirmed by the appearance of two 4H singlets in the 1H NMR spectrum. The sulfoxide 11 which could also be isolated when the oxidation was carried at 0 °C for a short time gave a typical AB quartet for the methylene attached to sulfur.

For the synthesis of the vinylogous sulfone 2 (Scheme 3), the mesylate 16 was first prepared from partially THP-protected butyne-1,4-diol 12. The alcohol was oxidized to the aldehyde 13 with Dess Martin reagent° and the aldehyde was subjected to Wittig reaction with phosphonium ylide derived from ethyl bromoacetate. The trans ester 14 isolated in high yield (90%) was reduced to the alcohol 15 with DIIBAL-H. The latter was then converted to the mesylate 16 which was used as the alkylation partner. However, in this case the monoalkylated product 17 was the major product even after prolonged hours of stirring at 50 °C. The expected biscoupled product 18 was isolated in very poor yield (~5%) which could not be processed any further. The mono-coupled product was then converted to the unsymmetrical bis-alkylated product 19 using the butyne-1,4-diol tosylate which turned out to be a more reactive system. The resulting diol 20, obtained after PPTS-deprotection of THP-ether was then converted to the sulfide 22 via the mesylate 21. Oxidation with mCPBA finally afforded the target sulfone 2. Gratifyingly, the double bond remained intact during the peracid oxidation.

Having successfully prepared the target sulfones,° we turned our attention to study the effect of UV-irradiation on these molecules. For this, the sulfone 1 in CH₂Cl₂ (0.005 M) was irradiated with a high pressure Hg lamp for 3 h. 1H-NMR showed the occurrence of isomerization from E to Z (a ratio of 1 : 3), as confirmed by the appearance of new singlets at δ 4.59 and 3.96. Upon heating at 60 °C for 2 h these signals disappeared, leaving only the signals for the starting E-isomer. 1H-NMR based kinetic study at 37 °C showed the first order rate constant for thermal Z to E isomerization to be $5 \times 10^3$ min⁻¹. The other E-sulfone 2 behaved similarly when its methanol solution was irradiated for 3 h; in this case the ratio of E to Z isomer was also 1 : 3. The formation of the Z-isomer was indicated by the appearance of three new singlets at δ 4.90, 4.76 and 4.10. The Z-isomer can be thermally reisomerized back to the E isomer; the rate of thermal reisomerization was, however, much slower ($k = 3 \times 10^2$ min⁻¹).

The chemical reactivity of the sulfones 1 and 3 were then evaluated (Scheme 4). For this, a CDCl₃ solution of the sulfone was taken and triethylamine (1.5 eq.) added and the progress of reaction monitored by 1H-NMR. The E-sulfone 1 rapidly forms the monoallene, after which there was no further reaction and we ended up with an equilibrium mixture of 1 and its monoallenic counterpart (ratio 1 : 1). The formation of monoallene was confirmed by formation of only the mono methanol adduct (yield ~30%) when the experiment was run in presence of MeOH at 37 °C for 12 h. In the monoallene, the methylene attached to the
The results showed the higher cleavage reactivity of azo based bis propargyl sulfones. Currently, we are trying to design molecules for which the thermal reisomerism is slower as compared to those reported herein, by incorporating some strain parameters. Our strategy may find use in the development of anticancer molecules involving photodynamic therapy.  

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**Notes and references**

9. Selected spectral data (all 1H and 13C NMR were recorded at 200 and 50 MHz, respectively, in CDC13 unless mentioned otherwise). For I: δH 7.72 (1H, dd, J = 1.5 Hz, 8.5 Hz), 7.45 (2H, dt, J = 1.8, 7.5 Hz), 7.21 (4H, m), 4.93 (4H, s), 3.75 (4H, s); δC 154, 145, 131.9, 123.4, 119.6, 119, 83, 74, 60.3, 43.3: HRMS caled for C20H20N2O4S+H + 381.09101 found 381.09102. For δ4 (1H, d, J = 1.5 Hz, 8.5 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.42 (2H, m), 7.18 (3H, m), 6.30 (1H, d, J = 16 Hz), 6.10 (1H, d, J = 8.4 Hz), 4.98 (2H, s), 4.65 (2H, d, J = 5.0 Hz), 4.03 (4H, s); HRMS caled for C20H20N2O4S+H + 381.09101 found 381.09102. For δ7 (1H, d, J = 8.4 Hz), 7.45 (1H, t, J = 7.6 Hz), 7.25 (2H, m), 7.06 (2H, m), 6.84 (2H, d, J = 8.24 Hz), 4.59 (4H, s), 3.96 (4H, s); HRMS caled for C20H20N2O4S+H + 381.09101 found 381.0880. For δ8 (1H, d, J = 7.6 Hz), 7.59 (1H, d, J = 8.24 Hz), 7.38 (2H, s), 6.9 (3H, m), 6.31 (1H, dt, J = 2 Hz, 16 Hz), 6.11 (1H, d, J = 16 Hz), 4.90 (2H, bs), 4.76 (2H, bs), 4.10 (4H, bs); HRMS caled for C20H20N2O4S+H + 381.09101 found 381.0880.
10. Braverman has recently reported that the rearrangement to the thiophene dioxides is more facile by incorporating additional conjugation to the propargyl system. For the reference see Y. Zafarani, H. E. Gottlieb, M. Sprecher and S. Braverman, *J. Org. Chem.*, 2005, 70, 10166. This was the rationale for designing sulfone 2.
11. The cleavage efficiency was approximately 2.5 times for the Z-isomer than that for the E-isomer. This was determined by checking the relative UV-absorbance of the bands at 280 nm. It is to be noted that the control DNA specimen is usually contaminated with some nicked form (form II).