DOI: 10.1002/chem.200900521

Macrocyclic Disulfides for Studies of Sensitized Photolysis of the S-S Bond

Zhen Huang,^[a, b] Qing-Zheng Yang,^[a, b] Timothy J. Kucharski,^[a] Daria Khvostichenko,^[a] Steven M. Wakeman,^[a] and Roman Boulatov^{*[a]}

Sensitized photolysis of the disulfide bond underlies phenomena as diverse as quenching of indole fluorescence in proteins,^[1] photocuring of polymers^[2] and degradation of atmospheric pollutants. In addition, it is used to trigger rapid conformational changes in biophysical studies^[3] and to study transport phenomena in solids.^[4] Fundamental understanding of the mechanism of this process offers an opportunity to gain molecular insight in these phenomena.

Mechanistic studies of sensitized photolysis of the S-S bond have traditionally relied on intermolecular quenching of fluorescence of various polvaromatic hydrocarbons by disulfides. This approach is experimentally simple but allows no control over the separation and relative orientation of the fluorophore and the quencher or the conformational mobility of the generated thiyl radicals.^[5,6] Such control is essential, for example, for differentiating various mechanisms of energy transfer from the sensitizer to the S-S bond.^[7] To address these limitations we designed a series of macrocyclic disulfides incorporating stiff stilbene (bold, Scheme 1) as the photosensitizer. The small size of these macrocycles prevents photoisomerization of stiff stilbene, thus favouring other pathways of electronic relaxation. The average photosensitizer/quencher separation and the range of motion accessible to the resultant thiyl radicals are controlled by the length and the conformational flexibility of the linkers, X.

Stiff stilbene offers important advantages over the polyaromatic hydrocarbons typically used to study sensitized disulfide photolysis. First, its synthetic elaboration is simpler

[a]	Z. Huang, Dr. QZ. Yang, T. J. Kucharski, Dr. D. Khvostichenko,
	S. M. Wakeman, Prof. R. Boulatov
	Department of Chemistry, University of Illinois
	Urbana, IL 61801 (USA)
	Fax: (+1)217-244-3186
	E-mail: boulatov@uiuc.edu
r1 1	

 [b] Z. Huang, Dr. Q.-Z. Yang These authors made an equal contribution to this work.
 Supporting information for this article is available on the WWW

under http://dx.doi.org/10.1002/chem.200900521.



Scheme 1. Structures of disulfides 1–4 and their reactions when irradiated in cyclohexene or cumene; k is the rate constant of disulfide disappearance, I is the photo flux and ε_{ss} is the molar absorptivity of (Z)-stiff stilbene disulfide (See supporting information). Compounds **A** and **B** are transparent at 365–375 nm and do not isomerize to the Z form. The Cbased radical **R**' was not observed.

than that of many polyaromatics such as pyrene. Second, the absorption of the (Z)-stilbene derivative extends above 350 nm, where the S-S bond is transparent, thus avoiding its direct photolysis. Third, upon S-S bond homolysis, $Z \rightarrow E$ photoisomerization of stiff stilbene proceeds with a high quantum yield and is accompanied by significant hypsochromic shift, which eliminates secondary photoreactions by making the primary products transparent to the incident irradiation. The major limitation of stiff stilbene-photosensitizer is its relatively high internal conversion rates, aqueous insolubility, and photobleaching in the presence of free radical traps (Figure S7).

We synthesized **1–4** (Scheme 1) in six steps and 10–20% overall yield from C6-substituted indanones (Figure S1).

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Chem. Eur. J. 2009, 15, 5212-5214

Facile intramolecular McMurry coupling of two indanones connected by a short ester linker yielded exclusively (*Z*)-stilbene derivative.^[8] Reduction of the ester followed by the conversion of the diol to dibromide and subsequently to dithiol gives, upon oxidation with I₂ under dilute conditions, disulfides **1–4**. Oxidation proceeds cleanly without oligomerization, which often complicates syntheses of macrocyclic disulfides,^[9,10] reflecting the conformational rigidity of the stiff stilbene. This methodology allows easy access to many other macrocyclic disulfides and allows for a systematic study of sensitized S–S bond photolysis.

The chemical identity and purity of **1–4** were confirmed by ¹H NMR spectroscopy, high-resolution MS and HPLC measurements (see Supporting Information pp. S8–S10).^[11] The UV/Vis spectra of **1–4** (Figure 1A and S3) are typical of



Figure 1. A) UV/Vis spectral change during photolysis of **4** in cyclohexene at 375 nm, -10° C and the photon flux of 3 mmol m⁻² s⁻¹. Isosbestic points: 343, 350, and 360 nm. B) The absorbance of **4** (shown at $\lambda =$ 365 nm as example) decays exponentially with time with the rate constant k [Eq. (1)]. The red curve is the least-squares fit.

(Z)-stiff stilbene with an absorption band at ~350 nm arising from the π - π * transition. The σ - σ * transition of the disulfide moiety occurs at < 300 nm in **2–4**. In **1**, it probably accounts for a relatively strong absorption band at 310 nm, which would suggest a distortion of the C-S-S-C dihedral from its preferred 90° value.^[12]

Irradiation of 60 μ M solutions of **1–4** in cyclohexene or cumene (good H donors) at ~370 nm resulted in a gradual appearance of the (*E*)-stiff stilbene chromophore (Figure 1 and S5),^[13] indicating cleavage of the macrocycles. We analysed the reaction mixtures by reverse-phase HPLC, isolated the major components and characterized them by ¹H NMR and HRMS (see Supporting Information, pp. S12–S22).^[11] The major products were thiol/thioether **A** (Scheme 1) in cyclohexene and dithiol **B** in cumene. Irradiation of **1** in cyclo

hexene generated, besides **A** and **B**, vicinal thioethers **C**. Irradiation of **1** in cumene was complicated by photobleaching (Figure S8) and was not studied extensively. Under identical conditions irradiation of dibenzyl disulfide in cyclohexene gave no reaction, confirming the negligible importance of direct S–S bond photolysis in **1–4**.

The observed products are consistent with the known chemistry of thiyl radicals. Dithiol **B** is expected to result from each thiyl radical abstracting H atom from the same or different solvent molecules. Thiol/thioether **A** probably arose from H abstraction by one thiyl radical followed by recombination of the resultant α -allylic radical with the other thiyl group generated from the same disulfide. Such recombination is suppressed in more sterically hindered cumene, accounting for the dominance of dithiol **B**. The formation of **C** illustrates how conformational constraints affect reaction paths available after S–S bond photolysis: addition of acyclic thiyl radicals to the C=C bond never results in vicinal thioethers. Whereas direct photolysis of disulfides leads to both S–S and C–S cleavage,^[14] we did not observe products of the S–C bond scission in **1–4**.^[5]

The disappearance rate of **1–4** was first-order in the disulfide, zero-order in the H donor (when present at $\geq 2 \,\mathrm{M}$ concentration in hexanes), proportional to the photon flux and exponentially temperature-dependent. The photon-flux dependence of the rate reflects the quantum efficiency of sensitized S–S bond photolysis, ϕ_{photo} (Scheme 1; see page S24^[11] for further discussion). The activation energies, E_a , were obtained from measurements at five temperatures between –10 and 45 °C (Table 1 and Figure S9). Because the

Table 1. Kinetics of sensitized S-S bond homolysis in 1-4.

Disulfide	H donor	$\phi_{\mathrm{photo}} k_{\mathrm{RH}}^{\mathrm{[17]}} / k_{\mathrm{rec}}^{\mathrm{[a]}}$	$E_{\rm a} [m kcal mol^{-1}]$	$\phi_{\rm rel}{}^{[b]}$
1	cyclohexene	$(17\pm1) \times 10^{-4}$	4.3 ± 0.2	1
2	cyclohexene	$(1.44{\pm}0.01){\times}10^{-4}$	2.7 ± 0.1	10^{-2}
2	cumene	$(0.59 \pm 0.01) \times 10^{-4}$	3.8 ± 0.1	10^{-2}
3	cyclohexene	$(0.65 \pm 0.02) \times 10^{-4}$	2.1 ± 0.2	10^{-3}
4	cyclohexene	$(3.22\pm0.02)\times10^{-4}$	2.8 ± 0.1	10^{-2}

[a] At 45 °C. [b] Relative to ϕ_{photo} of **1**.

recombination of thiyl radicals is barrierless^[15,16] for each disulfide measured, E_a is a sum of the activation energies of the sensitized S–S bond photolysis and of H-atom abstraction. Since measured E_a values are at the low end of the reported activation energies of H atom abstraction by alkyl thiyl radicals (3–8 kcalmol⁻¹, p. S25^[11]), sensitized photolysis of the S–S bond in **1–4** must contribute <1 kcalmol⁻¹.

Assuming that the measured activation energies arise solely from the H-abstraction step, we estimated the relative quantum yields of the photosensitized S–S bond homolysis in macrocyclic disulfides 1–4, ϕ_{rel} (Table 1). Consistent with the assumption, the estimated values of ϕ_{rel} were independent of H donor. To gain further insights into the observed trend in ϕ_{rel} we calculated all conformers of 1–4 at the PW91P86/cc-pVTZ level of DFT (Table S4). In the series of homologous disulfides, 1–3, the quantum yield of sensitized

www.chemeurj.org

photolysis decreases exponentially with the Boltzmann-averaged separation between the S–S bond and stiff stilbene (Figure S10 and Table S5), which could be consistent with a superexchange mechanism^[17] of the proposed electron-transfer mechanism of sensitization.^[18] The structural motifs described here allow this hypothesis to be tested broadly.

Acknowledgements

The work was supported by the NSF, US AFOSR, the PRF, the University of Illinois. Predoctoral fellowships from the Bailar fund (Z.H.), ONR and NSF (T.J.K.) are gratefully acknowledged. NSF NCSA provided grants of computational time. We thank Drs. Olson and Xu of Protasis/ MRM Corp. for granting access to a CapNMR probe and assistance in using it for the analysis of photolysis products.

Keywords: hydrogen transfer • macrocycles • photolysis • radicals • reaction mechanisms

- [1] W. Qiu, L. Wang, W. Lu, A. Boechler, D. A. R. Sanders, D. Zhong, *Proc. Natl. Acad. Sci. USA* 2007, 104, 5366.
- [2] H. F. Gruber, Prog. Polym. Sci. 1992, 17, 953.
- [3] C. Kolano, J. Helbing, G. Bucher, W. Sander, P. Hamm, J. Phys. Chem. B 2007, 111, 11297.
- [4] Z. B. Alfassi, S-centered radicals, Wiley, New York, 1999.
- [5] W. L. Wallace, R. P. Van Duyne, F. D. Lewis, J. Am. Chem. Soc. 1976, 98, 5319.

- [6] L. B. Barrón, K. C. Waterman, P. Filipiak, G. L. Hug, T. Nauser, C. Schoneich, J. Phys. Chem. A 2004, 108, 2247.
- [7] W. Qiu, T. Li, L. Zhang, Y. Yang, Y.-T. Kao, L. Wang, D. Zhong, *Chem. Phys.* **2008**, 350, 154.
- [8] J. E. McMurry, Chem. Rev. 1989, 89, 1513.
- [9] J. Houk, G. M. Whitesides, J. Am. Chem. Soc. 1987, 109, 6825.
- [10] S. Otto, R. L. E. Furlan, J. K. M. Sanders, Science 2002, 297, 590.
- [11] See Supporting Information.
- [12] D. B. Boyd, J. Am. Chem. Soc. 1972, 94, 8799.
- [13] K. Ogawa, H. Suzuki, M. Futakami, J. Chem. Soc. Perkin Trans. 2 1988, 39.
- [14] A. Joshi, G. C. Yang, J. Org. Chem. 1981, 46, 3736.
- [15] S. J. Klippenstein, Y. Georgievskii, L. B. Harding, *Phys. Chem. Chem. Phys.* 2006, 8, 1133.
- [16] B. C. Garrett, D. A. Dixon, D. M. Camaioni, D. M. Chipman, M. A. Johnson, C. D. Jonah, G. A. Kimmel, J. H. Miller, T. N. Rescigno, P. J. Rossky, S. S. Xantheas, S. D. Colson, A. H. Laufer, D. Ray, P. F. Barbara, D. M. Bartels, K. H. Becker, K. H. Bowen, S. E. Bradforth, I. Carmichael, J. V. Coe, L. R. Corrales, J. P. Cowin, M. Dupuis, K. B. Eisenthal, J. A. Franz, M. S. Gutowski, K. D. Jordan, B. D. Kay, J. A. LaVerne, S. V. Lymar, T. E. Madey, C. W. McCurdy, D. Meisel, S. Mukamel, A. R. Nilsson, T. M. Orlando, N. G. Petrik, S. M. Pimblott, J. R. Rustad, G. K. Schenter, S. J. Singer, A. Tokmakoff, L.-S. Wang, T. S. Zwier, *Chem. Rev.* 2005, 105, 355.
- [17] Y.-T. Long, E. Abu-Irhayem, H.-B. Kraatz, Chem. Eur. J. 2005, 11, 5186.
- [18] Y. Chen, M. D. Barkley, Biochemistry 1998, 37, 9976.

Received: February 25, 2009 Published online: April 9, 2009

5214 —