J|A|C|S
COMMUNICATIONS

Published on Web 10/18/2006

Control of Pyramidal Inversion Rates by Redox Switching

Mark W. Davies,[†] Michael Shipman,*[,†] James H. R. Tucker,*[,‡] and Tiffany R. Walsh[†,§]

Department of Chemistry and Centre for Scientific Computing, University of Warwick, Coventry, CV4 7AL, U.K., and School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, U.K.

Received July 25, 2006; E-mail: m.shipman@warwick.ac.uk; j.tucker@bham.ac.uk

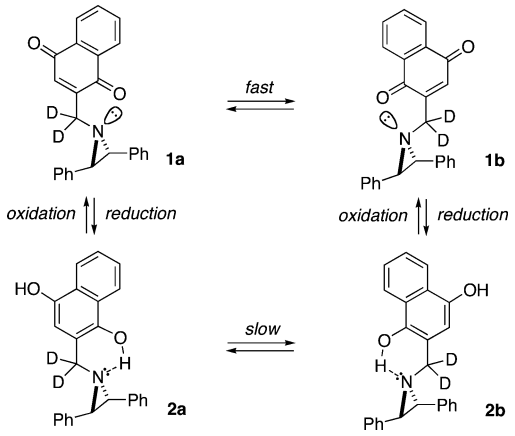
Redox switching provides one of the methods through which external control can be exerted over devices that operate at the molecular level.[1,2] Redox-switched binding is well established[3] and enables the strength of a binding interaction to be controlled by oxidation or reduction. Moreover, it has been shown that switchable binding can lead to external control of molecular motion, such as in interlocked structures. However, examples where an external input controls the *rate* at which motion occurs, be it a rotary[4] or a shuttling[5] process, are much rarer. Here we demonstrate how the dynamics of the motion associated with pyramidal inversion[6] can be controlled by redox switching.

A number of factors led to the design and construction of redox responsive aziridines **1** and **2**. First, upon reduction of the naphthoquinone unit to the corresponding 1,4-dihydroxynaphthalene (i.e., **1** → **2**, Scheme 1), it was anticipated that the formation of an intramolecular hydrogen bond between the lone pair of the pyramidal nitrogen atom and the adjacent phenolic OH group would raise the energy barrier for nitrogen inversion to a significant extent. Support for this hypothesis can be found in the work of Drakenberg and Lehn, who demonstrated that proton donating solvents markedly increase *N*-inversion barriers in simple aziridines (12−21 kJ mol^{-1}).[7] Second, kinetic parameters for the relatively slow pyramidal nitrogen inversion in aziridine-based systems (in this case, **1a** ⇆ **1b** and **2a** ⇆ **2b**) can be measured readily by dynamic NMR spectroscopy.[6,8] Third, reoxidation of 1,4-dihydroxynaphthalenes is well-documented,[9] suggesting that cycling between the oxidation states might allow reversible, external control over the rate of pyramidal inversion in this and related systems.

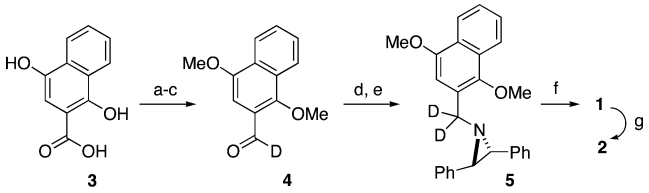
The synthesis of 1,4-naphthoquinone **1** was achieved in six steps from 1,4-dihydroxynaphthalene-2-carboxylic acid **3**. Exhaustive methylation of **3**, reduction to the primary alcohol with $LiAlD_4$, and reoxidation with pyridinium chlorochromate provided deuterated aldehyde **4** (Scheme 2). Reductive alkylation of **4** with (1*S**,2*R**)-2-amino-1,2-diphenyl-ethanol[10] using $NaBD_4$ yielded the corresponding amino alcohol which was closed to aziridine **5** using DIAD/PPh_3.[11] The introduction of the two deuteriums at the benzylic position was necessary to simplify the ^{1}H NMR spectra of **1** and **2** in the region of the aziridine resonances. In this way, better quality data could be obtained from dynamic NMR experiments (vide infra). To complete the synthesis, demethylation of **5** with concomitant oxidation to 1,4-naphthaquinone **1** was accomplished using the method of Syper et al.[12] Quantitative reduction of **1** to **2** was achieved using $Na_2S_2O_4$ in Et_2O/H_2O (1:1) under strictly anaerobic conditions.

To establish whether the rates of pyramidal inversion in **1** and **2** were substantially different, and to ascertain whether switching between these systems could be achieved in a reversible manner, the following in situ NMR experiment was conducted. The ^{1}H NMR

Scheme 1. Redox Control of Inversion Rates



Scheme 2. Synthesis of Aziridines **1** and **2**[a]



[a] Conditions: (a) K_2CO_3, Me_2SO_4, propanone, reflux, 97%; (b) $LiAlD_4$, THF, 50 °C; (c) PCC, CH_2Cl_2, 62% over two steps; (d) (1*S**,2*R**)-2-amino-1,2-diphenyl-ethanol, MeOH, $NaHCO_3$, reflux then $NaBD_4$, 0 °C; (e) PPh_3, DIAD, THF, 0 °C → room temperature, 59% over two steps; (f) AgO, pyridine-2,6-dicarboxylic acid *N*-oxide, MeCN/H_2O (7:3), 0 °C, 71%; (g) $Na_2S_2O_4$, degassed Et_2O/H_2O (1:1).

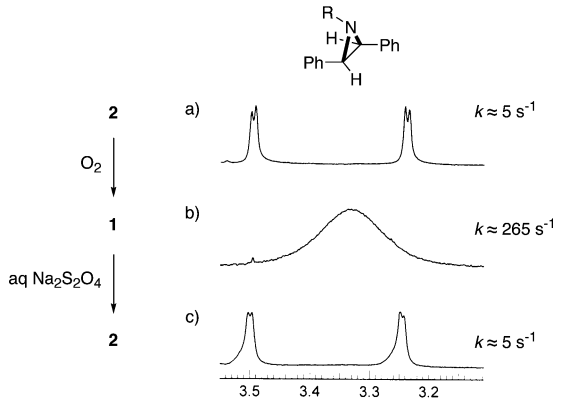
spectrum of a freshly prepared sample of **2** in *o*-xylene-d_{10}, 0.025 M at 332 K, was recorded (Scheme 3). The observation of two doublets at 3.49 and 3.23 ppm, assigned to the nonequivalent hydrogens of the aziridine ring, indicated that pyramidal inversion was slow on the NMR time scale. Bubbling molecular oxygen directly through the NMR sample resulted in oxidation to 1,4-naphthaquinone **1**, whose spectrum was again recorded at 332 K. Notably, now only a single broad resonance, centered at 3.33 ppm and integrating to two hydrogens, was observed for the aziridine hydrogens, indicating fast exchange on the NMR time scale. To complete the redox cycle, aqueous sodium dithionite was then added to facilitate reduction to 1,4-dihydroxynaphthalene **2**. As expected, the two signals pertaining to the nonequivalent aziridine hydrogens re-emerged. Inversion rate constants of 265 s^{-1} and 5 s^{-1} for **1** and **2**, respectively, at 332 K were calculated from additional VT−NMR experiments (vide infra). Thus, a >50-fold change in the rate of pyramidal inversion is achieved by application of this redox switch.

Quantitative data for the pyramidal inversion process for **1**, **2**, and **5** were obtained by recording the ^{1}H NMR spectra of each compound in *o*-xylene-d_{10} over a range of temperatures (279−380

[†] Department of Chemistry, University of Warwick.
[‡] University of Birmingham.
[§] Centre for Scientific Computing, University of Warwick.

10.1021/ja065325f CCC: $33.50

Scheme 3. Measurement of Inversion Rates in **1** and **2**[a]



[a] ^{1}H NMR spectra recorded at 500 MHz in *o*-xylene-d_{10} at 332 K: (a) 1,4-dihydroxynaphthalene **2**; (b) after in situ oxidation to 1,4-naphthaquinone **1** with molecular O_2; (c) after reduction to 1,4-dihydroxynaphthalene **2** with aqueous sodium dithionite.

Table 1. Measured and Calculated Activation Parameters for the Pyramidal Inversion Process in **1**, **2**, and **5**

	experimental values[a]			calculations[b]
aziridine	$\Delta G^{\ddagger}$ [c] (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})	$\Delta G^{\ddagger}$ [c] (kJ mol^{-1})
1	66.5	68.1	5.5	53.7
2	78.2	88.9	35.8	76.4
5	64.0	62.6	−4.6	53.9

[a] Determined using variable temperature NMR data (500 MHz in *o*-xylene- d_{10}) in conjunction with line shape analysis and Eyring plots. [b] Obtained using a density-functional theory based method. [c] At 298 K.

K) below and above the coalescence temperature of the aziridine hydrogen signals. In conjunction with dynamic line shape simulations of the aziridine AX spin system performed using WINDNMR,[13] the rates of exchange over a range of temperatures were obtained. Activation parameters extracted for each aziridine using Eyring plots [ln (k/T) vs 1/T] are presented in Table 1. The measured inversion barriers fall within the typical range for 2,3-disubstituted aziridines.[6] Consistent with our findings above, the Gibbs free energy of activation ($\Delta G^{\ddagger}$ at 298 K) for the inversion process for **2** is appreciably higher than that for **1** (11.7 kJ mol^{-1}). Furthermore, the data indicate that the decrease in nitrogen inversion rate upon reduction is enthalpically driven. Such a scenario is consistent with the ground-state of **2** being stabilized relative to **1** by the internal H-bond formed by the C-1 hydroxyl group, but with cleavage of this bond being required to surmount the energy barrier for *N*-inversion. Several pieces of data support this notion: (1) the inversion barrier for **5**, wherein the hydroxyl groups are blocked as methyl ethers, is very similar to naphthaquinone **1** (Table 1); (2) the two hydroxyl groups in **2** are observed at very different chemical shifts (10.82 and 3.87 ppm) and are fully consistent with one of them participating in H-bonding;[14] (3) the increase in the enthalpy of activation for **2** compared with **1** and **5** is similar to the strength of an intramolecular H-bond in a six-membered ring;[15] (4) the entropy of activation is more positive for **2**, indicating that the ground state of this aziridine is more ordered with respect to its transition state than **1** or **5**.

Calculated inversion barriers determined using density-functional theory (DFT) (see Supporting Information) bear out the same trend as the experimental values (Table 1). The discrepancies with experiment for **1** and **5** are ascribed to inherent deficiencies of DFT, namely that dispersion interactions are known to not be reliably recovered using these methods.[16] Unlike **2**, the intramolecular interaction in **1** and **5** will be mostly due to dispersion. Neglect of dispersion leads to a rise in total energy for the minima of **1** and **5** (with respect to their transition-states), and therefore yields a smaller barrier than expected compared with **2**.

To conclude, it has been successfully demonstrated that the rate of exchange between two *N*-invertomers can be controlled by redox switching. Future work is aimed at establishing whether umbrella motion can be controlled by other external inputs, with the aim of developing new types of molecular device.

Acknowledgment. This work was supported by the Leverhulme Trust (Grant No. F/00215/U). Computing resources at the Centre for Scientific Computing at Warwick are gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data; VT NMR studies and DFT calculations for **1**, **2**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For definitions and recent examples of various redox-switched processes, see (a) Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, Germany, 1995. (b) Feringa, B. L. *Molecular Switches*; Wiley-VCH: Weinheim, Germany, 2001. (c) Sporer, C.; Ratera, I.; Ruiz-Molina, D.; Zhao, Y. X.; Vidal-Gancedo, J.; Wurst, K.; Jaitner, P.; Clays, K.; Persoons, A.; Rovira, C.; Veciana, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5266−5268. (d) Kihara, N.; Hashimoto, M.; Takata, T. *Org. Lett.* **2004**, *6*, 1693−1696. (e) Gomar-Nadal, E.; Veciana, J.; Rovira, C.; Amabilino, D. B. *Adv. Mater.* **2005**, *17*, 2095−2098. (f) van Dijk, E. H.; Myles, D. J. T.; van der Veen, M. H.; Hummelen, J. C. *Org. Lett.* **2006**, *8*, 2333−2336 and references therein.

(2) For an example of redox-switched luminescence using the quinone/hydroquinone redox couple, see Goulle, V.; Harriman, A.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 1034−1036.

(3) (a) Tucker, J. H. R.; Collinson, S. R. *Chem. Soc. Rev.* **2002**, *31*, 147−156. (b) Bu, J. J.; Lilienthal, N. D.; Woods, J. E.; Nohrden, C. E.; Hoang, K. T.; Truong, D.; Smith, D. K. *J. Am. Chem. Soc.* **2005**, *127*, 6423−6429 and references therein. (c) For an intramolecular example, see Boyd, A. S. F.; Carroll, J. B.; Cooke, G.; Garety, J. F.; Jordan, B. J.; Mabruk, S.; Rosair, G.; Rotello, V. M. *Chem. Commun.* **2005**, 2468−2470.

(4) For examples where rotary (360°) motion rates are affected by complexation, see Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. *Chem. Rev.* **2005**, *105*, 1281−1376.

(5) For examples where shuttling rates in rotaxanes are controlled by external inputs, see (a) Lane, A. S.; Leigh, D. A.; Murphy, A. *J. Am. Chem. Soc.* **1997**, *119*, 11092−11093. (b) Ghosh, P.; Federwisch, G.; Kogej, M.; Schalley, C. A.; Haase, D.; Saak, W.; Lutzen, A.; Gschwind, R. M. *Org. Biomol. Chem.* **2005**, *3*, 2691−2700 and references therein.

(6) Jennings, W. B.; Boyd D. R. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takechi, Y., Eds.; VCH: Cambridge, U.K., 1992; pp 105−158.

(7) Drakenberg, T.; Lehn, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 532−535.

(8) The use of a trans-disubstituted aziridine results in the *N*-invertomers being identical (i.e., **1a** = **1b**; **2a** = **2b**), simplifying the data analysis.

(9) *The Chemistry of the Quinonoid Compounds;* Patai, S. Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1987; Vol. 2.

(10) Foglia, T. A.; Swern, D. *J. Org. Chem.* **1969**, *34*, 1680−1684.

(11) Pfister, J. R. *Synthesis* **1984**, 969−970.

(12) Syper, L.; Kloc, K.; Młochowski, J.; Szluc, Z. *Synthesis* **1979**, 521−522.

(13) Reich, H. J. *J. Chem. Educ.: Software, Ser. D* **1996**, 3D.

(14) Evidence for an intramolecular H-bond is provided by the fact that essentially no change in the chemical shift of the downfield OH in **2** was detected upon variation in sample concentration (δ 10.83 ppm, 0.021 M; δ 10.82 ppm, 0.006 M; δ 10.82, 0.001 M). Geometric constraints necessitate that the C-1-OH and not the C-4-OH is involved.

(15) A recent ab initio study found that the intramolecular H-bond energy in malonoaldehyde was 26 kJ mol^{-1}: Gromak, V. V. *J. Mol. Struct.: THEOCHEM* **2005**, *726*, 213−224.

(16) Wu, X.; Vargas, M. C.; Nayak, S.; Lotrich, V.; Scoles, G. *J. Chem. Phys.* **2001**, *115*, 8748−8757. Walsh, T. R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 443−451.

JA065325F