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A Redox-Mediated Molecular Brake: Dynamic NMR Study of 2-[2-(Methylthio)phenyl]isoindolin-1-one and *S*-Oxidized Counterparts

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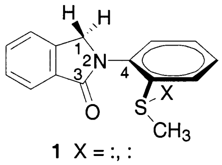
Abstract: A redox-mediated molecular brake based on the sulfide−sulfoxide redox cycle is illustrated by modulation of the rotation rate of an N−Ar "shaft" by varying the oxidation state of sulfur in 2-[2-(sulfur-substituted)phenyl]-isoindolin-1-ones. N−Ar rotational barriers in methylsulfinyl (**2**) and methylsulfonyl (**3**) derivatives (13.6 kcal mol^{-1}) are $\sim$5 kcal mol^{-1} higher than sulfide **1**. Rate reduction for N−Ar rotation is $\sim 10^4\ \text{s}^{-1}$ (280 K) upon oxidation. Correlated *N*-pyramidalization/N−Ar rotation reduces the effectiveness of the brake by decreasing the energy barrier to N−Ar bond rotation.

Rotational motion is an integral behavior of molecules. Controlling these motions in a reproducible fashion is a key design element for molecular machines. For a molecular brake,[1] an integral component of a molecular machine, reversibility and hindrance to motion are the two most important aspects. Recently, organic molecules designed specifically to achieve certain desired motions leading to a molecular motor have been reported.[2] For example, a ratcheted "drive shaft" containing intramolecular features which allow rotation of the shaft in only one direction has been reported,[3] and approaches to intramolecular brakes based upon changes of pH,[4] metal ion concentration,[1,5] or coordination number (or oxidation state of the metal)[6] have been disclosed.

We now wish to introduce the concept of an organic-based redox-mediated molecular brake. The system is based on the sulfide−sulfoxide redox cycle and is illustrated in a minimalist system by modulation of the rate of rotation of an N−Ar "shaft" by varying the oxidation state of a proximate sulfur atom in 2-[2-(sulfur-substituted)phenyl]isoindolin-1-ones **1**−**3**. Oxidized sulfur acts as the braking mode (rotation hindered) while the reduced [S(II)] counterpart shows "free" rotation. This approach is attractive because there are numerous high-yield chemical and electrochemical processes for both sulfur oxidation to sulfoxide[7,8] and sulfoxide deoxygenation to sulfide.[9,10] Thus, the processes of applying and removing the brake are readily reversible, easily controllable actions.



1 X = :, :
2 X = O, :
3 X = O, O

Simple isoindolin-1-ones exist as enantiomeric rotational isomers with slow rotation about the aryl C−N bond giving rise to diastereotopic methylene protons.[11] Ortho-substitution of the aryl group of 2-phenylisoindolin-1-one with sulfur-containing groups (compounds **1**−**3**) had a pronounced line broadening effect on methylene proton signals in the ^{1}H NMR spectra (25 °C) (Figure 1) indicating the sulfur oxidation level dramatically affects the rate of rotation about the N−Ar bond in these compounds.

On cooling below −20 °C, the methylene "bump" in sulfone (**3**) splits into an AB quartet ($\Delta\nu$ =191.5 Hz and J_{AB} = 16.8 Hz at 400 MHz in the absence of exchange)

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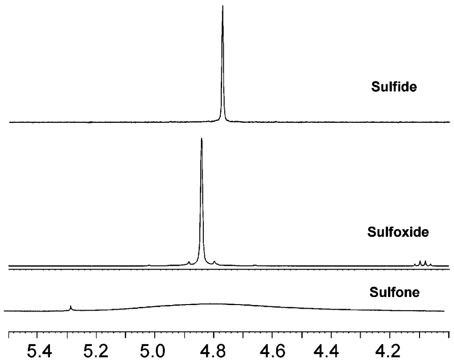

FIGURE 1. ^{1}H NMR spectra of isoindolin-1-one sulfide (**1**), sulfoxide (**2**), and sulfone (**3**) (400 MHz, $CDCl_3$, 25 °C).

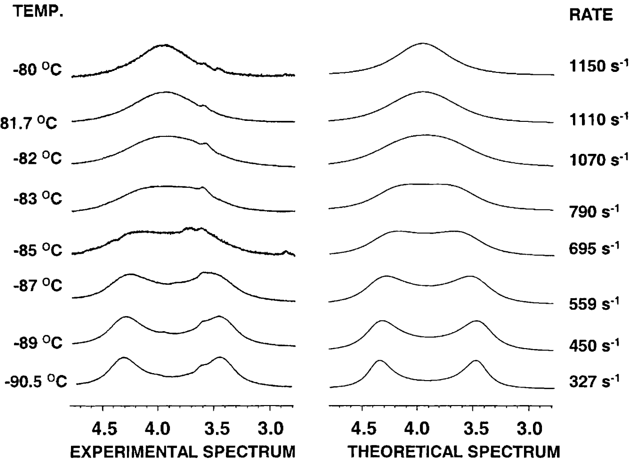

FIGURE 2. Line-shape analysis of **1**.

TABLE 1. NMR Parameters and Thermodynamic Data for Isoindolin-1-ones (1−3)

compd	T_C (K)	$\Delta H^{\mp}$ (kcal mol^{-1})	$\Delta S^{\mp}$ (cal mol^{-1})	$\Delta G^{\mp\,c}$ (kcal mol^{-1})	$\Delta G^{\mp\,d}$ (kcal mol^{-1}) (computed)
1[a]	<188	8.10	−1.5	8.4 (8.6)	9.2, 9.0
2[b]	280			(13.6)	10.4, 11.9
3[b]	295	12.2	4.9	13.6 (13.7)	17.2, 13.5

[a] NMR in toluene-d_8. [b] NMR in $CDCl_3$. [c] Experimental value from line-shape analysis or (coalescence measurement). [d] Calculated from minima on either side of the transition state.

with a coalescence temperature (T_c) of 22 °C. These data provide a value of 13.7 kcal/mol (57.2 kJ/mol) for the free energy of activation ($\Delta G^‡$) of **3**. Line-shape analysis of spectra obtained at various temperatures confirms this value ($\Delta G^‡ = 13.6$, 56.9 kJ/mol) and allows calculation of $\Delta H^‡$ and $\Delta S^‡$ (Table 1). Similarly, sulfide **(1)** gives $T_c = -85$ °C (188 K) and $\Delta G^‡ = 8.56$ kcal/mol (35.8 kJ/mol) [$\Delta G^‡ = 8.40$ kcal/mol (35.1 kJ/mol) by line-shape analysis]. The rate data obtained from line-shape analysis of ^{1}H NMR spectra of **1** are shown in Figure 2.

Analyses of the variable-temperature (VT) ^{1}H NMR spectra of sulfoxide **2** were problematic. The methylene signals appeared as an AB quartet in the absence of exchange ($H_a = 4.95$, $H_b = 4.85$, $J = 16.78$ Hz, $CDCl_3$, −60 °C). As the sample was warmed these peaks gradually collapsed to a single broad peak and, upon further heating, decoalesced into another AB quartet ($H_a = 4.86$, $H_b = 4.80$, $J = 16.78$ Hz, $CDCl_3$, 50 °C). Throughout this process, the centerline of the absorptions migrated linearly upfield, becoming constant in appearance and chemical shift at about 120 °C ($CDBr_3$). This behavior is unique to the sulfoxide; both the sulfide and the sulfone showed classical decoalescence upon warming from the absence of exchange regime to give a singlet having a chemical shift equal to the average values for H_a and H_b in the low-temperature AB quartet. In analogy with sulfide (**1**) and sulfone (**3**), coalescence of the low-temperature AB quartet in sulfoxide (**2**) is a physical manifestation of increased N−Ar rotation. However, in **2**, even as H_a and H_b rapidly exchange, they are diastereotopic due to the presence of the chiral sulfoxide moiety, hence the reappearance of separate signals for H_a and H_b at higher temperatures. In other words, as noted by Lunazzi,[12] sulfoxides which contain a chiral center and also a stereogenic axis (in our case the N−Ar bond) will display a set of conformational enantiomers (or atropisomers) at low temperature (under conditions of slow exchange) and a pair of configurational enantiomers when exchange is rapid.

For sulfoxide **2**, $\Delta G^‡$ and k were determined at the coalescence temperature (280 K, 13.6 kcal mol^{-1} and 1.3 $\times 10^2$ s^{-1}, respectively). By comparison, k_{280} for **1** and **3** are 1.6×10^6 and 1.4×10^2 s^{-1}, respectively. As expected from the scant literature available,[13] the sulfoxide and sulfone barriers to rotation are very similar. Thus, at 280 K, oxidation of sulfide **1** to either the sulfoxide **2** or sulfone **3** slows this rate of rotation by about 10^4 s^{-1}.[14]

Based on a "rigid shaft" model, we had expected an increase in rotational barrier of more than 5 kcal/mol upon sulfur oxidation. Examination in models of the N−Ar rotation reveals a severe steric interaction during

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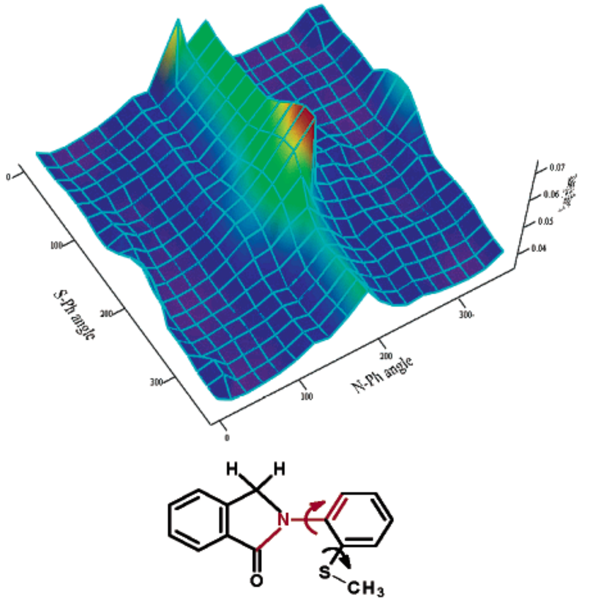

FIGURE 3. Potential energy surface plot for **1** (Gaussian 98).

the passage of the ortho substituents over the carbonyl group during rotational interconversion of enantiomers. Transition-state nitrogen pyramidalization to avoid steric interactions during rotational motion has been reported.[15] To get a better picture of rotational processes and to determine theoretical rotational barriers, semiempirical molecular orbital calculations were performed on compounds **1**−**3**.[16] Figure 3 shows the potential energy surface diagram for sulfide **1** for concurrent N−Ar and S−Ar rotations, with central maxima and minima on either side indicating noncorrelated N−Ar and S−Ar rotations.[17] The calculated barrier is ~9 kcal/mol for passage of *o*-SMeAr over the carbonyl group, which matches well with the values obtained from experimental

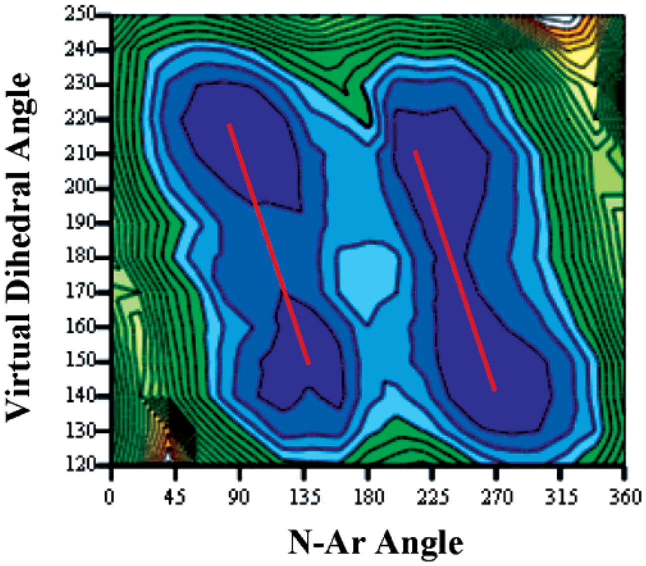

FIGURE 4. Surface plot of N−Ar angle and virtual dihedral angle for **1**.

work (~8.5 kcal mol^{-1}). Similar calculations were performed on **2** and **3** (Table 1). These values also agree quite well with experimental results but are not as close as for **1**. Theoretical values may deviate slightly from the experimental values due to chirality considerations or parametrizations in the PM3 program. The barrier to passage of *o*-SMeAr over the methylene portion of the isoindolinone is calculated to be much lower than for passage over the carbonyl (3.3 kcal mol^{-1}).

A major finding of the calculations is that pyramidalization of the amidic nitrogen is predicted in all three 2-(*o*-substituted phenyl)isoindolinone derivatives. This process cannot be observed by NMR in our model systems. Calculations show the degree of nitrogen pyramidalization[18] in the highest energy conformations greatly increases with the initial oxidation from −S− to S═O (9.6° to 13.3°), but changes little upon further oxidation (13.3° to 13.9° in the sulfone). One can visualize nitrogen pyramidalization during N−Ar bond rotation in our model system as a "wobbling" rotating shaft rather than a rigid rotating shaft. At torsion angles where steric repulsion of the indolinone ring and *o*-Ar substituent is minimal, N-pyramidalization is also minimal. However as the steric interaction increases so does N-pyramidalization.

The calculations suggest (and it is reasonable to expect) N−Ar rotation and N-pyramidalization to be coupled or correlated motions. The coordinated movement of two proximate groups in order to minimize steric interactions during rotation of these groups is termed correlated or cogwheel rotation and is a well-studied phenomenon.[17,19−21] Motions in which rotation is coupled to nitrogen inversion

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(14) As a practical matter, oxidation to the sulfone state offers little or no increase in the barrier to rotation, while methods for converting sulfones to sulfides are not nearly as diverse nor simply executed as for sulfoxide deoxygenation. This is why our focus is on the S ↔ S═O redox cycle even though DNMR studies are, in general, easier to conduct on sulfone derivatives.

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(18) Different measures have been used to describe nitrogen pyramidalization: (a) Degree of pyramidalization equals 360 − Σ bond angles to the nitrogen atom (Ganguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103). (b) Measurement of a virtual dihedral angle (Rankin, K. N.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 11168) and (c) measurement of the distance from the nitrogen atom to the plane containing by the three atoms bonded to nitrogen (Schweizer, W. B.; Procter, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783).

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have been studied extensively by both experimental and computational methods[22] and correlated rotation−nitrogen pyramidalization has been studied computationally.[23] Lunazzi[17] has developed a graphical method to demonstrate correlated bond rotations by generating a contour map of the potential energy surface described by incremental rotations of the dihedral angles about the bonds suspected of correlated rotation. Correlated rotation is present when the rotation pathways (indicated by lines joining energy minima) run diagonal to the $x-y$ axes and parallel to each other. To demonstrate computationally the correlated nature of N−Ar rotation and N-pyramidalization in **1**−**3**, we have developed a variant of the Lunazzi graphical approach: a "virtual dihedral angle" is plotted against the N−Ar torsion angle. Rankin and Boyd[18b] introduced the virtual dihedral angle as a means of quantitating nitrogen pyramidalization. The virtual dihedral angle given by C1−N2−C3−C4 (see structure **1**) in compounds **1**−**3** having a value of 180° corresponds to planar nitrogen (flat, sp^2, degree of pyramidalization[18a] = 0°) and a value of 120° corresponds to tetrahedral nitrogen (sp^3, degree of pyramidalization = 31.5°). In the calculations (PM3), the virtual dihedral angle and the N−Ar torsion angle were locked, and then the other angles and bond distances were allowed to relax to their minima for each of the locked values. The N−Ar torsion angle values were fixed in 20° increments from 0 to 360° and virtual dihedral angle values were fixed in 10° increments from −90° to +90°. The resulting plot (Figure 4) has the appearance of a Lunazzi diagram, but relates N−Ar rotation to N-pyramidalization. Thus, diagonal lines joining the energy minima in Figure 4 are indicative of correlated motions.

Redox disengagement/engagement of the molecular brake can be observed in situ in an NMR tube. Addition of a solution of Lawesson's reagent[9k] (in $CDCl_3$) to an NMR sample of compound **2** equilibrated to −40 °C in the NMR probe leads to a rapid replacement of the AB quartet (δ 4.95) observed for the methylene hydrogen atoms in the "stopped" sulfoxide with a broad singlet (δ 4.78) corresponding to the methylene hydrogen atoms in sulfide **1** as rotation about the N−Ar bond takes place. Conversely engagement of the brake may be observed by addition of a solution of *m*-CPBA (in $CDCl_3$) to an NMR sample of compound **1** equilibrated to −40 °C in the NMR probe. This leads to a rapid replacement of the broad singlet (δ 4.78) corresponding to the methylene hydrogen atoms in the slowly rotating sulfide with an AB quartet (δ 4.95) corresponding to the methylene hydrogen atoms in the absence of N−Ar rotation in sulfoxide **2**. These reagents are nearly ideal for these experiments because the reactions are rapid (even at −40 °C), quantitative, and exhibit no interfering peaks in the region δ 4−5. A sample spectrum from titration of **1** with *m*-CPBA to approximately 80% conversion at −40 °C in an NMR tube is shown in Figure 5 (Supporting Information). The redox conversions may also be monitored by changes in intensity of the methyl signals in **1** (δ 2.41) and **2** (δ 3.05).

In conclusion, we have shown that the rate of N−Ar rotation in isoindolin-1-ones **1**−**3** is controlled by the oxidation state of sulfur in a proximate ortho substituent. The rate difference between sulfane and the sulfinyl/sulfonyl forms is $\sim 10^4$ s^{-1}. The model compounds are shown computationally to undergo correlated N-pyramidalization and C−N bond rotation. As the *o*-Ar substituent passes the plane of the isoindolinone, N-pyramidalization reaches maximum, but the nitrogen becomes planar when the isoindolinone and Ar groups are nearly orthogonal. Pyramidalization of nitrogen causes the redox brake to be less effective than expected. Design of a system in which shaft element flexing (in the form of atom pyramidalization) is avoided should provide more dramatic rate reductions using this molecular brake concept.

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Supporting Information Available: Experimental details for preparation and characterization of compounds **1**−**3**, ^1H and ^{13}C NMR spectra for compounds **1**−**3**, 3D potential energy surface plots for **2** and **3**, PM3-computed *Z*-matrices for the lowest energy conformation of compounds **1**−**3** (when N−Ar and S−Ar torsion angles are locked and incremented), 2D surface plots of N−Ar torsion angle vs virtual dihedral angle for **2** and **3**, rate data for **3** from line-shape analysis, and PM3-computed *Z*-matrices for the lowest energy conformation of compounds **1**−**3** (when N−Ar and the virtual dihedral angle torsion angle are locked and incremented). This material is available free of charge via the Internet at http://pubs.acs.org.

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