Supramolecular Interactions

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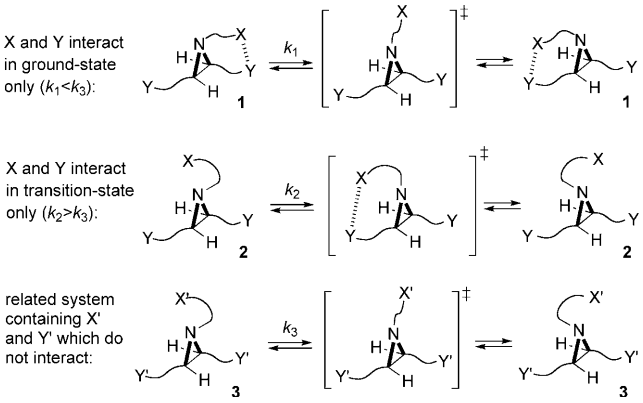
Aziridine Scaffolds for the Detection and Quantification of Hydrogen-Bonding Interactions through Transition-State Stabilization**

Luciana Giordano, Cam T. Hoang, Michael Shipman, James H. R. Tucker,* and Tiffany R. Walsh**

Accurately quantifying the strength, distance, and angular dependence of noncovalent interactions is central to understanding numerous aspects of biology and medicine, as well as supramolecular and synthetic chemistry.[1] However, specific weak interactions are often difficult to quantify. Known approaches[1,2] include computational modeling, informatics, and a variety of experimental techniques. Of the latter, most notable are systems in which internal motions are restricted to two conformations, interchangeable through bond rotation.[2] For example, the "molecular torsion balance", developed by Wilcox et al., has successfully quantified a range of weak interactions by determining the equilibrium population of these two conformers.[2b–d,g,h] Here, we demonstrate how molecular motion in the form of pyramidal inversion in aziridines may be used for detecting and assessing the strength of an individual H-bond.

The key concepts behind the use of aziridine scaffolds for measuring noncovalent interactions are summarized in Scheme 1. Suppose aziridine **1** benefits from a favorable noncovalent interaction between substituents X and Y in the ground state (GS); the rate of N inversion will *decrease* relative to aziridine **3** lacking this interaction (provided X···Y dissociation is required for N inversion). The difference in Gibbs free energy barrier between cases **1** and **3** ($\Delta\Delta G^{\neq}$) should provide a direct measure of the X···Y interaction strength in **1**, once secondary interactions (see below) are accounted for. Alternatively, suppose X and Y interact only in the transition state (TS). The inversion barrier for **2** will then be lowered by TS stabilization and hence the rate of N inversion will *increase* relative to **3**. Again, $\Delta\Delta G^{\neq}$ will correlate with the X···Y interaction strength. Geometric constraints placed on X and Y by linkers attaching them to the aziridine scaffold in any specific system will dictate whether X and Y can interact effectively in either the GS or TS and hence modulate the rate of N inversion.



Scheme 1. Proposed effect of a noncovalent interaction between X and Y on aziridine N inversion rate coefficients (in this particular study the situation as described for compound **2** is observed).

Aziridine based scaffolds confer a number of attributes making them well-suited for this application. These include: 1) favorable synthetic accessibility with respect to other systems;[2c,d] 2) inversion rates that can be accurately quantified by dynamic NMR spectroscopy;[3] 3) spatial control of ring substituents in predictable, well-defined orientations; 4) the relatively weak basicity of the aziridine nitrogen atom (less likely to compete with X···Y interactions); and 5) system sizes that are amenable to ab initio calculations.

To explore the potential of this new approach, a simple and well known intramolecular interaction was sought in the first instance, with a single H-bond between an *ortho*-substituted pyridine and a secondary amide fitting these criteria.[4] Compound **4** was accordingly synthesized, along with control compounds **5**–**8** (Scheme 2).

H-bonding in **4**, **5**, and **8** was probed by ^{1}H NMR spectroscopy (298 K, ca. 10 mM). Interestingly, only small downfield shifts for the amide NH signals of **4** in [D_2]tetrachloroethane were observed compared to those for compounds **5** and **8** (**4**: $\delta = 6.94$ and 6.25 ppm; **5**: $\delta = 6.34$ and 5.90 ppm; **8**: $\delta = 6.31$ and 5.90 ppm) indicating at best only a very weak intramolecular interaction in the GS.[5] This contrasts with data for related compounds in the literature[4b,c]

[*] Dr. L. Giordano,[+] Dr. J. H. R. Tucker
School of Chemistry, University of Birmingham
Edgbaston, Birmingham, B15 2TT (UK)
Fax: (+44) 121-414-4403
E-mail: j.tucker@bham.ac.uk
Homepage: http://www.chem.bham.ac.uk/staff/tucker.shtml
Dr. C. T. Hoang,[+] Prof. Dr. M. Shipman, Dr. T. R. Walsh
Department of Chemistry, University of Warwick
Coventry, CV4 7AL (UK)
E-mail: m.shipman@warwick.ac.uk
Dr. T. R. Walsh
Centre for Scientific Computing, University of Warwick
Coventry, CV4 7AL (UK)
E-mail: t.walsh@warwick.ac.uk
Homepage: http://www.warwick.ac.uk/go/walshgroup
[+] These authors contributed equally to this work.

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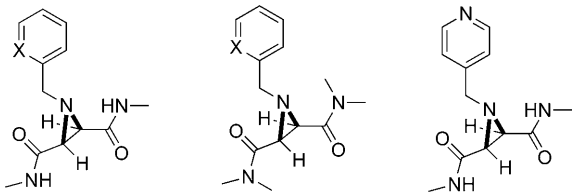


4 X = N
5 X = CH
6 X = N
7 X = CH
8

Scheme 2. Aziridines synthesized for this study.

which give pronounced ($\delta = 9$–10 ppm) downfield NMR shifts for amide resonances in chlorinated organic solvents due to intramolecular H-bonds with pyridine groups. Large downfield shifts in the amide signals were indeed observed for compounds **4** and **8** in [D$_5$]pyridine (**4**: $\delta = 9.29$ and 8.20 ppm; **8**: $\delta = 9.28$ and 8.25 ppm) as a result of intermolecular H-bonding with the solvent.

Inversion rates and activation parameters for **4**–**8** were determined from variable-temperature NMR (VT-NMR) spectra. In conjunction with dynamic line-shape simulations,[6] 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.

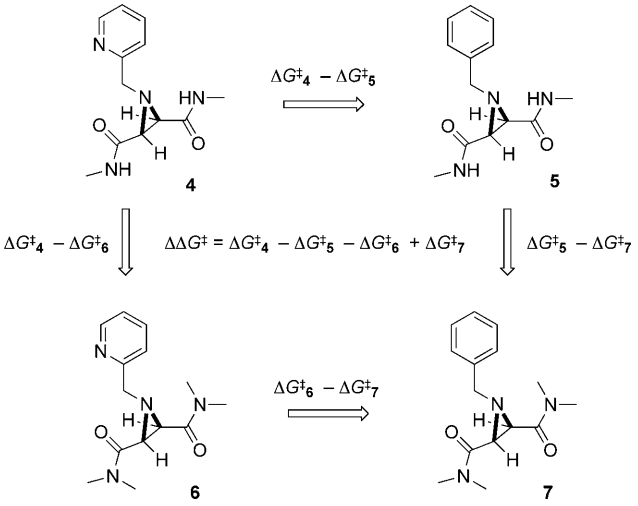
Table 1: Measured rates (in s^{-1}) and activation parameters (in kJ mol^{-1}) for the pyramidal inversion process in compounds **4**–**8**.

	Solvent	k[a]	$\Delta G^{\ddagger}$[b]	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$[c]
4	[D$_2$]TCE	268	59.4	50.4	−30.1	74.2
5	[D$_2$]TCE	7.2	68.1	66.9	−4.0	79.5
6	[D$_2$]TCE	1.2	72.7	82.6	33.4	–
7	[D$_2$]TCE	0.8	73.4	81.4	26.8	–
8	[D$_2$]TCE	3.8	69.7	66.1	−12.0	82.3
4	[D$_5$]Py	51	63.2	62.3	−3.0	–
8	[D$_5$]Py	3.4	70.0	70.5	1.7	–

[a] At 298 K. [b] Determined at 298 K using VT-NMR data in conjunction with line-shape analysis and Eyring plots (see the Supporting Information). [c] Calculated at 298 K using the MP2/6-31G* level of theory.

Strikingly, the rate of N inversion in **4** is significantly *higher* than that in compounds **5**–**8**. The activation barriers for **5**–**8** are uniformly higher, and fall within the normal range for 1,2-disubstituted aziridines.[3] Crucially, these structures are not able to participate in intramolecular H-bonding between the pyridine nitrogen atom and the amide NH. The lowering of the activation barrier in **4** compared to **5**–**8** (e.g. $\Delta\Delta G^{\ddagger} = -10.3$ kJ mol^{-1} for **4** relative to **8**), indicates that **4** benefits from transition-state stabilization, (i.e. as schematically illustrated for **2** in Scheme 1). The differences in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for **4** in comparison to **5**–**8** are also consistent with this. Upon changing the solvent from [D$_2$]TCE to [D$_5$]pyridine, the inversion rate for **8** is essentially unchanged but a fivefold reduction is observed for **4**. This is consistent with increased competition from the solvent for H-bonding with the amide hydrogen atoms in **4**.

In principle, secondary interactions involving X and/or Y and the linker unit (e.g. interactions with the aziridine nitrogen atom) could contribute to the measured inversion barriers. To confirm that an interaction between the pyridine and amide NH was the principal factor in the barrier reduction for **4** and to quantitatively determine this interaction, a chemical double mutant cycle (DMC)[1a,c,h,2c] was constructed using **4**–**7** (Scheme 3). Specifically, compound **4**



Scheme 3. Chemical double mutant cycle to measure the contribution of the amide–pyridine H-bond to the Gibbs free energy of activation.

contains the two moieties required for H-bond formation, whereas compounds **5** and **6** lack a H-bond acceptor and H-bond donor, respectively. Compound **7**, the double mutant, lacks both moieties (see **3** in Scheme 1). Together, secondary interactions are cancelled out so that any resulting differences in the kinetic data can be solely attributed to a change in the interaction strength between the pyridine and secondary amide groups on **4** as it changes between its GS and TS. Application of the equation shown in Scheme 3 clearly shows there is a significant interaction between the amide and the pyridine, with an overall calculated $\Delta\Delta G^{\ddagger}$ value of -8.0 kJ mol^{-1}. The negative value confirms that the interaction facilitates rather than hinders the inversion. That the inversion facilitates a bond formation rather than bond breaking is supported by $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values of -17.7 kJ mol^{-1} and -32.7 J K^{-1} mol^{-1}, both of which can also be accessed using the relevant VT data in the DMC.[7] The $\Delta\Delta H^{\ddagger}$ value can be considered to be (at the very least) a lower limit quantification[8] of the strength of the H- between the secondary amide and the pyridine nitrogen in **4**, and is in line with the expected value for an N−H···N interaction.[9] The $\Delta\Delta G^{\ddagger}$ value is slightly more negative than the ΔG value predicted for this interaction,[10] indicating a more favorable entropic component.

Ab initio calculations performed at the MP2/6-31G* level bear out the same trend as the experimental values (Table 1); the $\Delta G^{\ddagger}$ value for **4** is the lowest and $\Delta\Delta G^{\ddagger}$ values are also comparable [for example, $\Delta\Delta G^{\ddagger}$ for **4**–**8**: -10.3 kJ mol^{-1} (exp) and -8.1 kJ mol^{-1} (theory); $\Delta\Delta G^{\ddagger}$ for **4** and **5**: -8.7 kJ mol^{-1} (exp) and -5.3 kJ mol^{-1} (theory)].[11] The optimized structure for **TS4** has the pyridine nitrogen

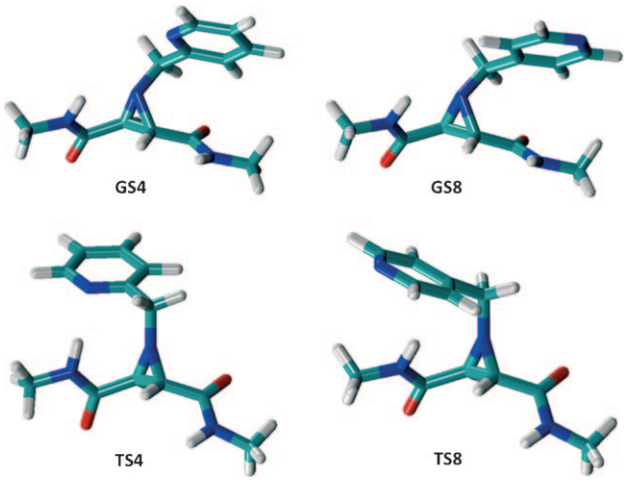


Figure 1. Transition-state (bottom, TS) and ground-state structures (top, GS) for **4** and **8** optimized at the MP2/6-31G* level. Cartesian coordinates of these structures are given in the Supporting Information.

pointing towards the amide (N···H-N angle 150.3°), consistent with an H-bonding interaction (Figure 1). Such an interaction is clearly lacking in the optimized structures of **GS4, GS8**, and **TS8**.

Measured and calculated infrared spectra of **4**, **5**, and **8** in the GS were then obtained, along with the calculated spectra of these compounds in the TS (see the Supporting Information for details). The average calculated value of the unperturbed amide NH stretch was found to be 3656 cm^{-1}. Red-shifting of this NH stretch is a signature of a H-bond.[12] Weak H-bonding in the cases of **GS4**, **GS5**, and **GS8** was evidenced by red-shifts of 67, 52, and 48 cm^{-1}, respectively, with respect to the unperturbed stretch. Inspection of the displacement vectors associated with these modes in each GS revealed that the principal atoms involved were the proton on the amide NH and the aziridine nitrogen, indicating an interaction between the amide NH and the lone pair of electrons on the nitrogen atom of the aziridine.[13] These observations are consistent with a lack of significant H-bonding overall. Similar trends were observed in the measured spectra in CH_2Cl_2. In contrast, a pronounced red-shift (112 cm^{-1}) for one NH stretch was observed in the calculated spectrum of **TS4**, indicating the formation of a strong intramolecular H-bond. Within **TS8**, the directionality of the amide NH group *syn* to the aziridine nitrogen substituent is suggestive of a NH···π interaction (Figure 1). However, the fact that both amide NH stretches within the computed IR spectra of **TS8** are located at almost the same frequency indicates that such an interaction must be rather weak. Similar results were observed for **TS5** (see the Supporting Information).[14]

To conclude, changes in inversion rates in aziridines can provide a simple and sensitive method for detecting and quantifying certain noncovalent interactions. In this particular study, an intramolecular H-bond between a pyridine nitrogen and an amide NH has been successfully characterized and quantified. The trend in the magnitude of the TS stabilization determined experimentally is in good agreement to that determined by ab initio calculations. This study highlights and exploits the fact that noncovalent interactions can be sensitive to subtle changes in geometry; in this particular example, an H-bonding interaction is triggered by a proximate nitrogen atom undergoing a change in hybridization from sp^3 to sp^2. Our findings are relevant to biological systems where the formation of transitory H-bonds provides a possible explanation for low-energy pathways in various protein folding processes.[15] Ongoing work is focused on testing the practical limits of this aziridine scaffold system through its application to the study of other weak noncovalent interactions.

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[5] Dilution studies in TCE between 10 mM and 1 mM did not significantly affect the values for the amide proton signals of **4**, suggesting that any weak H-bonding interaction is intramolecular in nature.

[6] The use of 1,2-disubstituted aziridines simplifies this analysis.

[7] The direct use of kinetic data in a DMC, which allows access to three separate parameters, is a convenient alternative to the standard approach of using thermodynamic data (e.g. equilibrium constants), as reviewed in Ref. [1c]. For indirect use of kinetic data in a DMC, see Ref. [1h].

[8] The magnitude of the three thermodynamic parameters calculated from the DMC can be considered to be at their lower limits due to the possibility of a weak H-bonding interaction in **GS4** (from NMR) and a non-additive weak secondary interaction in **TS5** (from modeling, see also Ref. [14]).

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[11] Our previous work[3a] has similarly shown that calculations at this level are capable of describing trends, but not reproducing the absolute values from experiment. A detailed discussion of sources of errors is given in the Supporting Information.

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[14] In the case of **TS5**, an NH···π interaction could represent a non-additive contribution to the DMC. However a comparison with spectroscopic data from the literature suggests that in this case, the interaction is rather weak: P. Ottiger, C. Pfaffen, R. Leist, S. Leutwyler, R. A. Bachorz, W. Klopper, *J. Phys. Chem. B* **2009**, *113*, 2937 – 2943.

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