Umbrella motion in aziridines: use of simple chemical inputs to reversibly control the rate of pyramidal inversion†

Mark W. Davies,[a] Adam J. Clarke,[a] Guy J. Clarkson,[a] Michael Shipman*[a] and James H. R. Tucker*[b]

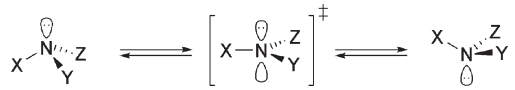
Received (in Cambridge, UK) 16th August 2007, Accepted 14th September 2007
First published as an Advance Article on the web 3rd October 2007
DOI: 10.1039/b712447c

The molecular motion associated with atomic inversion at an aziridine nitrogen can be essentially halted by metal complexation; addition of a second chemical input that decomplexes the metal from the aziridine restores fast inversion (k = 40 s^{-1} at 303 K).

Harnessing and controlling molecular motion is central to the fabrication of useful types of man-made devices such as molecular switches.[1] Important examples include interlocked structures (*e.g.* rotaxanes) whose translational movements can be controlled using external inputs, as well as rudimentary motors capable of 360° rotary motion.[2] Efforts in our own laboratories are focused on controlling and exploiting another type of molecular motion, namely pyramidal inversion (often called atomic or umbrella inversion).

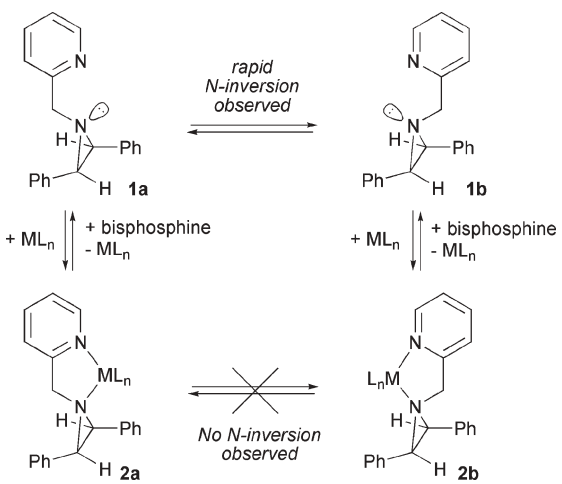
Pyramidal inversion has been the subject of intense experimental and theoretical investigations since it was first observed in 1929.[3] It is most often encountered in trivalent nitrogen compounds wherein rapid oscillation of the unshared electron pair through the XYZ plane converts the molecule into its enantiomer (Scheme 1). Although this inversion process is very rapid for ammonia and other simple amines, rates can be dramatically slowed by altering the nature of the X, Y and Z substituents.[4] For example, aziridines (X,Y = $-CH_2CH_2-$) undergo much slower inversion because the three membered ring has to accommodate an increase in angle strain in progressing from the ground to the transition state. This effect can be so pronounced that in certain cases, aziridine N-invertomers can be physically separated.[5]

To control umbrella motion, reversible external control over the rate of inversion and/or invertomer populations is required. Little work has been undertaken to systematically address this problem. Perhaps not surprisingly, it is known that changes in bulk solution pH do impact inversion rates, as the extent of quaternisation of the amine nitrogen increases with lowering pH.[6] More subtly, Drakenberg and Lehn have shown that pyramidal inversion barriers are impacted, albeit modestly, by changes in the solvent.[7] Recently, we have shown that rates of inversion can be successfully controlled by redox switching.[8] In this communication, we demonstrate for the first time that umbrella inversion can be repeatedly switched "off" and "on" using simple chemical inputs (Scheme 2).



Scheme 1 Umbrella inversion in a trivalent nitrogen compound.

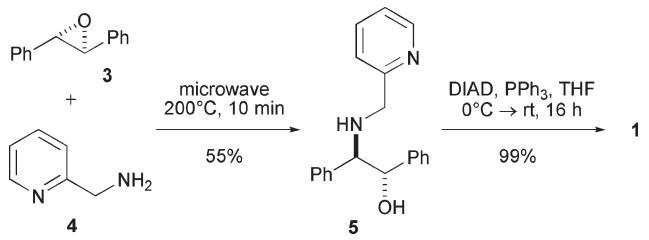
Aziridine **1** was selected for these investigations. Upon addition of a suitable metal salt (ML_n), bidentate coordination through both nitrogens was anticipated, leading to **2** in which the umbrella motion of the aziridine would be effectively halted. The use of metal salts as the chemical input was influenced by the work of Gagné *et al.*, who established that in acyclic 1,2-diamines, coordination to Pd(II) can lead to persistent N-chirality.[9] As the coordinating ability of aziridines is relatively weak,[10] regeneration of **1** and restoration of fast N-inversion was expected to be facile. For example, by addition of a second chemical input in the form of a bidentate ligand (*e.g.* bisphosphine) to sequester the metal. The design of **1/2** was guided by the following additional factors: (i) the pyridine group was introduced to aid metal coordination to the inverting nitrogen centre; (ii) an aziridine based system was chosen because accurate rates of inversion can be determined using dynamic NMR experiments; (iii) symmetry elements were included to make the N-invertomers identical (*i.e.* **1a** = **1b**) simplifying the NMR analysis; (iv) phenyl groups were placed on the ring to reduce the aziridine spin system to a simple, well-resolved AX pattern.



Scheme 2 Reversible control of umbrella inversion using metal salts as chemical inputs.

[a]*Department of Chemistry, University of Warwick, Coventry, UK CV4 7AL. E-mail: m.shipman@warwick.ac.uk; Fax: +44 24765 24429; Tel: +44 24765 23186*
[b]*School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT. E-mail: j.tucker@bham.ac.uk*

† Electronic supplementary information (ESI) available: Experimental procedures and compound characterisation data (**1**, **5–7**), NMR switching experiments and methods for the determination of activation parameters. See DOI: 10.1039/b712447c



Scheme 3 Two-step synthesis of aziridine **1**.

The synthesis of aziridine **1** was achieved in two simple steps from *trans*-stilbene oxide (**3**). Ring opening of this epoxide with 2-(aminomethyl)pyridine (**4**) under solvent-free microwave irradiation conditions[11] provided amino alcohol **5** in 55% yield (Scheme 3). Ring closure with diisopropyl azodicarboxylate (DIAD)–PPh_3[12] provided *trans*-aziridine **1** in near quantitative yield (see ESI†).

The rate of pyramidal inversion and activation parameters for **1** were obtained by recording the ^{1}H NMR spectrum in $CDCl_3$ over a range of temperatures (283–334 K) below and above the coalescence temperature of the aziridine hydrogen signals. In conjunction with dynamic line shape simulations of this AX spin system, performed using WINDNMR,[13] the rates of exchange over a range of temperatures were obtained. From an Eyring plot [$\ln(k/T)$ *vs.* $1/T$], the following activation parameters were extracted: $\Delta G^{\ddagger}$ = 65.5 kJ mol^{-1}; $\Delta H^{\ddagger}$ = 72.1 kJ mol^{-1}; and $\Delta S^{\ddagger}$ = 22.2 J K^{-1} mol^{-1} (see ESI†). The measured inversion barrier is in the range expected for a 1,2-disubstituted aziridine.[4b,8]

Next, a range of Zn(II), Hg(II) and Pd(II) salts were screened for their ability to arrest N-inversion. This was conveniently done by recording the ^{1}H NMR spectrum of **1** in $CDCl_2CDCl_2$ at 338 K. At this temperature, the aziridine hydrogens appear as a broad singlet centred at 3.32 ppm due to rapid nitrogen inversion on the NMR timescale (Fig. 1). Added metal salts that significantly slow the umbrella motion can thus be detected by the reappearance of non-equivalent aziridine hydrogens in the ^{1}H NMR spectrum. Of the many metal salts examined, the best results were obtained using $[PdCl_2(MeCN)_2]$.‡ Upon addition of 1.0 equivalent of this complex, the signal at 3.32 ppm disappeared and two doublets (J = 6.8 Hz), both integrating to one hydrogen, appeared at 5.13 and 3.54 ppm (Fig. 1). Crucially, N-inversion could be readily restored by the addition of 1,3-bis(diphenylphosphino)propane (dppp) (1.0 equiv.) to the NMR tube, which removed the Pd(II) from **6**, regenerating **1**.§ Up to 4 complete switching cycles have been demonstrated by the repeated sequential addition of these two chemical inputs (for details, see ESI†).

NMR titrations performed in $CDCl_2CDCl_2$ confirm that a 1 : 1 adduct is formed between aziridine **1** and Pd(II). Two sharp sets of signals corresponding to **1** and **6** are witnessed when sub-stoichiometric amounts of $[PdCl_2(MeCN)_2]$ are added, suggesting that ligand exchange is slow on the NMR timescale. Addition of >1.0 equivalent of $[PdCl_2(MeCN)_2]$ produced no further change in the ^{1}H NMR spectrum.

Both 1D- and 2D-exchange spectroscopy (EXSY)[14] experiments performed on aziridine **6** at temperatures up to 373 K in d_2-$CDCl_2CDCl_2$ provided no evidence for exchange between the aziridine hydrogens at 5.14 and 3.53 ppm. In contrast, experiments conducted on **1** at 298 K produced large reciprocal EXSY peaks between the aziridine hydrogens at 3.49 and 3.28 ppm. It is possible to deduce that the inversion rate of **6** is at least 10^4 times slower than that of **1** at 373 K.¶

Complex **6** is a stable orange solid that can be made and isolated in quantitative yield by simply adding $[PdCl_2(MeCN)_2]$ to **1** in CH_2Cl_2 (see ESI†). This material is spectroscopically identical to that produced in the NMR experiments described above. In comparison to **1**, significant downfield shifts in several resonances are seen in the ^{1}H NMR spectrum in $CDCl_3$; specifically, the *ortho*-hydrogen of the pyridine ring ($\Delta\delta$ = +0.49) and the aziridine hydrogens ($\Delta\delta$ = +1.05, averaged over both resonances). These observations are fully consistent with both nitrogens being involved in coordination to the Pd. Highly crystalline dibromide derivative **7** can also be produced ($PdBr_2$, CH_2Cl_2, 16 h, 100%) from **1**, which is spectroscopically analogous to **6**. In the case of **7**, the solid-state structure has been unambiguously established by XRD using a single crystal grown from MeOH–propanone,

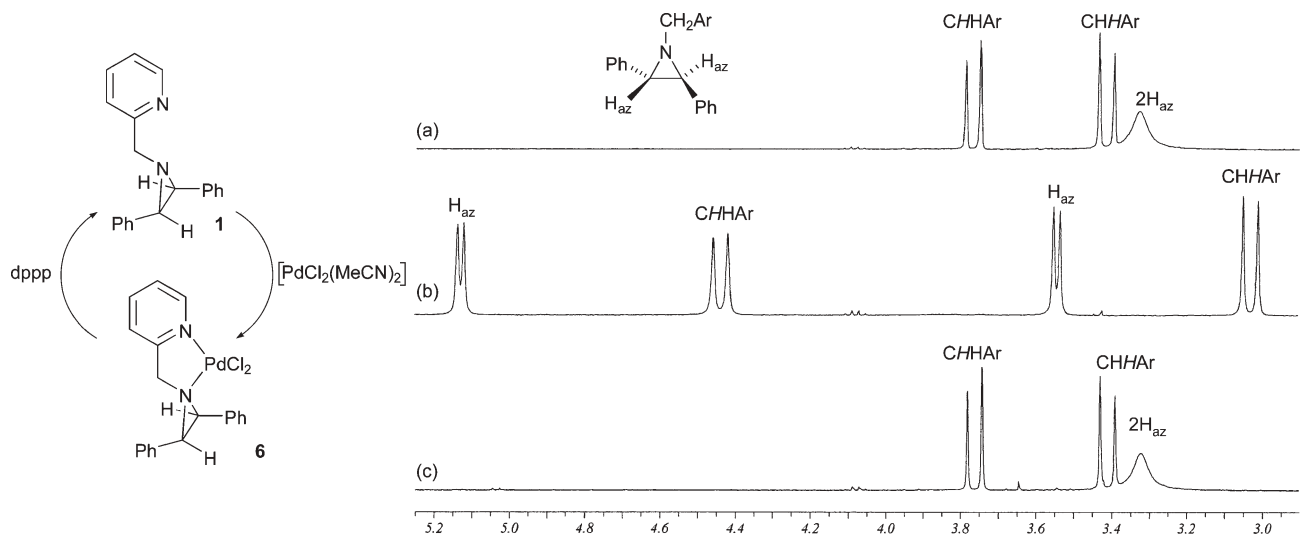


Fig. 1 ^{1}H NMR spectra (400 MHz, $CDCl_2CDCl_2$, 338 K): (a) of aziridine **1**; (b) with $[PdCl_2(MeCN)_2]$ (1.0 equiv.) added; (c) after addition of dppp (1.0 equiv.).

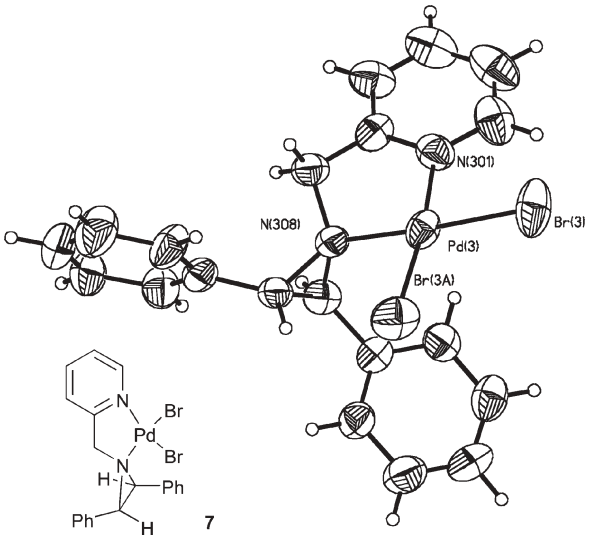


Fig. 2 Representation of the X-ray structure of **7** showing one of the crystallographically independent molecules in the asymmetric unit. Thermal ellipsoids drawn at 50% probability.

confirming the anticipated bidentate mode of coordination (Fig. 2).‖

To summarise, aziridine **1** can readily be prepared and its umbrella motion accurately quantified. In the absence of external inputs, it undergoes rapid N-inversion (k = 40 s^{-1} at 303 K) as a result of a relatively low activation barrier ($\Delta G^{\ddagger}$ = 65.5 kJ mol^{-1}). Upon addition of one equivalent of $[PdCl_2(MeCN)_2]$, coordination through both nitrogens occurs which effectively halts the motion. With respect to **1**, the process is fully reversible, and by introduction of a second input in the form of dppp, fast N-inversion can be completely restored. Multiple cycles of this switching process can be demonstrated.

It is informative to compare these results with earlier efforts to control N-inversion through the use of redox switching.[8] Importantly, much greater differences in the "on" and "off" inversion rates have been achieved herein, indicating that metal coordination is more effective than hydrogen bonding as a means to inhibiting the attainment of the trigonal transition state required for inversion (Scheme 1), presumably due to the Pd–N(aziridine) bond being stronger than an O–H···N(aziridine) H-bond. As such, this work represents a significant step forward. Future work will focus on developing other approaches for gaining external control over umbrella motion, and to integrating such motifs into rudimentary nanoscale devices.

This work was financially supported by The Leverhulme Trust. We thank Dr J. P. Rourke for helpful discussions, the EPSRC National mass spectrometry centre for high resolution mass spectra, and Dr S. van Meurs of Bruker Biospin for providing the modified SPTSIR pulse program.

Notes and references

‡ N-Inversion was halted using several other metal salts, including $Hg(OAc)_2$, $ZnCl_2$, $ZnBr_2$ and $Pd(OAc)_2$. With $Hg(OAc)_2$, the complex dissociated upon heating in d_2-TCE (d_2-tetrachloroethane) above 333 K, indicating weaker binding. With $ZnCl_2$ and $ZnBr_2$, **2** (ML_n = $ZnCl_2$ or $ZnBr_2$) was very stable up to 373 K in d_2-TCE, indicating strong binding. However, NMR switching experiments were hampered by the fact that we could not identify a solvent in which ZnX_2 (X = Cl or Br), **1** and **2** were all soluble. Using $Pd(OAc)_2$, the expected complex was produced but it underwent degradation to an unidentified product upon heating.

§ During the course of these investigations, a range of sequestering agents were examined, including *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), PPh_3, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), 1,2-bis(diphenylphosphinomethyl)benzene and 1,3-bis(diphenylphosphino)-propane (dppp). In an initial screen using **2** [ML_n = $Pd(OAc)_2$], dppp proved to be the most effective and hence this ligand was utilised for the subsequent *in situ* experiments performed using $[PdCl_2(MeCN)_2]$ (Fig. 1).

¶ The rate constant of pyramidal inversion in **1** at 373 K can be estimated to be $\approx 8.9 \times 10^3$ s^{-1} by extrapolation of the data obtained at lower temperatures (see ESI†). Since no exchange cross peaks were visible in the 2D-EXSY spectrum of **6**, this indicates that any exchange at 373 K, occurs with a rate constant below the $1/T_1$ limit associated with the EXSY technique.[15] Values for T_1, the spin lattice relaxation time of the exchanging aziridine sites, were determined using the inversion recovery technique.[14] From these values (2.61 and 1.32 s), we deduce that for **6**, $k \leqslant 0.75$ s^{-1} at 373 K *i.e.* at least 10^4 times slower than **1**.

‖ Crystal data for **7**: $C_{20}H_{18}N_2Br_2Pd$, M = 552.58, orange block, 0.60 × 0.25 × 0.10 mm, triclinic, $P\bar{1}$ (no. 2), a = 14.0049(14), b = 14.1051(14), c = 20.955(2) Å, α = 76.598(2), β = 88.601(2), γ = 89.842(2)°, T = 298 K, μ(Mo-Kα) = 4.897 mm^{-1}, U = 4025.6(7) $Å^3$, Z = 8, D_{cal} = 1.823 g cm^{-3}, 47727 reflections measured, 19482 unique [R_{int} = 0.0653], R [$I > 2\sigma(I)$] = 0.0645, wR [$I > 2\sigma(I)$] = 0.1788, *GooF* = 1.013. CCDC 657459. For crystallographic data in CIF format or other electronic format see DOI: 10.1039/b712447c.

1 For a recent monograph, see: V. Balzani, A. Credi and M. Venturi, *Molecular Devices and Machines: A Journey into the Nanoworld*, Wiley-VCH, Weinheim, 2003.
2 For recent reviews, see: (*a*) E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2007, **46**, 72; (*b*) S. Saha and J. F. Stoddart, *Chem. Soc. Rev.*, 2007, **36**, 77; (*c*) A. Credi, *Aust. J. Chem.*, 2006, **59**, 157; (*d*) W. R. Browne and B. L. Feringa, *Nat. Nanotechnol.*, 2006, **1**, 25; (*e*) K. Kinbara and T. Aida, *Chem. Rev.*, 2005, **105**, 1377; (*f*) G. S. Kottas, L. I. Clarke, D. Horinek and J. Michl, *Chem. Rev.*, 2005, **105**, 1281.
3 E. F. Barker, *Phys. Rev.*, 1929, **33**, 684.
4 For reviews, see: (*a*) A. Rauk, L. C. Allen and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 400; (*b*) J. B. Lambert, *Top. Stereochem.*, 1971, **6**, 19; (*c*) W. B. Jennings and D. R. Boyd, in *Cyclic Organonitrogen Stereodynamics*, ed. J. B. Lambert and Y. Takechi, VCH, Cambridge, 1992, pp. 105–158.
5 For an example, see: S. J. Brois, *J. Am. Chem. Soc.*, 1968, **90**, 508.
6 M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, 1963, **85**, 1882.
7 T. Drakenberg and J. M. Lehn, *J. Chem. Soc., Perkin Trans. 2*, 1972, 532.
8 M. W. Davies, M. Shipman, J. H. R. Tucker and T. R. Walsh, *J. Am. Chem. Soc.*, 2006, **128**, 14260.
9 K. A. Pelz, P. S. White and M. R. Gagné, *Organometallics*, 2004, **23**, 3210. See also: E. Rafii, B. Dassonneville and A. Heumann, *Chem. Commun.*, 2007, 583; V. Diez, J. V. Cuevas, G. García-Herbosa, G. Aullón, J. P. H. Charmant, A. Carbayo and A. Muñoz, *Inorg. Chem.*, 2007, **46**, 568.
10 The availability of the *N*-lone pair for coordination to a metal can be approximated from its pK_a values. pK_a $EtNH_3^+$ = 10.6 *cf.* aziridinium ion = 8.1.
11 Concurrent to this work, the use of 2-(aminomethyl)pyridine in other microwave-assisted epoxide openings has been described, see: A. Robin, F. Brown, N. Bahamontes-Rosa, B. Wu, E. Beitz, J. F. J. Kun and S. L. Flitsch, *J. Med. Chem.*, 2007, **50**, 4243.
12 L. Syper, L. K. Kloc, J. Młochowski and Z. Szluc, *Synthesis*, 1979, 521.
13 H. J. Reich, *J. Chem. Educ.: Software, Ser. D*, 1996, 3D.
14 S. Berger and S. Braun, *200 and More NMR Experiments*, Wiley-VCH, Weinheim, 2003.
15 C. L. Perrin and T. J. Dwyer, *Chem. Rev.*, 1990, **90**, 935.

