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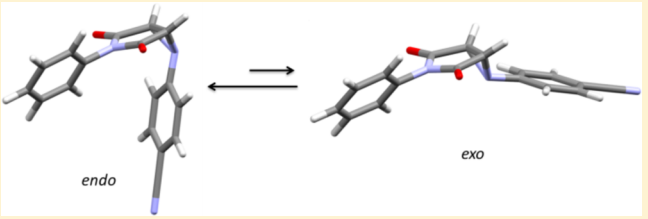
Aziridine Nitrogen Inversion by Dynamic NMR: Activation Parameters in a Fused Bicyclic Structure

Denisse de Loera, Fang Liu, K. N. Houk, and Miguel A. Garcia-Garibay*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

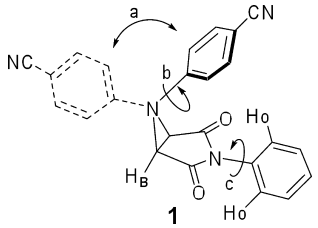
Supporting Information

ABSTRACT: The nitrogen inversion of a *N*-phenyl aziridine fused to a succinimide ring is influenced by the presence of a phenyl ring in the succinimide moiety. The endo invertomer is favored, showing an unsymmetrical equilibrium in variable ^{1}H NMR studies.



In recent work, we reported an efficient synthesis of fused *N*-phenyl-aziridino-[2,3-*c*]-*N*-phenyl-succinimides via a solid state photodenitrogenation of fused triazolino-succinimides.[1] A representative structure is shown in Scheme 1 with *N*-(4-cyanophenyl)-aziridino-[2,3-*c*]-*N*-phenyl succinimide **1**. When the aziridines were analyzed by ^{1}H NMR, their spectra showed a singlet by 4.0 ppm for the equivalent bridgehead hydrogens H_B and a broad low frequency signal by 6.5 ppm corresponding to the *ortho*-hydrogens H_O of the *N*-phenyl succinimide moiety, which suggested the presence of one or more site exchange processes in the intermediate regime. As illustrated in Scheme 1, several possibilities need to be considered: aziridine nitrogen inversion leading to *endo*- and *exo*-forms (process "a"),[2,3] rotation of the phenyl group linked to the aziridine (bond "b")[4] and rotation of the phenyl group linked to the succinimide (bond "c").

Scheme 1. Possible Dynamic Processes in 1



Aziridines are useful intermediates in the synthesis of several heterocyclic compounds by ring-opening reactions.[5] Fused aziridines are source of azomethine ylides for 1,3-dipolar cycloaddition chemistry to produce complex polyheterocylic compounds.[6] It is known that the ring-opening of aziridines could take place through a S_N2-like nucleophilic reaction. Alternatively, and depending on the substituents, homolytic ring-opening may occur by single electron transfer, SET, near the transition state for nitrogen inversion where the ring strain is maximal and the conformation planar.[7] As there are no reports on dynamic processes in fused aziridines, we thought it would be valuable to analyze *N*-(4-cyanophenyl)-aziridino-[2,3-*c*]-*N*-phenyl-succinimide **1** (Scheme 1) as a test model by variable temperature ^{1}H NMR (dynamic NMR).[8]

The ambient temperature (298 K) ^{1}H NMR spectrum of fused aziridino-succinimide **1** in $CDCl_3$ displayed a sharp singlet at about 3.95 ppm corresponding to the equivalent aziridine hydrogens (H_B), an AA′BB′ pattern at about 7.19 and 7.63 ppm for the *p*-cyanophenyl linked to the aziridine, a low frequency broad singlet at 6.58 ppm, unambiguously assigned by 2D NMR (Supporting Information) to the *ortho*-phenyl hydrogens attached to the succinimide (H_O), and a set of signals at 7.31−7.33 ppm for the *meta*- and *para*-hydrogens of the same ring.

We determined that the *N*-phenyl succinimide portion of the molecule cannot be responsible for the unusual ^{1}H NMR spectrum on its own by documenting that the ^{1}H NMR spectra of several *N*-(aryl)-succinimides display sharp signals in the normal range, between 7.3 and 7.5 ppm.[9] It seemed reasonable to postulate that the low frequency shift in the ^{1}H NMR spectrum of the *N*-phenyl-succinimide *ortho*-hydrogens in **1** may be due to the anisotropic effect of the nearby aziridine *N*-aryl-group in the *endo*-position (Scheme 1). A similar shielding effect was reported by Marshall and Rothchild[4c] in the *endo*-phencyclone derivative **2**, where the fused succinimide phenyl experiences a strong anisotropic effect with a time-averaged shielding effect on the *ortho*-hydrogens of about 1.3 ppm (Scheme 2). If this hypothesis is correct, the shielding and broadening of the *N*-phenyl succinimide *ortho*-signals can be considered reporters for the aziridine nitrogen inversion.

To determine the activation parameters for the conformational exchange, the dynamics of compound **1** were analyzed by variable temperature ^{1}H NMR (VT NMR) in CD_2Cl_2 (acid free) in the range of 188−298 K. The rotation of phenyl groups along bonds "b" and "c" in Scheme 1 was not analyzed due to their fast rotation on the NMR time scale. As illustrated in the

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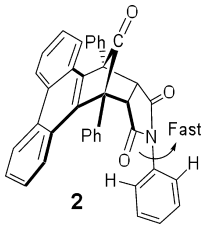
Scheme 2. *endo*-Phencyclone Derivative 2



left panel in Figure 1, the most notable changes in the spectrum were observed in the signals corresponding to H_B and H_O. The signal corresponding to the *ortho*-protons in the *p*-cyanophenyl ring (about 7.15 ppm) was removed for the purpose of normalizing and comparing them with the simulated signals. As the temperature is decreased (from top to bottom in the Figure 1), the two signals at about 4.04 and 6.37 ppm broaden and move to higher and lower frequencies, respectively. Around 238 K, the appearance of a second set of smaller signals was observed in the two spectral areas. The full low temperature spectrum at 188 K (Figure 2) shows the signal corresponding to the *ortho*-phenyl protons in the succinimide moiety as two sets with very different intensities at about 6.28 ppm (large, Ho-*endo*) and 7.19 ppm (small, Ho-*exo*), and the signal corresponding to the aziridine hydrogens also splits into large (*endo*) and small (*exo*) peaks at 4.07 and 3.87 ppm, respectively.[10]

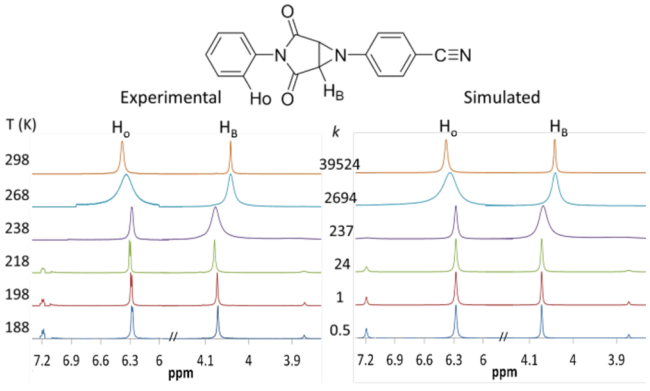


Figure 1. (Left) Temperature dependence of ^{1}H signals (600 MHz in CD_2Cl_2 acid free) of the aziridine protons H_B and *ortho*-phenyl protons H_O in representative spectra. (Right) Corresponding spectra simulated[11] with a model that considers inversion of the aziridine nitrogen, from the most populated conformer (*endo*) to the less stable conformer (*exo*), with the rate constants indicated in units of s^{-1}. Aromatic signals at about 7.1 ppm in the experimental spectra were removed to facilitate comparison with the simulated spectra (the full spectrum at 188 K is shown in Figure 2).

As indicated in Figure 2, it is reasonable to assume that the *endo* structure is the major isomer with the two *ortho*-hydrogens of a rapidly rotating aryl succinimide at about 6.28 ppm experiencing the shielding effect of the nearby *N*-aryl group (i.e., H_O in the structure on the left).[12] The relative integration of the two peaks at 188 K is consistent with an equilibrium constant K_{eq} = 9.9 and a free energy difference ΔG° = 0.9 kcal/mol. This assignment was supported by density functional theory (DFT) calculations performed with Gaussian 09. Geometry optimization of aziridine **1** carried out at the M06-2X level of theory with the 6-31G(d) basis set (see Supporting Information for details) predicts that the *endo* configuration is 3.6 kcal/mol more stable than that of the *exo* configuration in terms of free energy in gas phase. Solvent effects in dichloromethane were computed at the M06-2X/6-311+G-(d,p) level using the gas-phase optimized structures; the *endo* configuration is 2.6 kcal/mol more stable than the *exo* configuration in solution. The distance between the two phenyl groups (~3.2 Å) in the *endo* configuration is approximately that known to give slightly stabilizing interactions due to dispersion effects.[13] The barrier of nitrogen inversion from *endo* configuration to *exo* configuration was calculated to be 12.4 kcal/mol in gas phase and 11.4 kcal/mol in solution. This theoretical value is consistent with the value obtained by dynamic analysis of aziridine **1** which is discussed in the text.

With a model that considers the dynamics of compound **1** to be the result of an exchange process between the *endo*- and *exo*-aziridine structures shown in Scheme 1 and using the chemical shift values obtained at 188 K as the ones corresponding to the two nitrogen invertomers, we were able to simulate the experimental line shapes between 298 and 188 K quite well, as

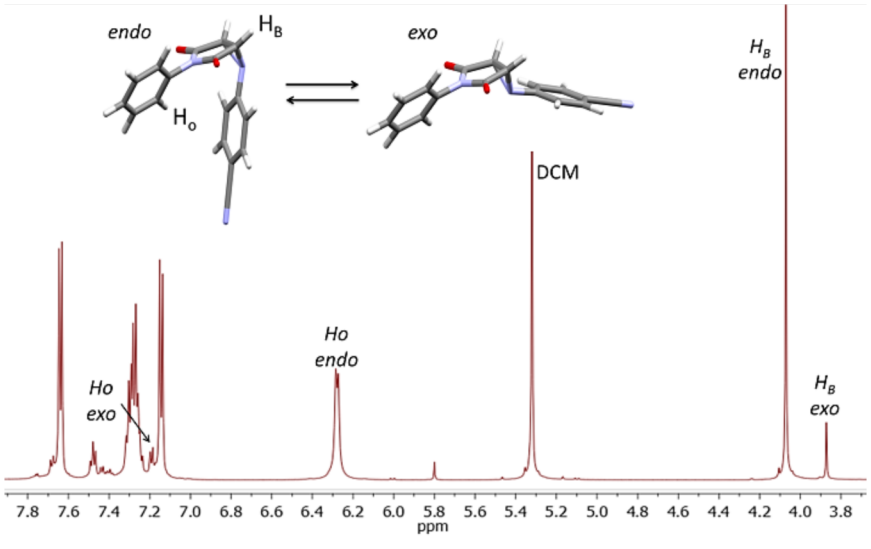


Figure 2. NMR spectrum showing the presence of the two isomers in CD_2Cl_2 acid free at 188 K.

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shown in the right panel of Figure 1. The coupling of Ho with the *meta* protons (7.62 Hz) observed below 228 K was not simulated with the model used. Between 228 and 198 K, the intensity of the coupling increased, but a spectral broadening observed at 188 K can be attributed to changes in the solvent viscosity. Using the experimental temperatures and the exchange frequencies derived from the model, we were able to calculate the activation parameters for nitrogen inversion. An Arrhenius plot gave a modest activation energy (E_a) of 11.6 kcal/mol and a pre-exponential factor A = 9.2 ± 0.5 × 10^{12} s^{-1} (Supporting Information). An Eyring plot (Figure 3) revealed an activation enthalpy, $\Delta H^{\ddagger}$ = 11.1 kcal/mol, and a small negative activation entropy, $\Delta S^{\ddagger}$ = −0.8 cal mol^{-1} K^{-1}.

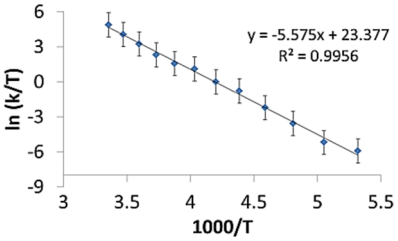

Figure 3. Eyring plot for the nitrogen inversion and phenyl rotation processes in compound **1**. The corresponding activation enthalpy and entropy are 11.1 kcal/mol and −0.8 cal mol^{-1} K^{-1}, respectively.

The energy barriers for nitrogen inversion in acyclic amines are in the order of 6.0−6.9 kcal/mol.[14] The energy barrier is increased when hydrogen bonds are present or when there is a combination of inversion and rotation processes.[15] In the case of aziridines, the incorporation of the nitrogen atom into a three-membered ring results in a barrier increase of up to 18−20 kcal/mol. Computational studies suggest that electronegative substituents, either in the aziridine ring or in the nitrogen atom, increase the energy barrier up to values between 16 and 25 kcal/mol.[16] On the other hand, *N*-phenyl substitution leads to lower activation energies in the range of 12−15 kcal/mol, depending on the effects of substituents.[17] *N*-Acyl and *N*-sulphonyl aziridines present efficient nucleophilic ring-opening[7] with energy barriers of 14 and 11 kcal/mol, respectively.[17b,c] Thus, an activation enthalpy $\Delta H^{\ddagger}$ = 11.1 kcal/mol and a very small activation entropy $\Delta S^{\ddagger}$ = −0.8 cal mol^{-1} K^{-1} result in a free energy barrier with a $\Delta G^{\ddagger}$ = 11.3 kcal/mol, all of which fall within the expected range for a good ring-opening reaction. Nonactivated aziridines are generally not liable to nucleophilic ring-opening without prior activation through protonation, *N*-substitution with electron-withdrawing groups, or quaternization. However, the succinimide-fused aziridines studied in this work may be prone to nucleophilic ring-opening even in the absence of electron-withdrawing groups.[1]

In conclusion, variable temperature ^{1}H NMR studies of *N*-(4-cyanophenyl)-aziridino-[2,3-*c*]-*N*-phenyl maleimide allowed us to confirm that the aziridines fused with succinimide rings present observable nitrogen inversion in solution. The presence of the phenyl ring linked to the succinimide moiety moderately decreases the energy barrier for the nitrogen inversion. The nitrogen inversion equilibrium is unsymmetrical, where the *endo* invertomer is more stable. A regio-controlled ring-opening reaction can develop a useful tool in organic synthesis for the synthesis of several functionalized nitrogen-containing target compounds. Moreover the nitrogen inversion energy barrier has very important effects in the lithiation and trapping with electrophiles, formation of azomethine ylides, and *N*-oxidation of tertiary alkylamines.[18] The likelihood of dispersion effects stabilizing this conformer is suggestive of strategies to control aziridine energetics.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Calculation details, M06-2X-optimized geometries of endo- and exo- conformers and nitrogen inversion transition state, and optimized Cartesian coordinates, as well as spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mgg@chem.ucla.edu.

Notes

The authors declare no competing financial interest.

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