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Restricted rotations and stereodynamics of aziridine-2-methanol derivatives

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Dedicated to Professor Alfredo Ricci of the University of Bologna on the occasion of his retirement

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ABSTRACT

'Gear-like' rotations of simple C–C bonds have been observed in some aziridine methanol derivatives. These restricted rotations have been studied by dynamic and multinuclear magnetic resonance experiments, and the barrier for rotations of Csp^3–Csp^3 and Csp^3–Csp^2 bonds have been calculated. The role of an intramolecular hydrogen bond on the stereodynamics has also been demonstrated.

1. Introduction

One of the most fascinating subjects for many chemists deals with the control and understanding of molecular motion.[1–4] Such investigation is particularly appealing either intellectually, for the scientist that faces the challenge to control even a single molecule, or for potential applications. The concept of molecular devices and molecular machines could be traced back to the resolution of the first conformationally restricted biphenyl by Christie and Kenner in 1922.[5] Since then, the idea of a molecular device has been often associated with molecules showing 'correlated', 'geared', and 'restricted' rotations, allowing the development of ingeniously designed molecular structures that exhibit controlled movements, upon energy input, such as artificial muscles,[6] molecular switches, and molecular motors.[7–9] Therefore, investigation of molecular rotors freely floating in a solution is fascinating in its own right, and also for their potential use in nanotechnology.[10] Nevertheless, before it makes much sense to mount rotor molecules on surfaces or into devices, it is necessary to synthesize and to establish their basic characteristics, such as the rotational barriers. Such synthesis and characterization are nearly always performed in solution.

With this premise, we wish to report here the results concerning the restricted rotations observed in some aziridine-2-methanol derivatives and the study of this phenomenon by dynamic nuclear magnetic resonance (DNMR).[11] This investigation allowed us to calculate some Csp^2–Csp^3 and Csp^3–Csp^3 rotational barriers and highlight a sort of 'geared' rotation between aryl and alkyl substituents.

2. Results and discussion

We have recently reported on the stereoselective hydroxyalkylation of lithiated diphenylaziridines (*S*,*S*)-**1a**,**b** observing that the use of sterically hindered aldehydes, such as mesityl aldehyde, furnished, respectively, the trapping products **2a**,**b** in THF and **3a**,**b** and *diast*-**3a**,**b** in toluene (Scheme 1).[12] At that time, we noticed, during the spectroscopic characterization of the above derivatives, the presence of broad signals in the NMR spectra likely ascribed to a slow nitrogen inversion often observed in *N*-alkyl aziridines.[13–17] Nevertheless, we had the doubt that such signal broadening could be the result of restricted rotations around some C–C bonds. In order to fulfill our curiosity, and aware of the importance of dynamic phenomena, we decided to run a variable temperature (VT) NMR investigation on aziridines **2a**,**b**, **3a**,**b**, and *diast*-**3a**,**b**.

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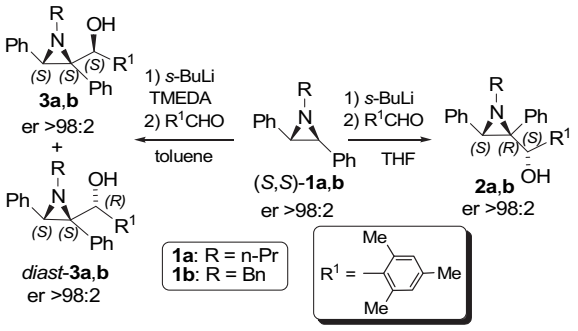


Scheme 1.

Aziridines **2a**,**b** were initially investigated by ^{1}H NMR in CD_3OD solution at room temperature, and it was verified that the *meta* protons and the protons of the two *ortho* methyl groups of the mesityl ring showed featureless lumps, likely as a consequence of a hindered rotation around the Csp^3–Csp^2 bond between the carbinolic carbon and the *ipso* carbon of the mesityl ring.

The relative and absolute configurations of **2a**,**b** were ascertained by X-ray analysis, which furnished also useful structural information (see Supplementary data). In the solid state, an almost identical arrangement of the mesityl ring, with respect to the other two phenyl rings, was observed in both **2a** and **2b**. In both cases, the aziridine nitrogen substituent was found in a *syn* relationship with respect to the carbinolic group so preventing the formation of a hydrogen bond with the hydroxyl group.[18] This evidence, observed in the solid state, suggested that the broad signals seen in the ^{1}H NMR spectra likely could be ascribed to hindered rotation instead of a nitrogen inversion.[19]

To prove this hypothesis, CD_3OD solutions of aziridines **2a**,**b** were analyzed by NMR in the range of temperature 203–340 K. It was found that below 253 K the signals of the *meta* protons and of the two *ortho* methyl groups of the mesityl ring became sharper as a result of a slowed down rotation of the mesityl ring with respect to the NMR timescale. In the case of **2a** (Fig. 1), at 203 K very sharp signals were observed for the *meta* protons ($H_{c/d}$) and the two *ortho* methyl groups ($Me^{a/b}$) of the mesityl ring. At this temperature the mesityl ring rotates so slowly that rotation of the phenyl ring bonded to the quaternary aziridine carbon atom is also slowed down. The slow rotation of the aromatic rings produced, in the NOESY 2D spectra of **2a**,**b**, exchange peaks between slow exchanging anisochronous protons ($H_{o/o'}$, $H_{m/m'}$ $H_{c/d}$, and $Me^{a,b}$ in Fig. 1).[20–23] Another important evidence coming from the low-temperature NMR spectra of **2a**,**b** was that a single conformer, with a fixed configuration at the aziridine nitrogen, was populated because the spectra were not complicated by conformational or configurational diastereoisomers, and anisochronous signals were observed for $H_{c/d}$ and $Me^{a,b}$ in a 3/1 ratio.[24] Likely for steric reasons, the restricted rotation around the single C–C bond between the quaternary aziridine carbon and the carbinolic carbon could allows a sort of 'geared rotation' of the aromatic rings.[25–28] In fact, in the case of **2a**, the NOESY 2D spectra (Fig. 1) showed spatial interactions between the two *ortho* protons ($H_{o/o'}$) of the phenyl ring bonded to the quaternary aziridine carbon, and just one *ortho* methyl group of the mesityl ring ($Me^{a/b}$) at 203 K. Such spectroscopic evidence could be likely explained assuming that the mesityl ring rotates, at this temperature, slower than the phenyl ring and that they are close to each other just like in a 'gear'.[29]

By lineshape analysis of the ^{1}H NMR spectra of **2a**,**b** in the range 203–340 K (see Supplementary data), the Csp^2–Csp^3 barriers for rotation of the mesityl ring were obtained (Table 1).

The corresponding diastereoisomeric aziridines **3a**,**b** and *diast*-**3a**,**b** were also subjected to a similar multinuclear and VT NMR investigation.

By single crystal analyses of **3a**,**b** and *diast*-**3a** it was ascertained that the nitrogen substituents sat to the opposite side with respect the carbinolic carbon (Fig. 2). In the crystal structures, the presence of hydrogen bonds between the hydroxyl group and the aziridine nitrogen lone pair was ascertained for both **3a**,**b** but not for *diast*-**3a**.[30]

Such a hydrogen bond, which has been demonstrated to be persistent also in solution,[30] could prevent the formation of conformational diastereoisomers by rotation around the bond between the carbinolic carbon and the aziridine quaternary carbon.[31]

This hypothesis has been supported by NMR experiments (Fig. 2). At 200 K, under slow exchange conditions, a main conformer was populated for aziridines **3a**,**b** and different rotation rates were observed for the two trans configured phenyl rings as a consequence of this hydrogen bond-promoted locked conformation (Fig. 2).[32]

In striking contrast, FT-IR analysis of aziridines *diast*-**3a**,**b** demonstrated the absence in solution of either an inter- or intramolecular hydrogen bond (Fig. 3) just as found by X-ray analysis on *diast*-**3a**. Experiments run in CD_3OD and toluene-d_8, under slow and fast exchange conditions, proved once more the presence of a main conformer with different rotation rates between the two trans configured phenyl rings, and a restricted rotation for the C–C bond between the aziridine quaternary carbon and the carbinolic carbon (Fig. 3). In the case of *diast*-**3a**, again a gear-like rotation between the phenyl ring (in blue in Fig. 3) and the mesityl ring has been hypothesized. In fact, NOESY 2D spectra showed single spatial correlations for each *ortho* proton $H_{o/o'}$ and each methyl group ($Me^{a/b}$) of the mesityl ring (Fig. 3) proving a mutual hindered rotation under these experimental conditions (200 K).[33]

Lineshape analysis of VT NMR spectra of **3a**,**b** and *diast*-**3a**,**b** (see Supplementary data), allowed to evaluate only the rotational barriers for the Csp^3–Csp^2 bond between the carbinolic carbon and the *ipso* carbon of the mesityl ring (Table 1).

Next, we investigated the effect of the *t*-Bu group using aziridines **4** and **5** obtained from aziridine **1a** in toluene.[34] The VT NMR of **4** in CD_3OD demonstrated again the presence of a single conformer at low temperature (200 K), and an interesting dynamic phenomenon involving the *t*-Bu group (Fig. 4).[35] Even in this case, X-ray and FT-IR analyses demonstrated the presence of an intramolecular hydrogen bond-promoted fixed conformation likely responsible of a correlated rotations between the phenyl rings (depicted as A–C in Fig. 4) and the *t*-Bu group. In fact, upon cooling to 200 K of **4**, three signals were seen for the *t*-Bu group assigned to three non equivalent methyls (1/1/1 relative ratio) by HSQC-DEPT experiment (Fig. 4). The aromatic region of the spectrum showed several anisochronous signals for the phenyl protons as a consequence of a slowed down rotation of each phenyl ring (Fig. 4, rings A–C).

Upon warming to 330 K, the signals of the three methyl groups merged into a broad signal, and a more complex situation was found in the aromatic region at this temperature. However, lineshape analysis gave the Csp^3–Csp^3 rotational barriers of the *t*-Bu group (Table 1).[36–38] In order to evaluate if the substituent on the carbinolic carbon could affect the correlated rotations between groups, aziridine **5** was analyzed by VT NMR. The ^{1}H NMR spectra of aziridine **5** showed two sets of signals in a different ratio depending on the solvent (Fig. 5). At 200 K, two main conformers in 67/33, 75/25, and 90/10 ratios were detected in toluene-d_8, $CDCl_3$, and CD_3OD solution, respectively. This was in striking contrast with the results on aziridine **2a**,**b**, **3a**,**b**, *diast*-**3a**,**b**, and **4** where one main conformer was always observed. In the case of **5**, FT-IR analyses demonstrated the presence of both free and intramolecularly bonded OH group, up to high dilution, likely ascribed to different conformers.

By comparison of ^{1}H NMR chemical shifts, we were able to propose **B** as the main conformer in CD_3OD while **A** should persist in toluene (Fig. 5).[39] Attempts to obtain suitable crystals of **5** failed.

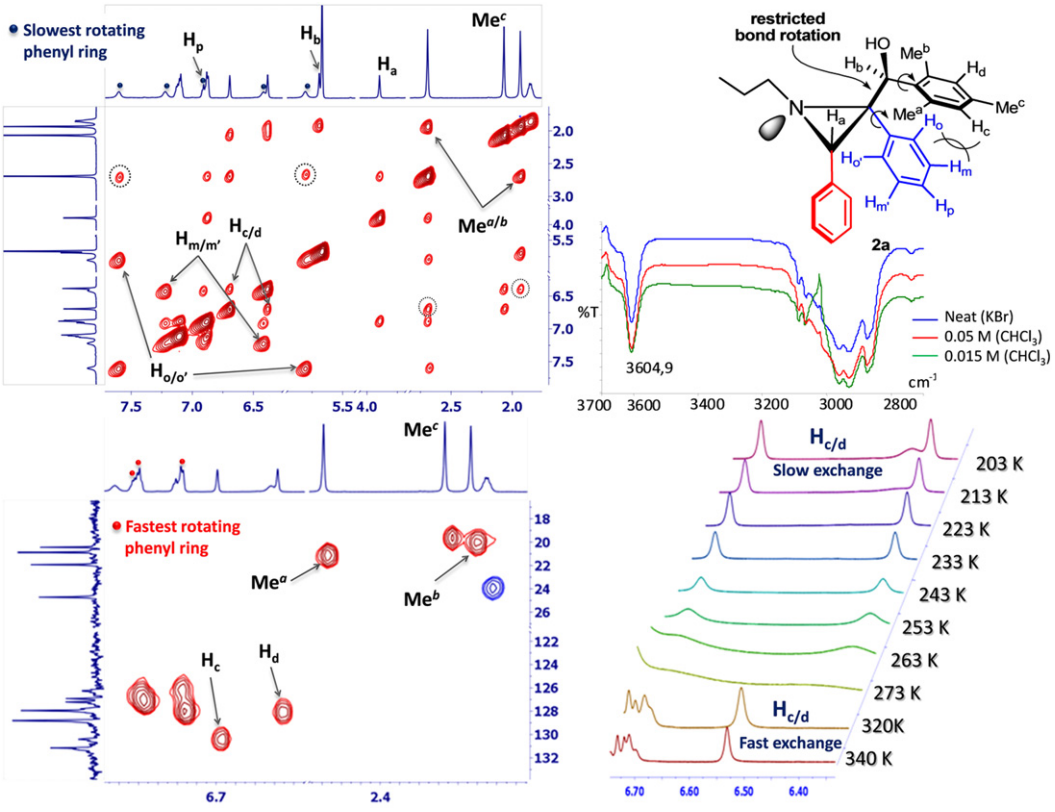
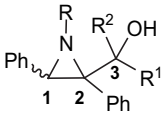


Fig. 1. Spectroscopic analysis of **2a** in CD_3OD. (top, left) 600 MHz ^1H NOESY 2D (203 K), dotted circles highlight the interactions of the methyl groups ($Me^{a/b}$) of the mesityl ring with $H_{o/o'}$ of the slowest rotating blue phenyl ring; (bottom, left) $^1H-^{13}C$ HSQC DEPT showing CH and CH_3 in red and CH_2 in blue; (top, right) FT-IR spectra neat and in solution showing a free OH; (bottom, right) ^1H VT NMR experiments.

Table 1
Rotational barrier in aziridine-2-methanol derivatives



Aziridine[a]	R	R^1	R^2	Configuration[a]	Rotation	$\Delta G^{\neq b}$
2a	*n*-Pr	Mes[c]	H	(*S*,*R*,*S*)	Csp^2-Csp^3	12.7[d]
2b	Bn	Mes[c]	H	(*S*,*R*,*S*)	Csp^2-Csp^3	13.2[d]
3a	*n*-Pr	Mes[c]	H	(*S*,*S*,*S*)	Csp^2-Csp^3	11.2[d]
diast-**3a**	*n*-Pr	Mes[c]	H	(*S*,*S*,*R*)	Csp^2-Csp^3	13.5[d]
3b	Bn	Mes[c]	H	(*S*,*S*,*S*)	Csp^2-Csp^3	11.1[d]
diast-**3b**	Bn	Mes[c]	H	(*S*,*S*,*R*)	Csp^2-Csp^3	11.3[d]
4	*n*-Pr	Ph	*t*-Bu	(*R**,*S**, *S**)[e]	Csp^3-Csp^3	13.6[d]
5	*n*-Pr	*t*-Bu	H	(*S*,*S*,*R*)	Csp^3-Csp^3	12.4[f]

[a] See Scheme 1 for configuration.
[b] Error range±0.10 (see Supplementary data).
[c] Mes=2,4,6-$(Me)_3C_6H_2$.
[d] Barrier for C_3-R^1 bond.
[e] Barrier for C_2-C_3 bond at 273 K.

However, by calculation two conformers (**A** and **B** in Fig. 5) were found and their structure optimized at the B3LYP 6311+G(d,p) level. According to NMR experiments in toluene, it was found that in the gas phase conformer **A** was more stable of 0.8 kcal/mol with respect to conformer **B**.[40] By lineshape analysis the Csp^3-Csp^3 rotational barrier for the **A**⇆**B** interconversion was calculated (Table 1).

3. Conclusion

This work reports an interesting dynamic phenomena observed in aziridine-2-methanol derivatives showing a kind of gear-like rotations between groups. This study also demonstrated the role of hydrogen bond and steric hindrance in favoring restricted rotations around a single Csp^3-Csp^3 bond responsible of a preferential conformation. In addition, for all the compounds investigated, a configurational preference of the aziridine nitrogen has been found. The stereodynamics and the rotational barriers calculated could be important in organic reactivity[41–45] and in the design of new catalysts[46,47] or new molecular devices.[48–50] More work is underway on more simple systems in order to establish gear-slippage, directionality, dynamics of slow moving substituents, and possible applications.

4. Experimental section

4.1. General

Tetrahydrofuran (THF) was freshly distilled under a nitrogen or argon atmosphere over sodium/benzophenone ketyl. Toluene, hexane, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were distilled over finely powdered CaH_2. *s*-BuLi was purchased as cyclohexane solution. All other chemicals were commercially available and used without further purification. For the ^1H and ^{13}C NMR spectra (^1H NMR 600 MHz, ^{13}C NMR 150 MHz), $CDCl_3$, CD_3OD, and toluene-d_8 were used as the solvents. GC–MS spectrometry analyses were carried out on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Infra-red spectra of the compounds were recorded as a film or as KBr disc as indicated, or in chloroform solution (0.05 M and 0.015 M) by an FT-IR spectrometer. For flash chromatography silica Gel 60, 0.040–0.063 mm particle size was used. CHN analyses were performed on a EuroEA 3000 analyzer. All air- and water-sensitive reactions were carried out in

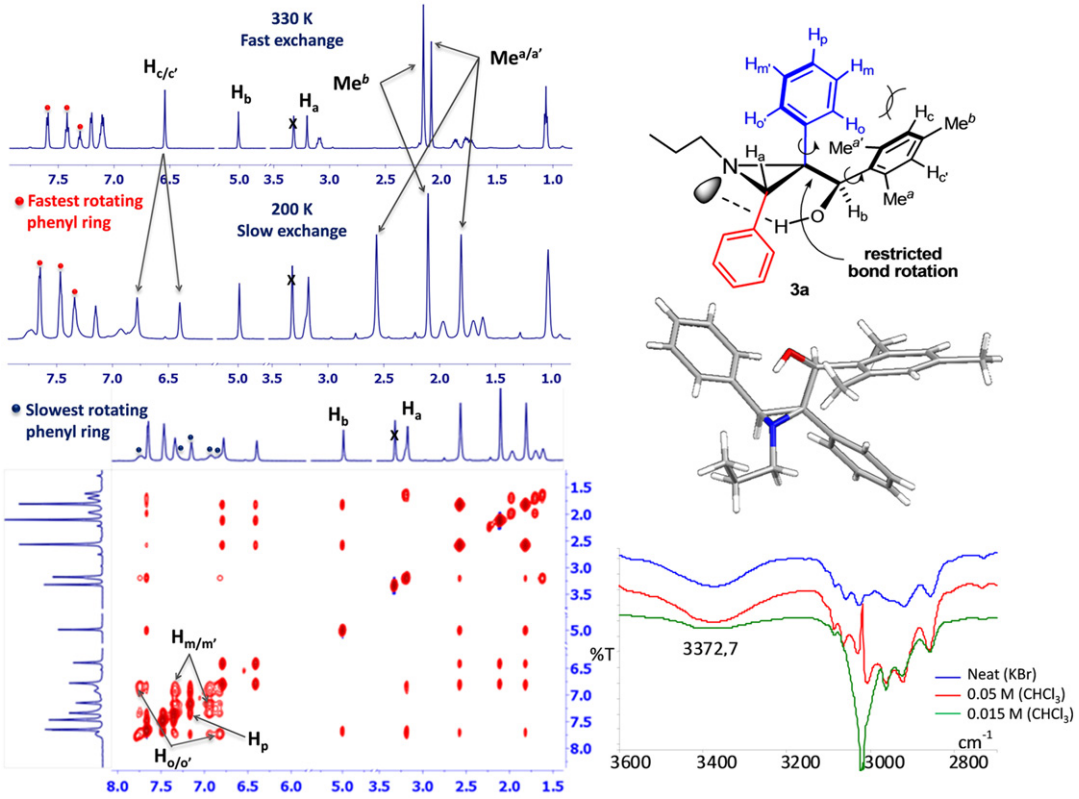


Fig. 2. Spectroscopic analysis of **3a** in CD_3OD. (top, left) 600 MHz, ^1H NMR spectra under slow and fast exchange conditions; (bottom, left) ^1H NOESY 2D (200 K) showing exchange and spatial correlation peaks; (bottom, right) FT-IR spectra showing intramolecularly bonded OH group; (center right) X-ray structure of **3a**.

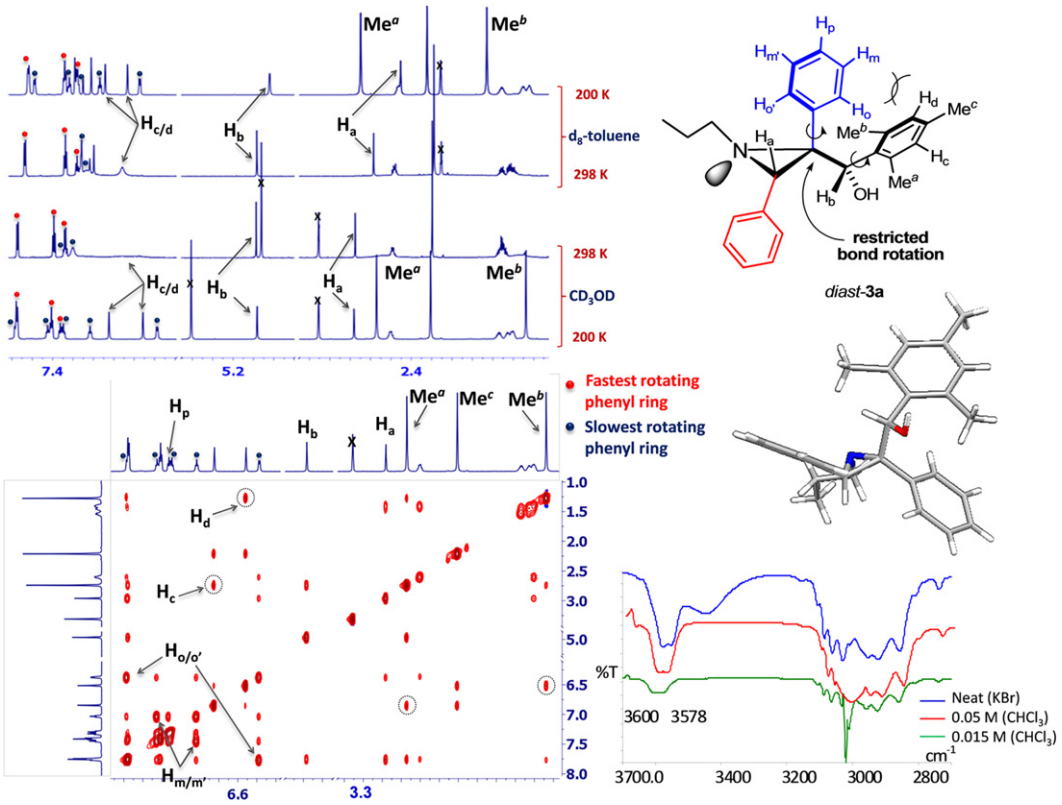


Fig. 3. Spectroscopic analysis of *diast*-**3a**. 600 MHz, (top, left) ^1H NMR spectra under slow and fast exchange conditions; as a consequence of the restricted rotation around the bond between the carbinolic carbon and the aziridine quaternary carbon, solvent and temperature were not affecting the chemical shift of H_b; (bottom, left) ^1H NOESY 2D showing exchange and spatial correlation peaks, dotted circles highlight spatial interactions due to the slow rotation (with respect to the NMR timescale) of the mesityl ring; (bottom, right) FT-IR spectra showing free OH group even in solution; (center, right) X-ray structure of *diast*-**3a**.

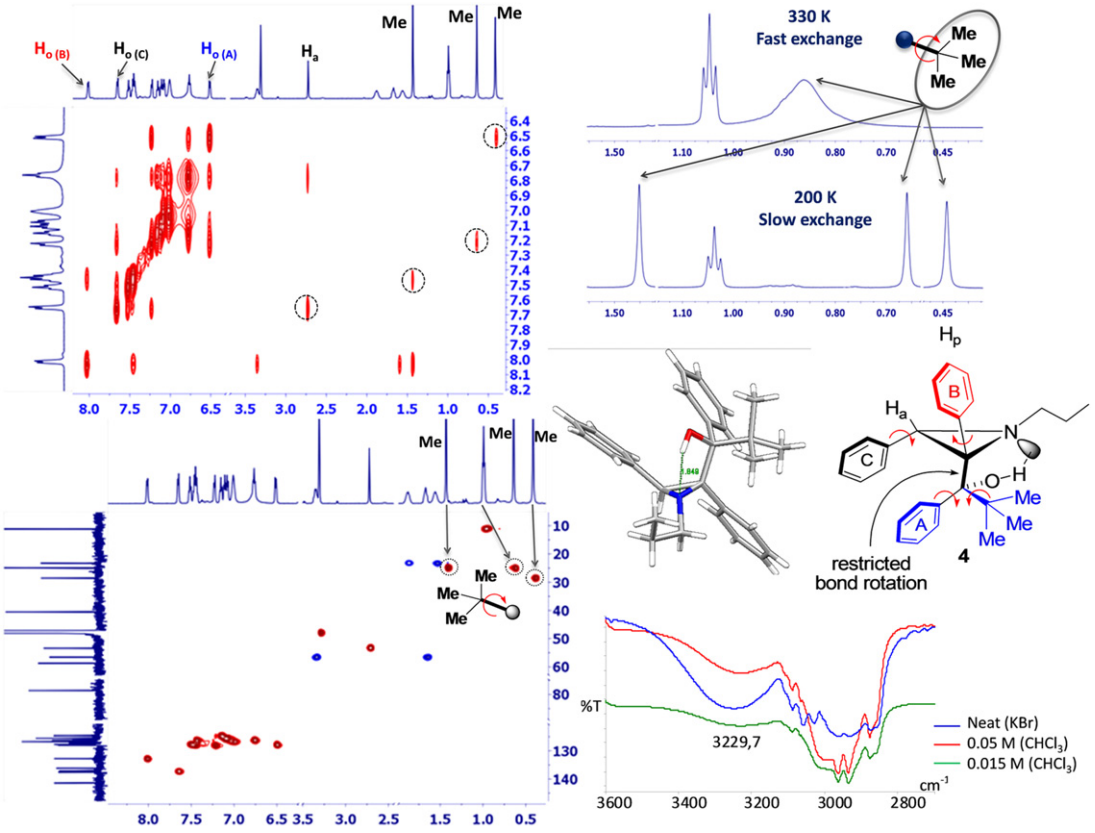


Fig. 4. Spectroscopic analysis of **4** in CD_3OD. (top, right) 600 MHz ^1H NMR spectra under slow and fast exchange conditions; (top, left) ^1H NOESY 2D showing exchange and spatial correlation peaks, dotted circles highlight the slow rotation (with respect to the NMR timescale) of the *t*-Bu group and phenyl rings A–C; (bottom, right) FT-IR spectra proving intramolecular hydrogen bond; (bottom, left) HSQC DEPT at 200 K showing anisochronous *t*-Bu methyl groups; (center, right) X-ray crystal structure of **4**.

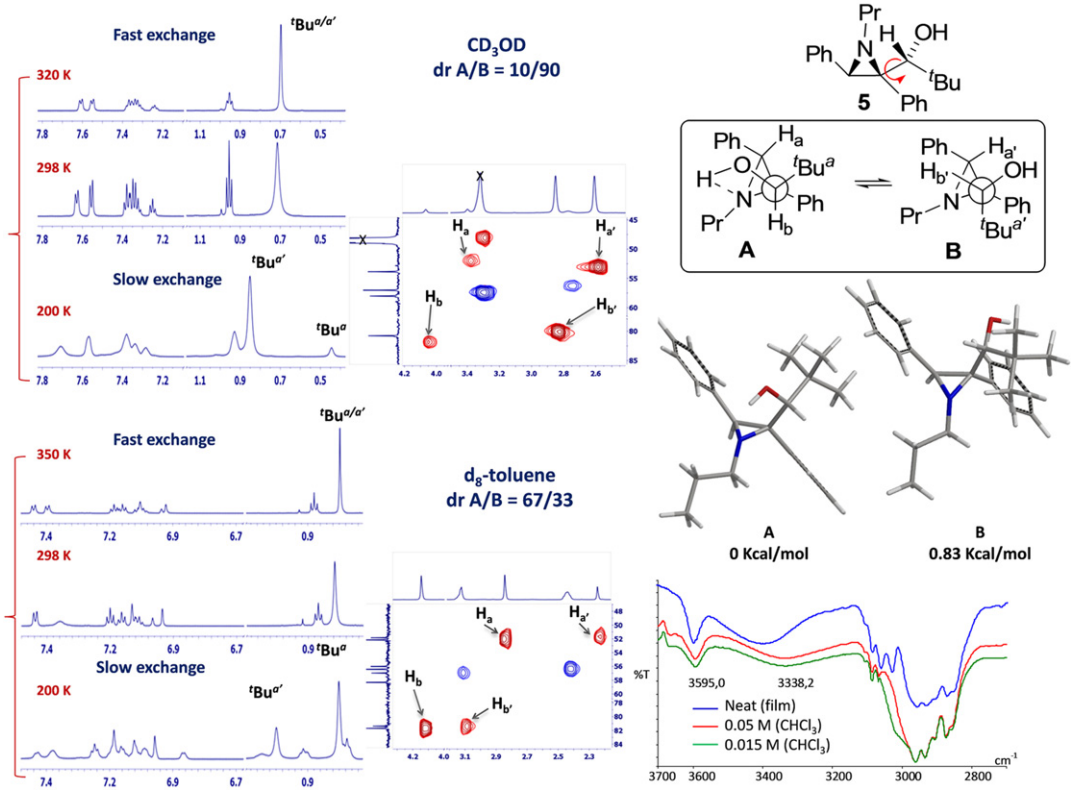


Fig. 5. Spectroscopic analysis of **5**. 600 MHz, ^1H NMR spectra under slow and fast exchange conditions in CD_3OD and toluene-d_8; in conformer A, the *t*-Bu group is shielded by the phenyl ring on the adjacent carbon (top, left); in conformer B, $H_{b'}$ is shielded by the phenyl ring on the adjacent carbon (bottom left); FT-IR spectra showing intramolecularly bonded and free OH group (bottom right); HSQC DEPT at 200 K showing proton correlations; optimized structure for **A** and **B** in the gas phase at B3LYP/6311+G(d,p) level (center right).

oven-dried glassware under argon or nitrogen atmosphere using syringe–septum cap techniques.

4.2. General procedure for the synthesis of 4

To a solution of one of the aziridines (*S*,*S*)-**1a**,**b** (1 mmol) in 10 mL of dry toluene, at −78 °C and under N_2 atmosphere, *s*-BuLi (1.4 M cyclohexane solution, 1.5 equiv) was added dropwise. The resulting yellow solution was stirred for 3 h at this temperature before quenching by dropwise addition of the carbonyl compound (diluted in 2 mL of toluene). The reaction mixture was stirred at −78 °C until consumption of the starting aziridine (TLC, GC–MS monitoring) and warmed up to room temperature. After this time, a solution of satd aq NH_4Cl (3 mL) was added and the mixture poured in 20 mL of water and extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc/hexane) to yield pure aziridine **4**.

4.2.1. (1R,2S*,3S*)-2,2-Dimethyl-1-(2,3-diphenyl-1-propylaziridin-2-yl)-1-phenylpropan-1-ol (**4**).* White solid, mp: 87.9–88.4 °C (hexane), 32%. ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ=0.85 (br s, 9H), 1.04 (t, *J*=7.1 Hz, 3H), 1.61–1.69 (m, 1H), 1.79–1.85 (m, 2H), 2.71 (s, 1H), 3.22–3.27 (m, 1H), 6.79 (d, *J*=7.1 Hz, 2H), 6.91–6.93 (m, 4H), 6.97 (t, *J*=7.7 Hz, 2H), 7.04 (t, *J*=7.1 Hz, 2H), 7.42 (br s, 3H), 7.67 (br s, 1H), 7.90 (br s, 1H). ^{13}C NMR (150 MHz, CD_3OD, 210 K): δ=12.6, 24.7, 26.4, 26.5, 30.0, 42.0, 54.9, 58.0, 60.2, 80.1, 126.1, 127.0, 127.0[2], 127.6, 127.8, 128.2, 128.7, 129.1, 129.4, 129.5, 129.5[3], 134.2, 137.6, 138.6, 139.1, 142.9. FT-IR (KBr) cm^{-1}: 3248, 3057, 2960, 2874, 1602, 1495, 1446, 1393, 1265, 1075, 1058, 1030, 744, 706. ESI-MS *m*/*z* (%): 400 $[M+H]^+$ (100). Anal. Calcd for $C_{28}H_{33}NO$: C, 84.17%; N, 3.51%; H, 8.32%. Found: C, 83.94%; N, 3.57%; H, 8.31%.

The experimental procedures for the preparation of aziridine-2-methanol derivatives **2a**,**b**, **3a**,**b**, *diast*-**3a**,**b**, and **5** have been reported elsewhere.[12]

4.3. NMR Spectroscopy

NMR spectra were obtained at 600 MHz for ^{1}H and at 150.8 MHz for ^{13}C. The assignments of the ^{1}H and ^{13}C signals were obtained by 2D experiments (HSQC DEPT and COSY sequences). The variable-temperature spectra were recorded at 600 MHz for ^{1}H and the temperature was calibrated. NOESY 2D spectra were recorded with a mixing time of 750 ms.

4.4. Computational methods

All calculations were performed using the Spartan 08 program1. Geometry optimizations were performed with the B3LYP DFT functional and the 6-311G* basis set, followed by frequency calculations at the same level of theory. A search for most stable conformers was first executed at lower level of theory. All conformers with relative energy in the range 0–2 kcal/mol underwent search for equilibrium geometry and two local minima were found. The two more stable conformation were optimized at higher level (B3LYP/6311+G-d,p).

4.5. X-ray crystal structure of aziridines 2a,b, 3a,b, *diast*-3a,b

Suitable crystals were grown by slow evaporation of ether/hexane solution or methanol. Crystallographic data for structures **2a**,**b**, **3a**,**b**, and *diast*-**3a**,**b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 830542–830547. Copies of the data can be obtained, free of charge, on application to the CCDC or email: deposit@ccdc.cam.ac.uk.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.128.

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18. FT-IR analysis demonstrated the absence of either inter- or intramolecular hydrogen bond in **2a**. A sharp signal of free OH around 3600 cm^{-1} was observed (Fig. 1, top right).
19. It is expected that, for steric reasons, the invertomers showing a cis relationship between the *N*-alkyl group and the two phenyl rings should be disfavoured. For other examples aziridine nitrogen dynamics and preferential nitrogen configuration see: Ref. 42.
20. NOESY 2D experiments can be used to highlight exchange phenomena just using a suitable mixing time (750 ms), see Refs. 21,22.
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24. HSQC-DEPT experiments were helpful to unequivocally assign the signals of the *meta* protons and the two *ortho* methyl groups of the mesityl ring (see Fig. 1 bottom left and Supplementary data)
25. No change in the chemical shifts was observed for Ha and Hb in the range 203–340 K. For other example of correlated rotation see Refs. 26–28.
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29. In the NOESY 2D spectrum of **2a**, cross peaks between protons $H_{o/o'}$ and one *ortho* methyl group $Me^{a/b}$ (dotted circles in Fig. 1) revealed proximity relationship of the two aryl rings and a polarization transfer process.
30. FT-IR analysis confirmed the presence, in solution, of an intramolecular hydrogen bond in **3a**,**b** (see Fig. 2, bottom right and Supplementary data) and a free OH group in *diast*-**3a**,**b** (see Fig. 3 bottom right and Supplementary data)
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32. Nevertheless, even if it is difficult to demonstrate a geared rotation between the aromatic rings, NMR data confirmed a restricted rotation for the C–C bond between the quaternary aziridine carbon and the carbinolic carbon (i.e the chemical shifts of H_a and H_b were not affected by the temperature), and proximity relationships between $H_{o/o'}$ and $Me^{a/a'}$ (Fig. 2 and Supplementary data).
33. Recording the spectra at 298 K, a broadening of the signals was observed for the protons of the phenyl ring and the mesityl ring likely due to their hindered rotations.

34. Trapping reaction with *tert*-butylphenyl ketone occurred with high stereoselectivity in toluene (dr 80/20) but failed to provide the trapping product in THF.
35. It is likely that, in aziridine **4**, the steric hindrance of the substituents of the carbinolic carbon (*t*-Bu and Ph) and the hydrogen bond between the hydroxyl group and the aziridine lone pair, are again responsible of the restricted rotation around the bond between the carbinolic carbon and the aziridine quaternary carbon, giving only one conformer population.
36. Other examples of slow *t*-Bu group rotation have been reported see Refs. 37,38.
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39. The OH group could interact with a donor solvent, such as CD_3OD. The intramolecular hydrogen bond should then be favored in nonpolar solvent, such as toluene (or $CDCl_3$).
40. The value calculated for ΔG° ($-RT\ln K$) at 200 K in toluene (A/B ratio=67/33) for the conversion A→B was 0.28 kcal/mol.
41. For examples on the relationship between dynamic phenomena and reactivity see Refs. 42–45.
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