Research Article

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Conformational analysis and inversion process in some perhydrodipyrido[1,2-b;1′2′-e]-1,4,2,5-dioxadiazines

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The stereoselectivity in the cyclodimerization of several six-membered cyclic nitrones has been investigated. The configurational/conformational analysis of the dimers (i.e. perhydrodipyrido[1,2-b;1′2′-e]-1,4,2,5-dioxadiazines) has been carried out by NMR spectroscopy. The NMR spectra of the dimers at lower temperatures indicated the presence of either a single or two invertomer(s). The nitrogen inversion barriers are determined using complete line–shape analysis. The invertomer ratios have been used to estimate the relative energies associated with the *cis* and *trans* ring fusion in these tricycles. A mechanistic rationale for the observed stereochemistry of the dimerization process has been presented. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: conformational analysis; cyclic nitrones; cycloaddition reactions; dioxadiazines; inversion barriers; nitrogen inversion; nitrone dimerization; stereochemistry

INTRODUCTION

The mechanism of the formation of perhydrodipyrido[1,2-b;1′,2′-e]-1,4,2,5-dioxadiazine by an apparent (3 + 3) cycloaddition of nitrone **1** still remains a matter of speculation as a result of the forbidden nature of the thermal ($4\pi_s + 4\pi_s$) addition reaction.[1–4] The dimer **2** has been shown to be the *trans*-isomer (i.e. *trans* relationship of the bridgehead Hs), which exists both in crystal and in solution in the tetraequatorial (eeee) conformation with a *trans–trans* ring fusion (Scheme 1).[5] A group has studied the symmetric 4,9-dimethoxy-analogue and assigned the *trans*-configuration for the bridgehead Hs with a probable *cis–cis* ring fusion.[6] The configuration/conformation of 2,7-di-*t*-butyl and 4,9-dibutyl-analogues has been examined in a report.[7] However, the presence of equilibrating nitrogen invertomers in these tricyclic compounds has never been reported before. Here, we report the synthesis of some new dimers with the aim of determining, for the first time, the energetics associated with the equilibration of *trans* ⇌ *cis* ring fusion in this interesting tricycle using NMR spectroscopy. This study would also focus on the mechanistic aspects to provide rationale for the observed stereochemistry of the dimerization process.

RESULTS AND DISCUSSION

The configuration/conformation of the parent dimer **2** has been revisited in this report. The dimer **2** has been shown to be the *trans*-isomer having *trans–trans* ring fusion and tetraequatorial (eeee) conformation around the middle ring (Scheme 1).[5] The previous researchers were unable to detect the presence of ^{1}H signals for minor conformations even at −80 °C using an 100 MHz spectrometer. However, we were able to identify the presence of a minor invertomer *trans–cis*-**2**:eeae (2%) in the NMR spectra measured at temperatures below −40 °C (Figure 1). To the best of our knowledge, this is the first time that the actual presence of a nitrogen invertomer in this class of tricycle has been identified. This has indeed permitted us to calculate the energetics of the inversion process (*vide infra*). While the *trans–trans*-**2**:eeee invertomer ($C_{10}H_{18}N_2O_2$), being centrosymmetric, displayed five carbon signals, the minor invertomer *trans–cis*-**2**:eeae revealed the presence of 10 distinct carbon signals. The conformation of the minor invertomer as *cis–cis*-**2**:aeae is ruled out as it would also be an centrosymmeric isomer. The large coupling constant for the bridgehead C(6)Hs at δ4.33 (2*H*, dd, *J* 3.2, 10.4 Hz) indicated the axial orientation of the hydrogens in *trans–trans*-**2**:eeee, whereas axial C(6)H and equatorial C(6′)H in *trans–cis*-**2**:eeae appeared at δ4.59 (1*H*, dd, *J* 3.1, 9.8 Hz) and 5.40 (1*H*, app s), respectively. The absence of a larger coupling constant for the equatorial C(6′)H and its shift to a higher frequency by almost 1 ppm ascertained the conformation as depicted in *trans–cis*-**2**:eeae. The axial substituent (i.e. C-2′) at *N*(1′) will have γ–gauche interactions with C(6) and as such these carbon signals are expected to be shielded in comparison to the corresponding signals for the *trans–trans*-**2**:eeee isomer. As evident from Table 1, this is indeed the case; both C-2′ and C(6) are shifted to lower frequency by over 7 ppm.

The configurations of *trans–trans*-**2**:eeee and *trans–cis*-**2**:eeae differ in the nature of the ring fusion between the middle ring and the ring at the right terminal; while the former configuration is *trans*-fused, the ring fusion in the latter is *cis*. The thermodynamic parameters associated with the *trans–trans*-**2** ⇌ *trans–cis*-**2** equilibration must then be dictated largely by the energy difference between the *trans*- and *cis* ring fusions. For the

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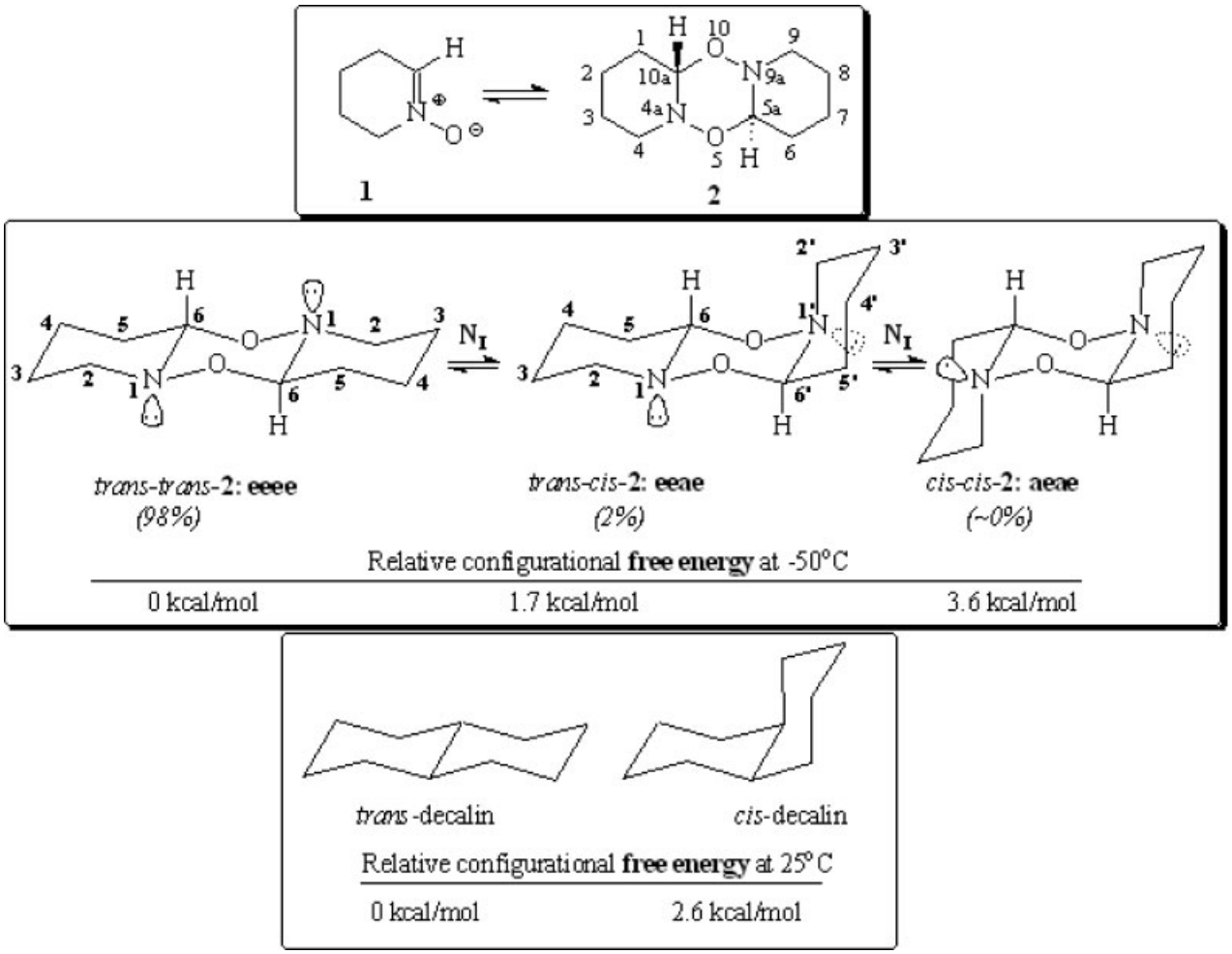

Scheme 1.

sake of comparison, it is worth mentioning the reported thermodynamic parameters for the similar *trans* ⇌ *cis* equilibration in decalins, the carbocyclic counterparts of the equilibrating bicyclic portions of the current tricycle (Scheme 1). For the decalins, a ΔH° value of 2.7 kcal mol^{-1} (11.3 kJ mol^{-1}) favours the *trans*-decalin over its *cis*-counterpart (Scheme 1).[8] While both decalins have a symmetry number of 2, the *cis*-decalin, by virtue of its *dl*-pair enjoys an entropy of mixing of R ln 2 (or 1.38 cal mol^{-1} K^{-1}); however, the experimental value 0.55–0.60 cal mol^{-1} K^{-1} is appreciably less than that, indicating the presence of additional factors affecting the entropy difference. The presence of major and minor invertomers in a ratio of 98:2 translates into a ΔG° value of 1.7 kcal mol^{-1}

Table 1. ^{13}C NMR chemical shifts of the dimers studied in $CDCl_3$

Dimer	Invertomer	C-2	C-3	C-4	C-5	C-6	C-2′	C-3′	C-4′	C-5′	C-6′
2[a]	Major	52.58	24.21	22.09	28.50	96.12	—	—	—	—	—
	Minor	53.31	24.79	22.45	29.27	85.94	44.99	24.21	18.11	28.38	88.96
4[b]	solo	58.43	29.23	18.71	35.25	78.61	—	—	—	—	—
5[b]	solo	67.10	28.54	22.32	35.65	86.27	59.01	29.60	19.03	35.51	90.18
8[c,d]	solo	51.16	26.81	39.30	30.46	94.56					
9[c,d]	major	51.15	26.81	39.33	30.50	94.65	49.49	25.43	36.99	29.46	93.39
	minor	51.65	27.43	39.64	31.29	84.68	44.00	26.63	35.34	29.46	87.95

[a] NMR recorded at −60 °C.
[b] NMR recorded at +25 °C.
[c] NMR recorded at −40 °C.
[d] Data taken from Reference [10].

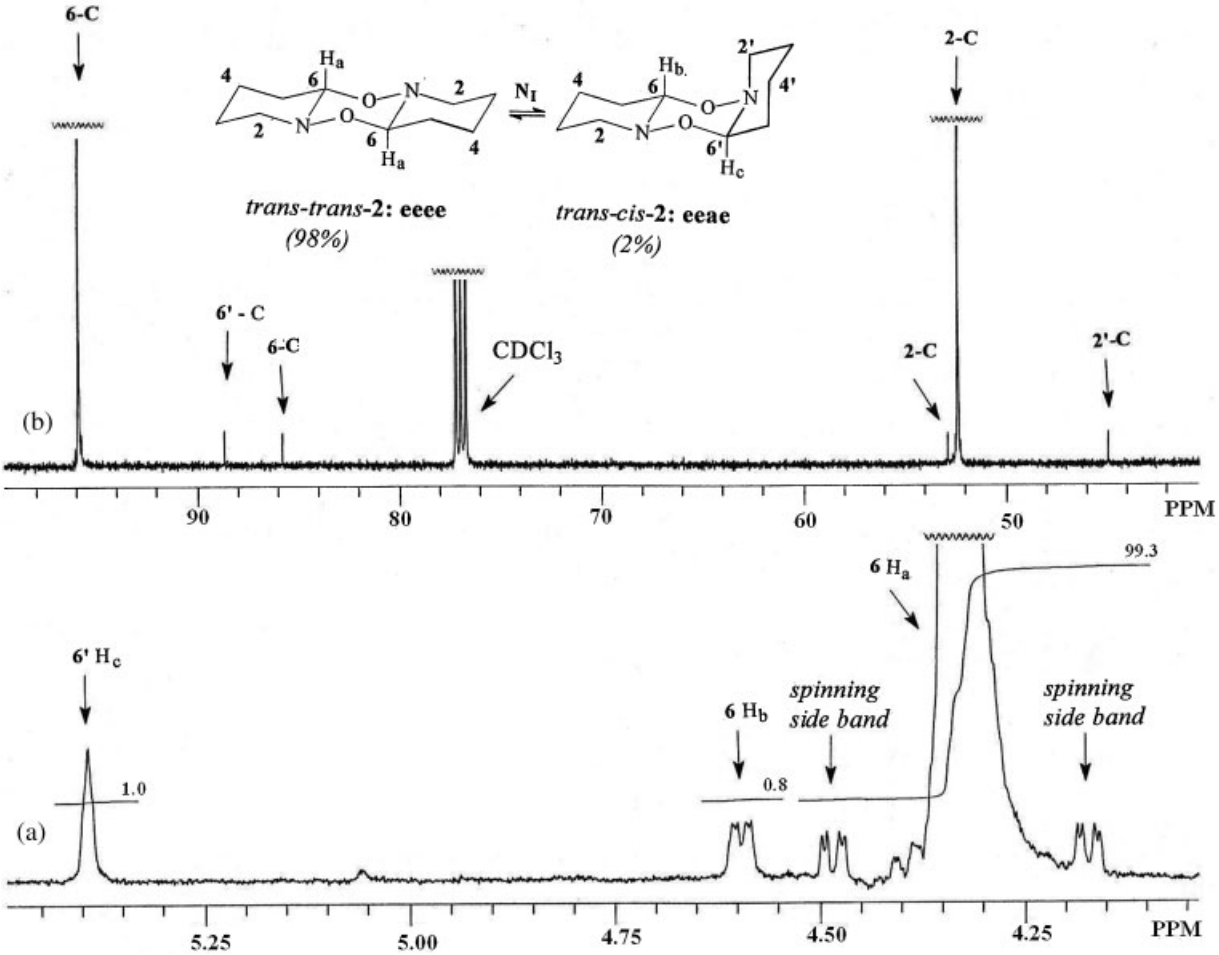

Figure 1. (a) H and (b) ^{13}C partial NMR spectra of **2** at −50 °C in $CDCl_3$

(7.1 kJ mol^{-1}) at −50 °C favouring the major invertomer *trans–trans*-**2**:eeee. While the *trans–trans*-**2**:eeee is centrosymmetric, the minor invertomer *trans–cis*-**2**:eeae is a *dl*-pair and as such, the enthalpy difference, ΔH° is calculated to be 1.8 kcal mol^{-1} (7.5 kJ mol^{-1}) by adding $T\Delta S$ to the ΔG° at −50 °C. $A\Delta S$ value of 0.60 cal mol^{-1} K^{-1}, the experimental entropy difference in the case of decalins, is used in the calculation. For the estimation of the ΔS, the use of decalins as models is quite a rough approximation, since the current compounds have three condensed rings and two oxygen atoms in the central ring. The enthalpy (ΔH°) preference of 2.7 kcal mol^{-1} for the *trans*-fusion in decalin is found to be greater than the 1.8 kcal mol^{-1} determined for the current tricycle. This difference may be attributed to the presence of stabilizing anomeric effect in the *trans–cis*-**2** isomer as a result of the antiperiplanar arrangement of the N(1′)-lone pair and C(6′)—O bond (Scheme 1).

4,9-Diphenylperhydrodipyrido[1,2-b:1′2′-e]-1,4,2,5-dioxadiazi--e]-1,4,2,5-dioxadiazine was prepared by Thesing and Meyer[9] by dimerization of nitrone **3**, but the group did not discuss its configuration or conformation. On revisiting the reaction, it was found that the dimerization process afforded a mixture of two compounds, **4** and **5**, in a kinetic ratio of 85:15 (Scheme 2). Both the dimers were found to equilibrate at 20 °C to a mixture of **3**:**4**:**5** in a ratio of ∼33:2:65, respectively. The major dimer **4** is, thus, found to be a kinetic product, while the minor **5** is the thermodynamic product. Note that the dimers **4** and **5** are not in direct equilibration; rather both **4** and **5** revert back to the monomeric nitrone **3**, which then recombines and partitions in favour of the more stable dimer **5**. The NMR spectra of major dimer **4** gave sharp signals at +25 or −50 °C; the spectral analysis revealed the absence of any minor invertomer. The spectral analysis enabled us to identify the conformation as depicted in *cis–cis*-**4** (Scheme 2). The compound **4** can, in principle, exist in three different configurations, equilibrating via nitrogen inversion. Note that the *trans–trans* configuration is conformationally frozen in the sense that it cannot undergo chair inversion. The chair inversion, although possible, is ruled out in the *cis–cis* and *trans–cis* isomers as it would place both the phenyl groups in destabilizing axial orientation. Spectral data revealed the centrosymmetric nature of the dimer **4** thereby by ruling out the presence of the *trans–cis* isomer. The presence of the other centrosymmetric *trans–trans* isomer is also ruled out as a result of diaxial orientation of the phenyl groups. The ^{13}C NMR spectrum revealed the presence of five aliphatic carbon signals. Both the C(6)Hs appeared at δ5.85 (2*H*, dd, *J* 2.0, 3.8 Hz); while the C(2)Hs were displayed at 4.84 (2*H*, dd, *J* 3.2, 10.8 Hz) ppm. The coupling constant values confirm the equatorial and axial orientations (with respect to the terminal chairs) of the C(6)Hs and C(2)Hs, respectively.

The minor dimer **5** was assigned the *trans–cis* configuration based on the ^{1}H and ^{13}C NMR spectroscopic analysis. Unlike the major dimer **4**, the minor isomer **5** ($C_{22}H_{26}N_2O_2$), in the absence

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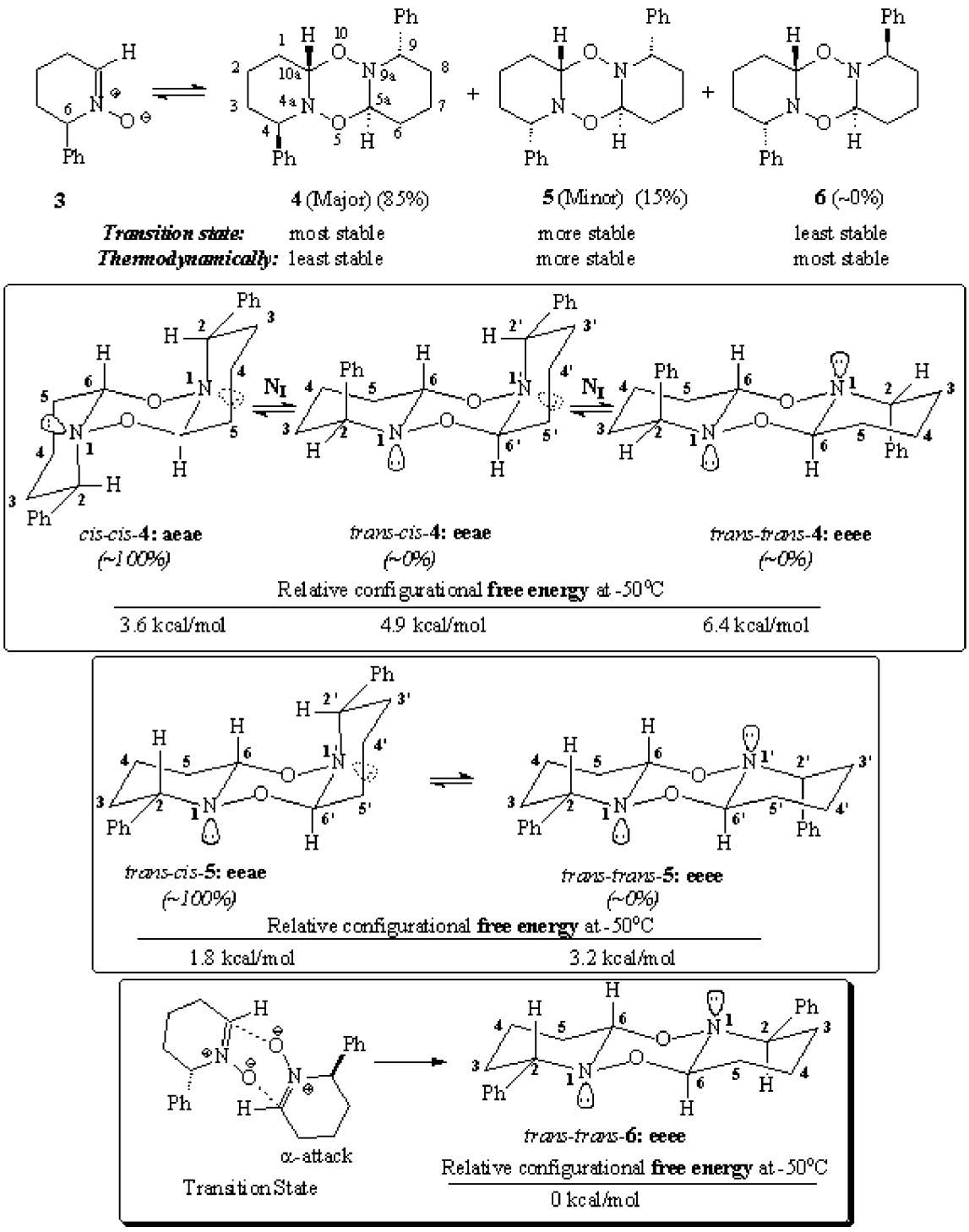
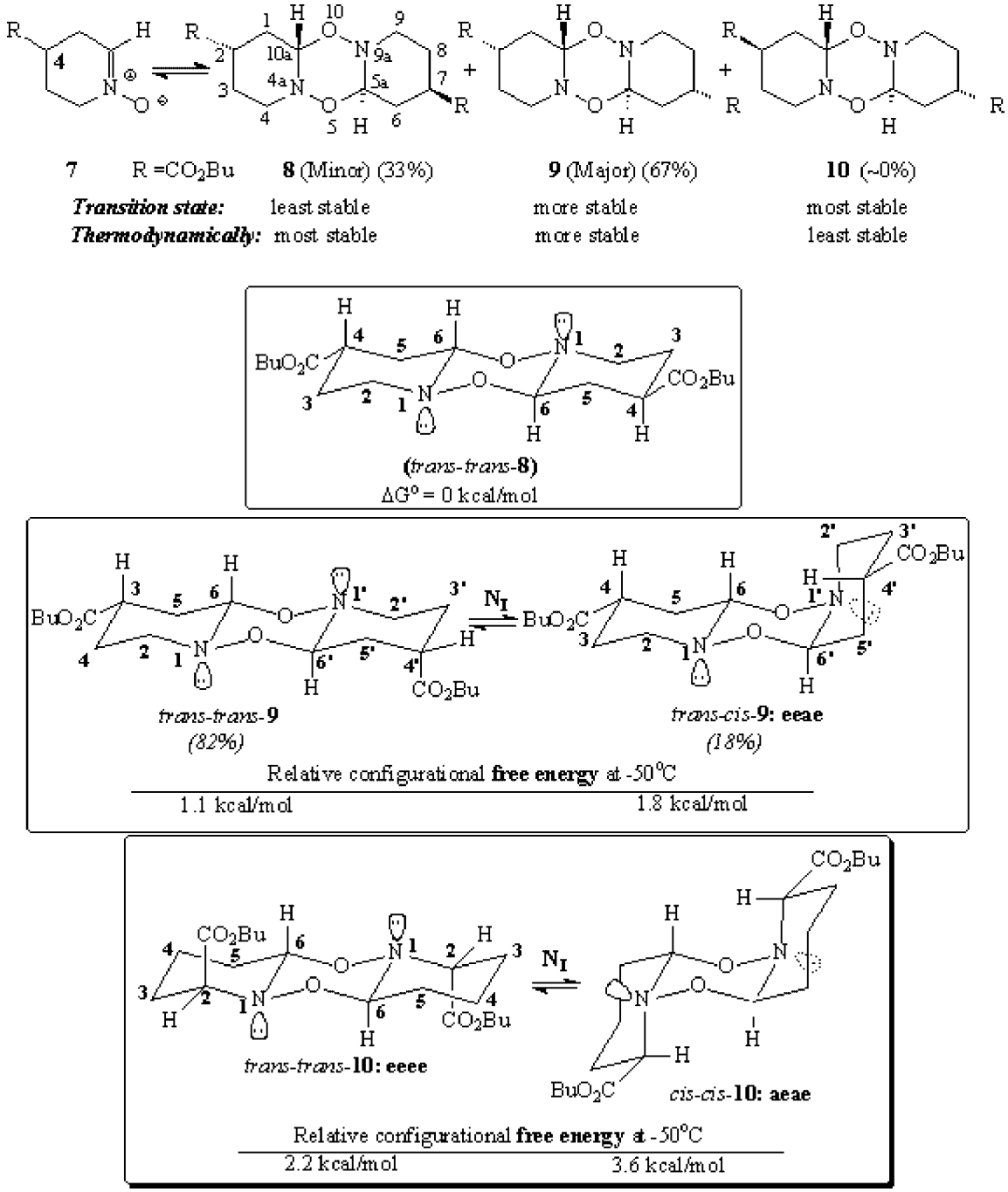


Scheme 2.

of any symmetry, displayed all the 10 possible signals for the aliphatic carbons. The NMR spectra gave sharp NMR signals at +25 or −50 °C; the spectral analysis revealed the absence of any minor invertomer. The signals at δ3.82 (1*H*, dd, *J* 3.2, 11.1 Hz), 4.76 (1*H*, dd, *J* 3.0, 11.0 Hz), 4.85 (1*H*, dd, *J* 3.8, 9.3 Hz), and 5.57 (1*H*, dd, *J* 2.8, 3.4 Hz) were assigned to the axial hydrogens at C(2), C(2′) and C(6), and equatorial proton at C(6′), respectively, with respect to the terminal chairs. As discussed earlier, the axial substituent (i.e. C-2′) at N(1′) will have γ–gauche interactions with C(6) and as such these carbon signals are shifted to considerable lower frequencies (Table 1). Note that the isomer *trans–cis*-**5** having one *cis* ring fusion is found to be more stable than *cis–cis*-**4** having two *cis* ring fusions as ascertained by the thermal equilibration of kinetic dimer **4** to thermodynamic dimer **5** (*vide supra*).

The correctness of the assigned configuration of **4** and **5** is further ascertained by considering the conformational energies of the isomers. The presence of two *cis*-fusions in *cis–cis*-**4** adds a destabilizing interaction of 3.6 kcal mol^{-1}, while its invertomer



Scheme 3.

Table 2. Free energy of activation ($\Delta G^{\neq}$) for nitrogen inversion, ratio of the invertomers, and standard free energy change (ΔG°) for major ⇌ minor isomerization in $CDCl_3$ and CD_3OD

	$CDCl_3$			CD_3OD		
Compound	$\Delta G^{\neq}$ (kcal/mol)[a]	Invertomer ratio[b]	ΔG° (kcal/mol)[b]	$\Delta G^{\neq}$ (kcal/mol)[a]	Invertomer ratio[b]	ΔG° (kcal/mol)[b]
2	16	98:2	+1.7	15	97:3	+1.5
9	14	82:18	+0.67	14	89:11	+0.93

[a] At 0 °C.
[b] At −50 °C.

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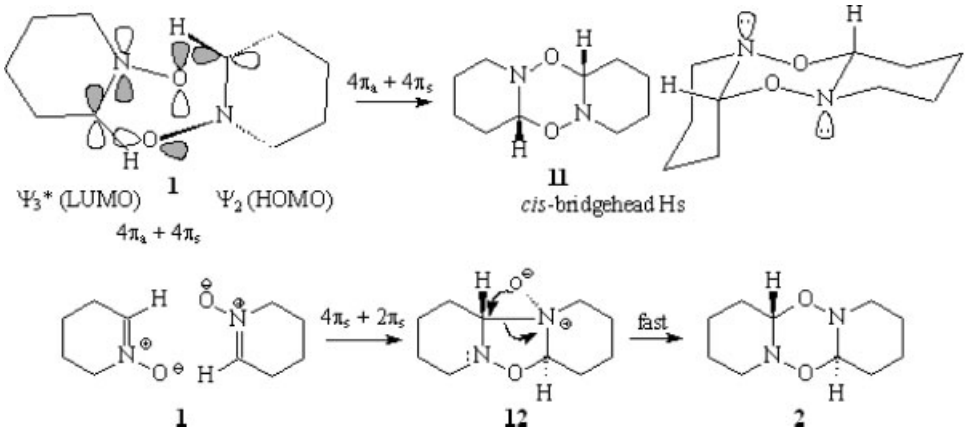

Scheme 4.

trans–cis-**4** has to bear the destabilizing energies of ~3.2 and 1.8 kcal mol^{-1} (i.e. a total of 5.0 kcal mol^{-1}) due to an axial phenyl group and a *cis* ring fusion, respectively (Scheme 2). The *cis–cis*-**4** thus enjoys stabilization enthalpy (ΔH°) of 1.4 kcal mol^{-1} over its counterpart *trans–cis*-**4**. Note that both the isomers have no axis of rotation, while *cis–cis*-**4** is centrosymmetric and *trans–cis*-**4** remains as a *dl*-pair; as such the ΔG° at −50 °C for the *cis–cis*-**4** ⇌ *trans–cis*-**4** equilibration is calculated to be 1.3 kcal mol^{-1} by subtracting the contribution of $T\Delta S$ from ΔH° [an experinmental ΔS value of 0.60 cal mol^{-1} K^{-1}, as in the case of decalins, is used in the calculation]. Likewise, the energy difference favouring the *trans–cis*-**5** over *trans–trans*-**5** is calculated to be 1.4 kcal mol^{-1}, since the former has a destabilizing energy of 1.8 kcal mol^{-1} for the *cis* ring fusion while the later has the conformational energy of 3.2 kcal mol^{-1} for the axial phenyl group. The entropy difference is assumed to be zero since both the invertomers remain as *dl*-pairs and have no axis of rotation. An energy difference of 1.3–1.4 kcal mol^{-1} at −50 °C would predict the presence of 4–5% of the minor invertomers. However, the absence of the minor invertomers indicates the presence of additional factors that contribute to the stabilization/destabilization of the invertomers. The energy difference between the stable configuration of *cis–cis*-**4** and *trans–cis*-**5** may now be calculated to be about 1.8 kcal mol^{-1} in favour of the latter; this is in line with observation of almost complete equilibration of *cis–cis*-**4** to *trans–cis*-**5** at 20 °C (*vide supra*).

Based on NMR findings, both the minor **8** as well as major dimer **9** ($C_{20}H_{34}N_2O_6$), obtained via nitrone **7**, were assigned[10] the *trans* configurations of the bridgehead Hs with a *trans–trans* ring fusion and 'eeee' conformation for **8** as depicted in Scheme 3. Dimer **8** showed NMR signals characterstic of its centrosymmetric structure and remained exclusively as a single invertomer. At ambient temperatures, the NMR spectra revealed that almost half the ring-protons as well as ring-carbon signals of **9** were sharp while the other half were broad. Thus, it is logical to assume that the ring on the right terminal is able to undergo nitrogen inversion that would place the ester group in an equatorial orientation. It would also impart stabilization derived from the anomeric effect of the *anti periplanar* arrangement between the N(1′) lone pair and C(6′)—O bond. The NMR spectra at −50 °C revealed the two invertomers of **9** in a ratio of 82:18, which translate into a ΔG° value of 0.70 kcal mol^{-1} (2.92 kJ mol^{-1}) at −50 °C. Analysis of the conformational energies (ΔH°) reveals that while the *cis*-ring fusion destabilizes the minor invertomer by 1.8 kcal mol^{-1}, the axial-oriented ester group adds 1.1 kcal mol^{-1} to the major invertomer. As a result the major invertomer is expected to be stable by 0.70 kcal mol^{-1}, which is similar to the experimental value of 0.70 kcal mol^{-1} as presented above. Note that both the isomers **9**-*trans–trans* and **9**-*trans–cis* remain as *dl*-pair and have no axis of rotation, and as a result the entropy difference (ΔS) is expected to be zero. While the minor dimer **8** remains stable for weeks in solution at ambient temperatures, the major dimer **9** equilibrates to the nitrone **7** within a week. As discussed earlier, the axial substituent (i.e. C-2′) at N(1′) will have γ–gauche interactions with C(6) of the minor invertomer of **9** and as such these carbon signals are shifted to considerable lower frequencies (Table 1).

At lower temperature, the ^{1}H NMR spectra of the dimers **2** and **9** show some well-separated signals for the two invertomers in $CDCl_3$ or CD_3OD. Integration of the relevant peaks gives the population trends in these systems (Table 2). The proton spectra in $CDCl_3$ and CD_3OD were used in the calculation of the nitrogen inversion barriers. The complete band shape analysis yielded the rate constants and the free energy of activation was calculated using Eyring equation. The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated from plots of ln(k/T) *versus* 1/T. It is well known[11] that NMR band shape fitting frequently gives rather large but mutually compensating errors in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and as such their values are not reported here. However, band shape fitting is viewed as a method of getting rather accurate values of $\Delta G^{\neq}$ (probably within ±0.1 kcal/mol) in the vicinity of the coalescence temperature. The $\Delta G^{\neq}$ values calculated at 0 °C are reported in Table 2, along with the invertomer ratios and ΔG° values at −50 °C. The nitrogen inversion barrier is expected to be high when an oxygen atom is directly attached to the nitrogen as in isoxazolidines.[12,13] The inversion barriers observed in the dimer **2** and **9** in $CDCl_3$ are 16 and 14 kcal mol^{-1}, respectively, while the corresponding values in CD_3OD are found to be 15 and 14 kcal mol^{-1}.

The mechanism by which the dimers are formed still remains a matter of speculation. A thermal ($4\pi_a + 4\pi_s$) symmetry allowed addition reaction, as depicted in Scheme 4, would lead to the formation of the dimer **11** having *cis* relationship of the bridgehead Hs. However, in all the dimerization processes, we were unable to detect the presence of any such *cis* dimer. A more likely mechanism should involve the symmetry allowed ($4\pi_s + 2\pi_s$) process to lead to the intermediate **12**, which is then quickly isomerized to the dimer **2** via the backside attack by the O^- from the α-face (Scheme 4). For such a scenario, there are three possible steric controlled dimerization processes involving the chiral nitrones **3** and **7**. For instance, the optical antipodes of **3**

would lead to the dimers **4** and **6** by two different approaches: either via crowded face of both the antipodes of the nitrones approaching the destabilized transition states (TS) (refer the TS leading to dimer **6** in Scheme 2) or the most favourable TS in which the least crowded faces of the nitrones approaches to give for the dimer **4**. However, identical enantiomers of **3** can undergo dimerization in a single possible way involving a transition state whereby the more crowded face of **3** faces the less crowded face of the other molecule of **3** having same configuration thereby leading to **5** (Scheme 2). The relative stability of the transition states are in line with composition of the dimers as displayed in Scheme 2. The approximate relative configurational free energies of the different dimers **4**, **5** and **6** are given in Scheme 2. The dimer **6** is not formed, even though it has the most stable configuration having *trans*-fused as well as equatorial oriented substituents (Scheme 2); note that the TS leading to **6** is the most destabilized since the crowded face of both nitrones approaches the TS. As expected the least stable dimer *cis–cis*-**4** equilibrates to more stable **5** (instead of the most stable **6**) in about three weeks' time at 20 °C; the extremely high energetics of the TS leading to **6** precludes its formation. The observations are in line with the concerted mechanism presented in this paper (*vide supra*); otherwise one could have expected the formation **6** via equilibration.

Likewise, the dimerization of the nitrone **7** may lead to three possible dimers: the identical enantiomers leading to **9** and the antipodes leading to **8** and **10**. The relative configurational energies and compositions are given in Scheme 3. Unlike the dimerization of **3**, here in the case of **7**, surprisingly the formation of dimer **10** via the most stable TS was not observed. This could be attributed to its least stable configurations (*trans–trans*-**10** or *cis–cis*-**10**, Scheme 3), which after its formation must be equilibrating to the more stable isomers via the nitrone **7**. It is worth mentioning that the dimer **8** is formed in appreciable quantity, even though the TS is least stable as the crowded face of both the nitrones approaches the TS. However, unlike the dimerization of **3**, the parallel plane approach of the nitrone functionality in **7** does not exhibit steric encumbrance since the substituents at C(4) of the nitrone is at the furthest point from the reacting centre.

Conclusion

The NMR study has successfully identified the configuration of the invertomers of the tricycles containing the 1,4,2,5-dioxadiazine moiety. The presence of relatively slowly equilibrating invertomers has permitted us, for the first time, to determine the energetics of the nitrogen inversion process as well as the energy difference between the *cis* and *trans* ring fusion in these tricycles.

EXPERIMENTAL

General

All m.p.s are uncorrected. I.r. spectra were recorded on a Perkin Elmer 16F PC FTi.r spectrometer. Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). All the solvents were of reagent grade.

The ^{13}C and variable temperature ^{1}H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz. Most of the compounds were studied as 25 mg/cm^3 solutions in $CDCl_3$ and CD_3OD with TMS as internal standard. Multiplicities of the carbons were determined using DEPT experiments.

Dimerization of nitrone 1

The dimer **2** was prepared as described in the literature, m.p. 127–127.5 °C (literature [4] m.p. 126–127 °C). The ^{1}H NMR spectrum in $CDCl_3$ at −50 °C revealed the presence of two invertomers in a 98:2 ratio as determined by the integration of several nonoverlapping major and minor ^{1}H NMR signals.

Major invertomer of 2

δ_H ($CDCl_3$, −50 °C) 1.42 (2*H*, tq, *J* 3.5, 13.4 Hz), 1.53 (2*H*, dq, *J* 3.5, 13.5 Hz), 1.67 (2*H*, tq, *J* 3.4, 13.1 Hz), 1.79 (4*H*, app d, *J* 12.2 Hz), 1.88 (2*H*, app d, *J* 12.5 Hz), 2.64 (2*H*, dt, *J* 2.5, 10.4 Hz), 3.31 (2*H*, d, *J* 9.8 Hz), 4.33 (2*H*, dd, *J* 3.2, 10.4 Hz); δ_C ($CDCl_3$, −60 °C) 22.09, 24.21, 28.50, 52.58, 96.12.

Minor invertomer of 2

δ_H ($CDCl_3$, −50 °C) Nonoverlapping signals at 4.59 (1*H*, dd, *J* 3.1, 9.8 Hz), 5.40 (1*H*, app s); δ_C ($CDCl_3$, −60 °C) 18.11, 22.45, 24.21, 24.79, 28.38, 29.27, 44.99, 53.31, 85.94, 88.96.

The ^{1}H NMR spectrum in CD_3OD at −60 °C revealed the presence of two invertomers in a 97:3 ratio as determined by the integration of several nonoverlapping major and minor ^{1}H NMR signals.

Major invertomer of 2

δ_H (CD_3OD, −60 °C) 1.42 (4*H*, m), 1.57 (2*H*, m), 1.74 (4*H*, m), 1.81 (2*H*, m), 2.59 (2*H*, dt, *J* 2.4, 10.3 Hz), 3.18 (2*H*, d, *J* 9.8 Hz), 4.28 (2*H*, dd, *J* 2.8, 9.5 Hz).

Minor invertomer of 2

δ_H (CD_3OD, −60 °C) Nonoverlapping signals at 3.72 (1*H*, m), 4.68 (1*H*, dd, *J* 3.1, 9.8 Hz), 5.25 (1*H*, m).

Dimerization of nitrone 3

The dimer was prepared as described in the literature.[9]

Thus, 2-phenyl-*N*-hydroxypiperidine was oxidized with yellow HgO to obtain a mixture of nitrone **4** and its regioisomeric ketonitrone as a liquid, which after 6 days at 0 °C triturated with small amount of ethyl acetate gave the colourless crystal of the dimer **4**. The mother liquor on TLC (silica, 1:1 ether/hexane) analysis revealed the presence of two spots belonging to the two dimers R_f (0.84, 0.80). The crystal obtained above represented the dimer **4** having the lower R_f value of 0.80. While the higher R_f spot belonging to the dimer **5** was clean and distinct, the crystalline dimer **4** was found to be unstable on the TLC plate, and gave a trailing spot. The mother liquor on chromatography over silica using 90:10 hexane/ether as eluant gave the higher R_f dimer **5**, which was further purified by crystallization from ether/dichloromethane. The ratio of the major/minor dimer **4** and **5** was approximately 85:15.

4-R*-9-S*-Diphenylperhydrodipyrido[1,2-b:1′2′-e]-5a-H-5a-R*-10a-H-10a-S*-1,4,2,5-dioxadiazine (4)

The major dimer **4** gave sharp ^{1}H and ^{13}C signals and almost identical spectra at +25 or −50 °C. The spectral analysis revealed the absence of any minor invertomer. Mp 200–201 °C (dec)

(ether-dichloromethane), (Found: C, 75.3; H, 7.4; N, 7.9. $C_{22}H_{26}N_2O_2$ requires C, 75.40; H, 7.48; N, 7.99%.) ν_{max} (KBr) 3033, 2942, 2869, 16001, 1493, 1436, 1360, 1310, 1273, 1240, 1188, 1120, 1066, 1036, 1008, 981, 911, 878, 842, 779, 753, and 699 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 1.35–1.95 (12*H*, m), 4.84 (2*H*, dd, *J* 3.2, 10.8 Hz), 5.85 (1*H*, dd, *J* 2.0, 3.8 Hz), 7.22–7.42 (10*H*, m); δ_C ($CDCl_3$, +25 °C) 18.71, 29.23, 35.25, 58.43, 78.61, 127.03, 127.24, 128.75, 142.20.

4-S*-9-S*-Diphenylperhydrodipyrido[1,2-b:1′2′-e]-5a-H-5a-R*-10a-H-10a-S*-1,4,2,5-dioxadiazine (5)

The minor dimer **5** gave sharp ^1H and ^{13}C signals and almost identical spectra at +25 or −50 °C. The spectral analysis revealed the absence of any minor invertomer. Mp 204–205 °C (dec) (ether-dichloromethane), (Found: C, 75.2; H, 7.4; N, 7.5). $C_{22}H_{26}N_2O_2$ requires C, 75.40; H, 7.48; N, 7.99%.); ν_{max} (KBr) 3028, 2924, 2863, 1601, 1491, 1451, 1378, 1349, 1301, 1234, 1182, 1111, 1065, 983, 912, 881, 848, 755, and 699 cm^{-1}; δ_H ($CDCl_3$, +25 °C) 1.35–1.90 (12 H, m), 3.78 (1 H, dd, *J* 3.2, 11.1 Hz), 4.74 (1 H, dd, *J* 2.9, 11.1 Hz), 4.80 (1*H*, apparent dd, *J* 6.4, 7.1 Hz), 5.53 (1*H*, dd, *J* 2.8, 3.4 Hz), 7.20–7.45 (10*H*, m); δ_H ($CDCl_3$, −40 °C) 1.35–1.90 (12*H*, m), 3.82 (1*H*, dd, *J* 3.2, 11.1 Hz), 4.76 (1*H*, dd, *J* 3.0, 11.0 Hz), 4.85 (1*H*, dd, *J* 3.8, 9.3 Hz), 5.57 (1*H*, dd, *J* 2.8, 3.4 Hz), 7.25–7.50 (10*H*, m); δ_C ($CDCl_3$, +25 °C) 19.03, 22.32, 28.54, 29.60, 35.51, 35.65, 59.01, 67.10, 86.27, 90.18, 126.70, 126.93, 126.99 (2C), 127.07 (2C), 128.08 (2C), 128.34 (2C), 142.38, 142.71.

Thermal equilibration of nitrone 4 and 5

A solution of the dimer **5** (10 mg) in $CDCl_3$ (0.7 cm^3) was equilibrated at room temperature for two weeks. ^1H NMR spectrum revealed the presence of **3**:**4**:**5** in a ratio of 35:1:64, respectively. The presence of the nitrone was revealed by nonoverlapping signals at δ 5.10 (1*H*, m), 2.65 (2*H*, m), 2.33 (1*H*, m), 2.1 (1*H*, m).

Likewise, a solution of the **4** nitrone in $CDCl_3$ was equilibrated at room temperature for two weeks. ^1H NMR spectrum revealed the presence of **3**:**4**:**5** in a ratio of 30:3:67, respectively.

Dimerization of nitrone 7

The dimers **8** and **9** were prepared as described in the literature.[10]

Thus a solution of nitrone **7** (3 mmol) in CH_2Cl_2 (5 cm^3), kept at room temperature for 3 days, which after chromatography over silica using 1:4 ether/hexane as eluant afforded the dimers **8** (127 mg) and **9** (240 mg) in a ratio of 1:2.

Minor dimer 8

^1H NMR and ^{13}C NMR spectra at −40 °C remained the same as that of 25 °C; no minor invertomer could be seen. The minor dimer is stable; no appreciable change in the NMR signals happened even after weeks in $CDCl_3$ solution. The ^1H NMR spectrum[10] in $CDCl_3$ at +25 or −50 °C revealed the bridgehead C(6) axial protons at δ 4.32 (2*H*, dd, *J* 3.3, 10.8 Hz); δ_C ($CDCl_3$, −40 °C) 13.84, 19.05, 26.81, 30.25, 30.46, 39.30, 51.16, 64.81, 94.56, 173.31.

Major dimer 9

The NMR spectrum in $CDCl_3$ at −50 °C revealed the presence of two invertomers in a 82:18 ratio as determined by the integration of several nonoverlapping major and minor ^1H NMR signals. The major dimer **9** was equilibrated to nitrone **7** in a ratio of 3:1 after 3 weeks at +20 °C in $CDCl_3$ solution (10 mg in 0.7 cm^3 $CDCl_3$). At lower temperatures the ^1H and ^{13}C NMR spectra of **9** revealed the presence of two invertomers in a ratio of 82:18.

Major invertomer of 9

δ_H ($CDCl_3$, −40 °C) 0.92 (3*H*, t, *J* 7.3 Hz), 0.94 (3*H*, t, *J* 7.3 Hz), 1.36 (4*H*, m), 1.55–2.22 (10*H*, m), 2.28 (1*H*, *J* 12.9 Hz), 2.37 (1*H*, d, *J* 12.8 Hz), 2.55 (1*H*, m), 2.68 (1*H*, app. T, *J* 11.9 Hz), 2.73 (1*H*, app t, *J* 13.4 Hz), 2.83 (1*H*, app s), 3.22 (1*H*, td, *J* 3.0, 10.4 Hz), 3.36 (1*H*, td, *J* 3.0, 10.7 Hz), 4.10 (4*H*, m), 4.33 (1*H*, dd, *J* 3.05, 10.7 Hz), 4.42 (1*H*, dd, *J* 3.05, 11.0 Hz); δ_C ($CDCl_3$, −40 °C) 13.83, 13.89, 19.04, 19.09, 25.43, 26.81, 29.46, 30.24, 30.28, 30.50, 36.99, 39.33, 49.49, 51.15, 64.79, 65.06, 93.39, 94.65, 173.23, 173.31.

Minor invertomer of 9

δ_H ($CDCl_3$, −40 °C) non-overlapping signals at δ3.04 (1*H*, td, *J* 3.0, 10.0 Hz), 3.33 (1*H*, td, *J* 3.0, 10.7 Hz), 3.69 (1*H*, app t, *J* 11.0 Hz), 4.57 (1*H*, dd, *J* 2.5, 11.0 Hz), 5.43 (1*H*, app s); δ_C ($CDCl_3$, −40 °C) 13.83, 13.89, 19.04, 19.09, 26.63, 27.43, 29.46, 30.24, 30.50, 31.29, 35.34, 39.64, 44.00, 51.65, 64.64, 64.79, 84.68, 87.95, 173.37 (2C).

The ^1H NMR spectrum in CD_3OD at −40 °C revealed the presence of nonoverlapping signals at δ 4.33 (1*H*, dd, *J* 2.2, 10.1 Hz) and 4.41 (1*H*, dd, J 3.0, 11.3 Hz) attributed to the NCHO protons of the major invertomer. The corresponding protons of the minor invertomer appeared at δ 4.69 (1*H*, dd, *J* 2.5, 9.8 Hz).

Inversion barrier calculations

Simulations of exchange-affected proton spectra for all the compounds were carried out using a computer program AXEX,[14] corresponding to a two noncoupled sites' exchange with unequal populations. Simulations of exchange affected signals were carried out by modifying the two-site exchange program.[15] The first order coupling to these protons is simply assumed as giving two overlapping site exchanges with the same population ratio and equal rates of exchange. For **2** in $CDCl_3$, signals at δ4.33 (2*H*, dd, *J* 3.2, 10.4 Hz) (major) and 5.40 (1*H*, app s) (minor) were utilized. While for **2** in CD_3OD, signals at δ4.28 (2*H*, dd, *J* 2.8, 9.5 Hz) (major) and 4.68 (1*H*, dd, *J* 3.1, 9.8 Hz) (minor) ppm were utilized. The small coupling of the dd is ignored and assumed as a 'd' with a slight broadening of the doublets. For the minor peak of very low intensity (~2%), the complete analysis was not possible, so we used the width at half height of the minor peak to calculate the approximate rate constant.

For **9** in $CDCl_3$, signals at δ4.42 (1*H*, dd, *J* 3.05, 11.0 Hz) (major) and δ4.57 (1*H*, dd, *J* 2.5, 11.0 Hz) (minor) were utilized, while in CD_3OD, signals at δ4.41 (1*H*, dd, J 3.0, 11.3 Hz) (major) and 4.69 (1*H*, dd, *J* 2.5, 9.8 Hz) (minor) were utilized.

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