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Intramolecular Inversion of Configuration at Tetrahedral Carbon Centres in Dipolar Spiro-σ-Complexes of Amino-, Diamino- and Aminothiotropones: a Dynamic NMR Spectral Study

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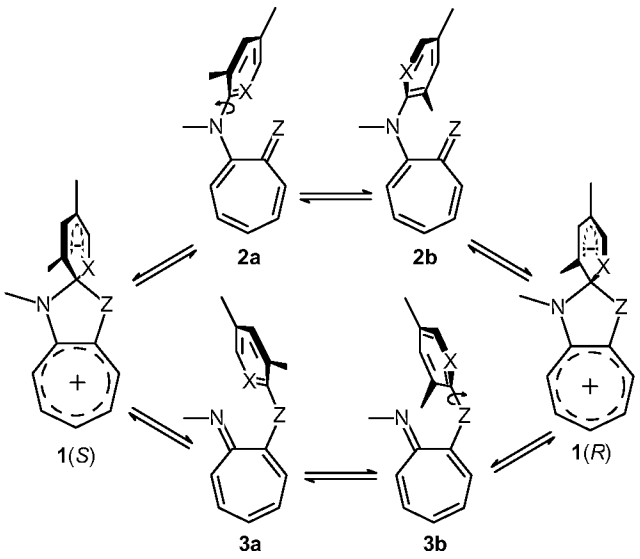
Inversion of configuration at the tetrahedral carbon centres of dipolar spiro-σ-complexes formed by coupling 2-(*N*-benzylamino)tropone, 2-(*N*-benzylamino)thiotropone or *N,N'*-dibenzyl-2-aminotroponimine with electrophilic aromatic and heterocyclic compounds has been found to occur intramolecularly with energy barriers accessible to measurement by means of dynamic ^{1}H NMR spectral techniques.

A broad series of stable dipolar spiro-σ-complexes **1** formed on coupling tropolones and aminotropones with highly electrophilic aromatic and heterocyclic substrates has already been prepared and X-ray structurally characterized.[1–5] In general, compounds of type **1** serve as intermediates in nucleophilic rearrangements caused by fast **2** ⇌ **1** ⇌ **3** migration of aryl and heteroaryl groups activated by strong electron-withdrawing substituents (NO_2, SO_2CF_3, CN) or electro-

negative heteroatoms in the ring. When at least two such activating units are present in the migrating moiety and one or both nucleophilic centres are imino groups NR, spiro-σ-complexes **1** appear to be a thermodynamically more stable species than **2** and can be readily isolated as deeply-coloured crystalline compounds. The topic of fast and reversible nucleophilic rearrangements of compounds of type **2** has been comprehensively reviewed.[1,6,7]

Molecules of spiro-σ-complexes **1** with non-symmetrical aryl or heteroaryl rings contain a stereogenic spiro-carbon centre and are, therefore, chiral. Assuming that the energy barriers to rotation around the C_{aryl}–Z bonds (Z = O, N, S) are sufficiently low, it may be concluded that the sequence of **1**(*R*)⇋**2a**⇋**2b**⇋**1**(*S*) reaction steps involves inversion of configuration at the tetrahedral spiro-carbon centre (Scheme 1).



Scheme 1

Here we report on the quantitative assessment of the energy barriers to such an inversion in a series of stable spiro-σ-complexes **4–6** by means of a dynamic ^{1}H NMR spectral technique. The general feat of placing a prochiral group in the vicinity of a chiral (another prochiral) centre has been implemented to make it possible to measure energy barriers to enantiomerization (enantiotopomerization) without prior separation of the enantiomers. Examples of the successful application of this approach to studying enantiomerization processes proceeding through dissociation–recombination of a bond formed by stereogenic tetrahedral carbon[8,9] or other main group element[10,12] centres are ample in the literature.

Fig. 1 portrays a typical temperature dependent spectral pattern of the diastereotopic methylene protons of the benzyl

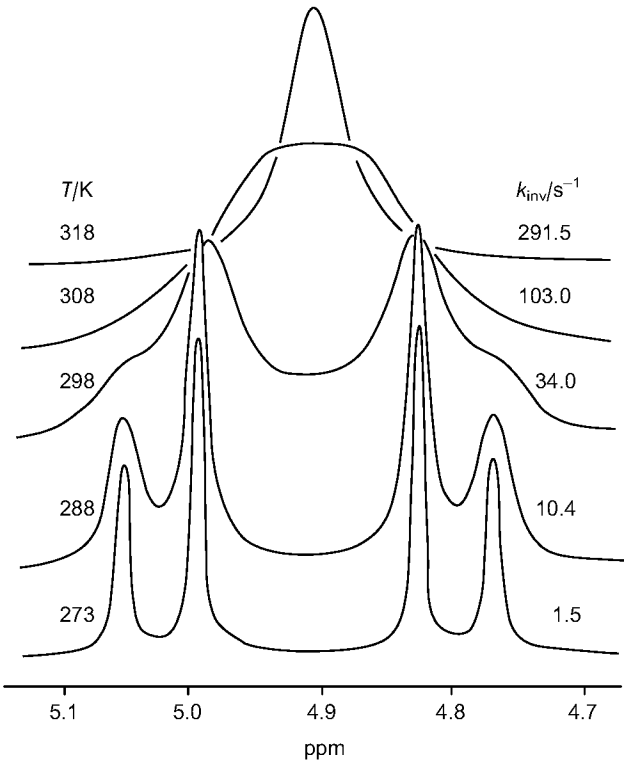


Fig. 1 Temperature evolution of the AB spectral pattern of methylene protons of **5b** (solvent, [$^2H_5$]nitrobenzene).

group in compound **5b**. Averaging the AB spectrum observed at elevated temperature witnesses a loss of the chirality of the molecule due to fast (on the ^{1}H NMR time scale) breaking of the C–S or C–N bond at the C_{spiro} atom with subsequent recombination, as shown in Scheme 1.

By total line-shape analysis of the temperature dependent spectra of compounds **4–6**, kinetic parameters for the racemization reaction **1**(*R*)⇋**1**(*S*) have been calculated and are listed in Table 1. These were found not to be appreciably affected by the concentration of the solutions.

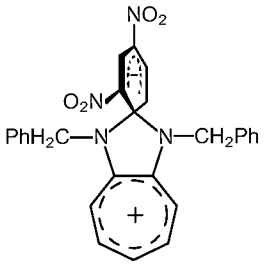
Among various questions to be answered in elucidating the intrinsic mechanism governing the observed stereodynamic behaviour of compounds **4–6**, the following seem to be the most important.

(a) Which of the two possible pathways featured in Scheme 1, the one associated with cleavage of the C–Z (O, S) or that related to cleavage of the C–N bond, represents the energy-favourable intramolecular mechanism of the dissociative inversion of configuration at the C_{spiro} centre?

(b) Which process, dissociation of the C–Z (C–N) bond in **1** or hindered rotation **2a**⇋**2b** (**3a**⇋**3b**) represents the rate-limiting step of the inversion reaction?

Table 1 Kinetic parameters for the racemization reaction **1**(*R*)⇋**1**(*S*).

Compound	M.p./°C	Solvent	k_{25}/s^{-1}	$H^{\ddagger}$/kcal mol^{-1}	$S^{\ddagger}$/e.u.	$G^{\ddagger}$/kcal mol^{-1}
4	235–236	[$^2H_5$]Nitrobenzene	1.3×10^{-1}	11.5 ± 0.3	−24.0 ± 0.8	18.6
		[$^2H_6$]DMSO	2.5×10^{-2}	14.7 ± 0.3	−16.4 ± 0.7	19.3
5a	290–291	[$^2H_5$]Nitrobenzene	$<10^{-9}$	–	–	>30
		[$^2H_6$]DMSO	$<10^{-9}$	–	–	>30
5b	210–211	[$^2H_5$]Nitrobenzene	3.4×10^{1}	19.6 ± 0.4	14.3 ± 0.8	15.3
		[$^2H_6$]DMSO	2.5×10^{0}	21.6 ± 0.3	15.8 ± 0.6	16.9
5c	154–155	$CDCl_3$	1.2×10^{3}	11.0 ± 0.2	−7.5 ± 0.5	13.2
		[$^2H_6$]Acetone	9.2×10^{2}	11.5 ± 0.2	−6.4 ± 0.3	13.4
6a	280–281	[$^2H_5$]Nitrobenzene	2.0×10^{-2}	10.4 ± 0.2	−31.4 ± 0.6	19.8
		[$^2H_6$]DMSO	1.1×10^{-2}	12.6 ± 0.2	−25.0 ± 0.5	20.1
6b	150–151	[$^2H_5$]Nitrobenzene	3.0×10^{2}	17.5 ± 0.5	11.7 ± 1.2	14.1
		[$^2H_6$]DMSO	7.9×10^{1}	17.7 ± 0.5	9.7 ± 1.3	14.8



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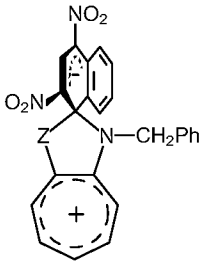
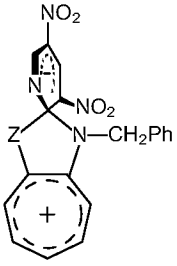
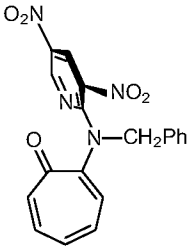


5a Z = NCH_2Ph
5b Z = S
5c Z = O



6a Z = NCH_2Ph
6b Z = S



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(c) How sensitive is the position of the pre-equilibrium **1**⇋**2** (or **1**⇋**3**) to temperature, *i.e.*, could it be thermally shifted to the right to the extent of allowing the observation of both isomeric forms coexisting in solution?

No noticeable changes were observed in the UV-VIS absorption ($\lambda_{max} \sim 480$–540 nm) and NMR spectra of spirocyclic compounds **4–6** at elevated temperatures (up to 180 °C) at which the racemization reaction is a rather fast process. This indicates a very low equilibrium amount of the ring-opened isomers **2** (or **3**) in solution. Although **2** (or **3**) are, therefore, unattainable for direct observation, there are good reasons for believing that the reaction path related to dissociation of the C–O and C–S (but not C–N) bonds, *i.e.* **1**(*R*)⇋**2**⇋**1**(*S*), serves as an energy favourable reaction mechanism for the inversion of tetrahedral configuration of the C_{spiro} centres in compounds **5b**, **5c** and **6b**. Indeed, as seen from the data in Table 1, energy barriers to the stereoisomerization for these compounds are 5–15 kcal mol^{-1} lower than those of derivatives of aminotropone imines **4**, **5a** and **6a**. This conclusion is well supported by the fact that treatment of 2-(*N*-alkylamino)tropones and 2-(*N*-alkylamino)thiotropones with 1-chloro-2,4-dinitrobenzene, 2-chloro-3,5-dinitropyridine or 2,4,6-trichloro-1,3,5-triazine affords invariably only *N*-aryl and *N*-heteroaryl derivatives, but not their respective *O*- and *S*-isomers.[2,5,6]

From the sequence of reaction steps in Scheme 1, it follows that the energy barrier to inversion of configuration at the C_{spiro} atoms is the sum of the free energy differences between the ring-closed and ring-opened isomers (**1** and **2**, respectively) and the free activation energy of internal rotation about the C_{aryl}–N bond in **2**: $G^{\ddagger}_{inv} = G^{0}_{\mathbf{2-1}} - G^{\ddagger}_{rot}$. To evaluate the latter term, the energy barrier to rotation of the 3,5-dinitropyridine ring about the C_{aryl}–N bond has been determined from diastereotopic averaging of methylene protons of the *N*-benzyl group in **7**: $G^{\ddagger}_{25} = 11.1$ kcal mol^{-1}, $H^{\ddagger} = 13.2 \pm 0.3$ kcal mol^{-1}, $S^{\ddagger} = 9.6 \pm 0.7$ kcal mol^{-1} (solvent CD_2Cl_2). The magnitude of the energy barrier $G^{\ddagger}_{25}$ thus fits the range 9.9–12 kcal mol^{-1} known for energy barriers to internal rotation of the dialkylamino group in dinitrobenzene and various nitropyridine and nitropyrimidine derivatives.[13] By comparison with the $G^{\ddagger}$ values listed in Table 1, it can be concluded that the C–N rotation **2a**⇋**2b** is to be regarded as the principal energy component of the total barrier to inversion of tetrahedral configuration at the C_{spiro} centre in the derivatives of 2-aminotropone and 2-aminothiotropone **5b**, **5c** and **6b**, the $\Delta G^{0}_{\mathbf{2-1}}$ values being estimated as 2–6 kcal mol^{-1}. Assuming early transition state structures inherent in **1**⇋**2** rearrangements,[6,7] energy barriers to dissociation of C–O and C–S bonds in these compounds are expected not to appreciably exceed the magnitude of $\Delta G^{0}_{\mathbf{2-1}}$.

By contrast, for compounds **4**, **5a** and **6a** in which the bond cleavage step **1**→**2** is associated with breaking C–N bonds, $\Delta G^{0}_{\mathbf{2-1}}$ ($G^{\ddagger}_{C-N}$) values 7.5–19 kcal mol^{-1} are comparable to or even larger (**5a**) than those of $G^{\ddagger}_{rot}$. Dissociation of the C–N bond thus substantially or crucially contributes to the observed energy barrier to inversion of configuration. Large negative values of entropy of activation $S^{\ddagger}$ (Table 1) have been calculated for stereoisomerization of **4** and **5a**. In accordance with commonly accepted arguments,[12] negative values of entropy of activation manifest increasing ionic character in the transition state of a reaction. Accounting for the positive value of entropy of activation for the C–N rotation in **7**, and for the inversion in spiranes **5b** and **6b** (Table 1), one may suppose that the rate-limiting transition state structure for the stereoisomerization of **4** and **5a** emerges in the dissociation step of the C–N bonds.

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