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DETECTION AND MECHANISTIC IMPLICATION OF A DYNAMIC EQUILIBRIUM IN SOME NOVEL *SPIRO*-HETEROCYCLIC SYSTEMS

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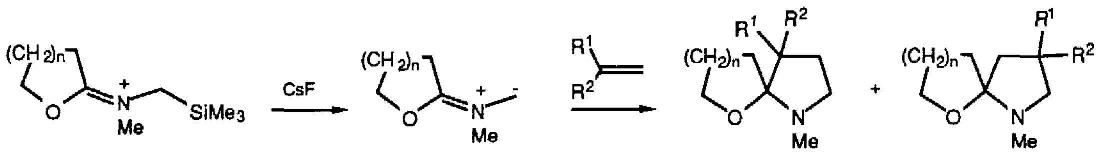
Summary: Evidence is presented based upon NMR analysis for a novel dynamic equilibrium in a number of spiro-heterocyclic compounds which involves inversion at only one of two asymmetric centres present in each system.

We have reported[2] previously that the novel spirocyclic systems **3** and **4** (n=1, 2) are obtained from the 1,3-dipolar cycloadditions of imidate methylides **2**, which are generated via desilylation of salts **1** (Scheme 1). It was found that the reaction of methyl methacrylate with azomethine ylide **2**, n=1, yielded only **3a** (R^1 = Me, R^2 = COOMe); in every other case only regioisomers of type **4** were isolable. These regioisomers were also found to exist as mixtures of diastereoisomers, which was evident by the presence of strong saturation transfer effects that relate analogous protons of the epimers in the one-dimensional ^1H-^1H NOE difference experiments,[3] are in dynamic equilibrium involving inversion at only one of the two asymmetric centres present.

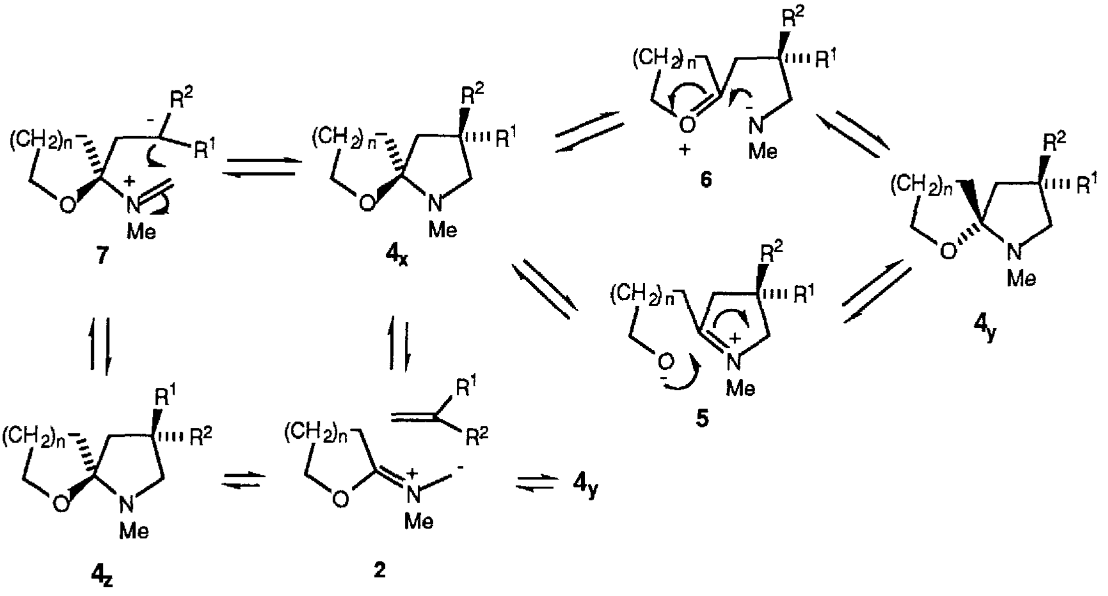


1 **2**

3a R^1=Me, R^2=CO_2Me **4a**
3b R^1=H, R^2=CO_2Me **4b**
3c R^1=H, R^2=CN **4c**

Scheme 1

However, although it was proposed that this process probably involves inversion at the spiro-carbon centre via stabilized intermediate **5**, or less likely **6**, it is clearly possible for inversion to occur at the other asymmetric centre in **4** via stabilized intermediate **7** (Scheme 2). In addition, there also exists the unlikely possibility that the equilibrium involves a [3+2] cycloreversion to re-generate ylide **2** (Scheme 2).



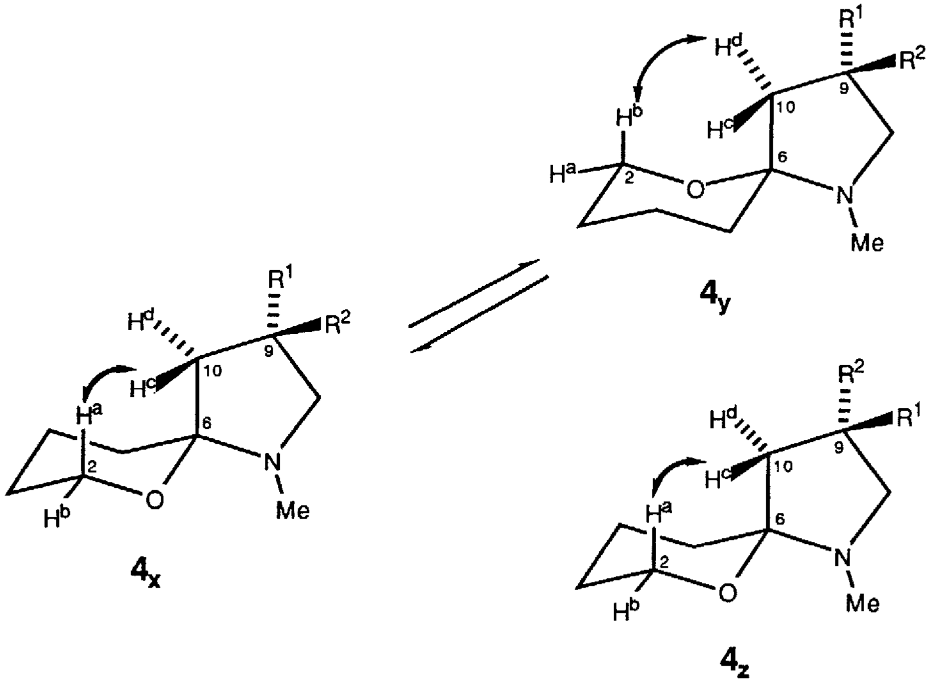
Scheme 2

We present here evidence that this equilibrium is of type **4** $\rightleftharpoons$ **5** and/or **6** only, and can exclude the other mechanistic possibilities outlined in Scheme 2.

The structures of the spirocycles, including the identification of the relevant epimeric forms, were verified by a combination of high-field NMR techniques, notably: 2D $^1H,^1H$- and $^1H,^{13}C$- shift correlation, and 1D ^1H-^1H NOE experiments[4] (full details will be published elsewhere).

For those members of the series which contain a six-membered ring (**4**, n=2), a strong NOE connection is observed between the axial H_{ax}-2 proton (which is easily distinguished from the equatorial H_{eq}-2 hydrogen due to their characteristically different multiplet patterns) and one of the H-10 protons (Figure). On the one hand, this indicates that the conformer in which C-10 is axial relative to the six-membered ring must be significantly populated and, more importantly, identifies H_β-10 in epimer $\mathbf{4_x}$, and H_α-10 in epimer $\mathbf{4_y}$.

Consideration of the chemical exchange process occuring in these molecules, as are revealed by the saturation transfer effects connecting specific protons of the interconverting diastereoisomers, allows some interesting mechanistic deductions to be made. The Figure illustrates the possible epimeric equilibria involving inversion at either C-6 ($\mathbf{4_x} \rightleftharpoons \mathbf{4_y}$), or C-9 ($\mathbf{4_x} \rightleftharpoons \mathbf{4_z}$). Identically labelled hydrogens denote those proton pairs that are expected to be in chemical exchange for the two different cases, and in practical terms are also the easiest to monitor in these compounds.



$\mathbf{4_y}$

$\mathbf{4_x}$

$\mathbf{4_z}$

Figure

Experimental observations show that saturation transfer effects relate the *axial* H-2 proton in one isomer and the *equatorial* H-2 proton in the other (and not the relevant axial-axial and equatorial-equatorial partners), which clearly excludes the $\mathbf{4_x} \rightleftharpoons \mathbf{4_z}$ equilibrium, but is consistent with the $\mathbf{4_x} \rightleftharpoons \mathbf{4_y}$ equilibrium. Moreover, similar considerations apply to the observed exchange of the H-10 protons: As mentioned earlier, for both interconverting isomers irradiation of the H_{ax}-2 proton gave NOE to only one of the H-10 protons. It is thus noted that, for example, H_β-10 (=H^c) in $\mathbf{4_x}$, which may be considered as being "labelled" by its NOE contact to H_{ax}-2, has proved to be in exchange with H_β-10 in $\mathbf{4_y}$, whereas H_β-10 lacks an NOE connection to H_{ax}-2. Clearly, in a hypothetical $\mathbf{4_x} \rightleftharpoons \mathbf{4_z}$ equilibrium *both* H_β-10 protons which should be related through chemical exchange are those that show NOEs to H_{ax}-2, and such a saturation transfer connectivity was in practice absent. Obviously, analogous conclusions can be drawn regarding the H_α-10 (=H^d) protons. It is also noted that consideration of the observed saturation transfer effects, for the analogues in which both rings are five-membered (including **3a**), provide the same inference.[5]

This appears to be an interesting case where, by monitoring the chemical exchange connectivities between interconverting diastereoisomers in racemic compounds containing two asymmetric centres, it is possible to establish on which stereocentre the inversion takes place.

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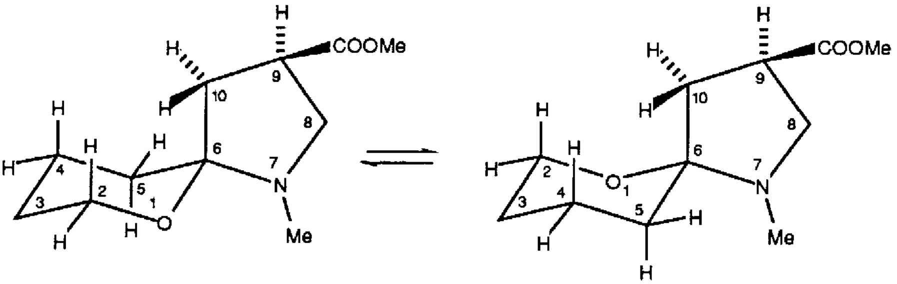
References and notes

1. On leave from the NMR laboratory of the Institute for General and Analytical Chemistry, Technical University, H-1521 Budapest, Hungary.
2. Alanine, A. I. D.; Fishwick, C. W. G. *Tetrahedron Lett.,* **1989**, in press.
3. As was noted in ref.2., these saturation transfer effects were, interestingly, absent in both **4c** (n=1,2) compounds, suggesting a considerably slower interconversion process. Further investigations in this regard are underway.
4. All NMR spectra of the spirocycles were recorded on a Bruker AM-400 spectrometer operating at 400.13 and 100.61 MHz for ^1H and ^{13}C nuclei, respectively, with internal deuterium lock in $CDCl_3$ at ambient temperature (297K). All 1D ^1H-^1H NOE experiments were carried out in non-degassed samples, using 4 s pre-irradiation times.
   Representative data for one member of the series are given below:



$4b_x$ **$4b_y$**

Isomeric ratio at room temperature in $CDCl_3$: **1** : **1.2**

$4b_y$ ^1H NMR ($CDCl_3$), δ: 1.40-~1.49 (3H, m, H_2-3, H_x-5); ~1.49-~1.60 (2H, overlapping, H_x-4); ~1.73 (1H, overlapping, H_x-5); ~1.76-~1.84 (1H, overlapping, H_y-4); 1.87 [1H, dd, H_β-10 ($J_{H\beta\text{-}10,H\alpha\text{-}9}$=7.1Hz)]; 2.33 (3H, s, NMe); 2.56 [1H, dd, H_α-10 ($J_{H\alpha\text{-}10,H\alpha\text{-}9}$=8.5Hz)]; 2.97-3.07 (2H, m, H_x-8, H-9); 3.22-3.28 (1H, m, overlapping, H_y-8); 3.46-3.59 (1H, m, overlapping, H_{ax}-2); 3.68 (3H, s, OMe); 3.81 (1H, m, H_{eq}-2).
^{13}C NMR ($CDCl_3$), δ: 22.0 (C-4); 25.9 (C-3); 32.1 (C-5); 32.1 (NMe); 35.5 (C-10); 38.8 (C-9); 51.9 (OMe); 55.8 (C-8); 94.0 (C-6); 175.6 (C=O).
$4b_x$ ^1H NMR ($CDCl_3$), δ: 1.36 (1H, m, H_x-5); 1.40-~1.49 (2H, overlapping, H_2-3); ~1.49-~1.60 (2H, overlapping, H_x-4); ~1.73 (1H, overlapping, H_x-5); ~1.76-~1.84 (1H, overlapping, H_y-4); 1.81 [1H, dd, H_α-10 ($J_{H\alpha\text{-}10,H\alpha\text{-}9}$=10.0Hz)]; 2.34 (3H, s, NMe); 2.68 [1H, dd, H_β-10 ($J_{H\beta\text{-}10,H\alpha\text{-}9}$=4.5Hz)]; 2.97-3.07 (2H, m, H_x-8, H-9); 3.22-3.28 (1H, m, overlapping, H_y-8); 3.46-3.59 (1H, m, overlapping, H_{ax}-2); 3.67 (3H, s, OMe); 3.77 (1H, m, H_{eq}-2).
^{13}C NMR ($CDCl_3$), δ: 22.0 (C-4); 25.8 (C-3); 31.9 (NMe); 32.5 (C-5); 35.0 (C-10); 39.4 (C-9); 51.8 (OMe); 55.7 (C-8); 93.3 (C-6); 174.6 (C=O).

5. Although these experiments do not exclude the possibility of a $\mathbf{4_x} \rightleftharpoons \mathbf{4_y}$ equilibrium involving 1,3-dipolar cycloreversion, this process would be expected to lead to formation of regioisomers **3** in addition to **4**, and would also very likely result in the simultaneous presence of a $\mathbf{4_x} \rightleftharpoons \mathbf{4_z}$ equilibrium which, in practice, is never observed.

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