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Chemical exchange in novel spirobicyclic zwitterionic Janovsky complexes using dynamic ^{1}H NMR spectroscopy

A. S. Culf,[a,b]* M. Čuperlović-Culf[c] and R. J. Ouellette[a]

Highly coloured Janovsky complexes have been known for over 120 years, being used in many colourimetric analytical procedures. In this present study, two novel and stable nitrocyclohexadienyl spirobicyclic, zwitterionic Janovsky anionic hydantoin σ-complexes, rac-1,3-diisopropyl-6-nitro-2,4-dioxo-1,3-diazaspiro[4.5]deca-6,9-dien-8-ylideneazinate, ammonium internal salt (1) and 1,3-diisopropyl-2,4-dioxo-1,3-diazaspiro[4.5]deca-6,9-dien-8-ylideneazinate, ammonium internal salt (2) have been prepared and characterised by NMR, electrospray ionization mass spectrometry (ESI-MS) and UV/visible methods. For the *p*-mononitro-substituted complex (2), we discovered chemical exchange behaviour using 1D saturation transfer and 2D exchange spectroscopy (EXSY) ^{1}H NMR techniques. The coalescence temperature was determined to be 62 °C in d_3-acetonitrile. Analysis of these data provided a Gibbs free energy of activation, $\Delta G\ddagger$, of +67 kJ mole^{-1}, a rate constant, *k*, coalescence of 220 Hz and an equilibrium constant, K_{eqm}, of 0.98 as estimates of the exchange process in this solvent. Of the two mechanisms proposed for this fluxional behaviour, ring opening to a substituted benzene or proton exchange, a further theoretical modelling study of 1D ^{1}H NMR spectra was able to confirm that simple proton exchange between the two nitrogen sites of the hydantoin ring provided an accurate simulation of the observed experimental evidence. Interestingly, the *o*,*p*-dinitro-substituted complex (1) did not show any chemical exchange behaviour up to 150 °C in d_3-acetonitrile (to 75 °C) and d_6-dimethyl sulfoxide (DMSO). Molecular modelling at the MM2 level suggests that steric collisions of an *N*-acyl isopropyl substituent of the hydantoin ring with the *ortho*-nitro group of the spirofused cyclohexadienyl ring prevents the proposed proton exchange mechanism occurring in this case. **Copyright © 2008 Crown in the right of Canada. Published by John Wiley & Sons, Ltd**

Keywords: NMR; ^{1}H; ^{13}C; EXSY; saturation transfer; proton exchange; Janovsky σ-complex; spirohydantoin; NMR modelling

Introduction

The elegant structures of spirocyclic molecules are represented as important molecular skeletons in natural products and an emerging architecture in medicinal chemistry. Many spirocyclic compounds possess broad-ranged bioactivity including potent activity against cancers[1–4] and allergic inflammatory diseases.[5] Recently described structures include: 2-azaspiro[4.5]decanes;[6] spirodiiminodihydantoins;[7] stemonamide alkaloids;[8] spirofuranone lactams[9] and the spirodiketals goniodomin A[10] and spirastrellolides C to G.[11] Synthetic spirocycles have shown wide-ranging utility as β-turn peptide mimics,[12] switchable fluorophores,[13] nitrogen fixation[14] and as chemosensors for toxic metal ions, such as mercury(II), in aqueous solution.[15] Chromophoric spirocyclic compounds can be created by appropriate molecular associations, explaining their use as analytes in the environmental sciences for persistent nitro-organics.[16] Current synthetic methodologies being pursued include three component one-pot reactions of alkyl cyanoacetates, guanidinium carbonates and N-substituted 4-piperidinones giving spiro-2-aminopyrimidinones;[17] the creation of spiro[4.5]trienyl acetates by the intramolecular electrophilic *ipso*-iodocyclization of arylalkynes;[18] *ipso*-oxidative radical spirolactamization yielding azaspirocyclic cyclohexadienones[19] and the preparation of [4.4]spirolactams from L-proline,[20] among others. Alternative approaches enable the facile synthesis of enantiomeric centres at the tetrahedral spiro-junction.[21]

Janovsky (variant spelling, Yanovskii) anionic σ-complexes are intensely coloured having been discovered at the end of the nineteenth century.[22] Janovsky complexes can be defined as possessing only one, or no, heteroatom (typically, O, N or S) at the tetrahedral (potentially spiro) junction, all other atoms at this site being carbon.[23] Formally, tetrahedral anionic σ-complexes are considered the anionic intermediates in the S_NAr mechanism of electron-poor aromatics.[24] Consequently, these complexes have been useful as tools for the description of the S_NAr mechanism and much of the literature to date deals with kinetics and equilibrium measurements of the related Meisenheimer complexes.[25] Structural characterisation methods include NMR,[26–30] UV/visible spectrophotometry,[30] MS[31] and X-ray structure determination.[32] Owing to the emphasis on mechanistic and kinetic work, the study and innovative use of thermodynamically stable Janovsky spirocyclic complexes has been largely neglected.[33] The vast majority of reports on spiro-Meisenheimer complexes involve the 1,3-dioxolane[34] and

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3-methyloxazolidine[35] ring systems, there being no reports of spiro-Janovsky complexes known to these authors.

Chemical exchange processes in molecular systems have been amenable to NMR investigation since the 1970s.[36,37] NMR presents a rich source of information for dynamic processes that takes a nucleus from one magnetic environment to another. As the rate of the process approaches the difference in Larmor frequencies for the two environments (usually accessed by a temperature increase), the observed NMR spectrum undergoes marked changes. In the classic exchange between two equally populated non-coupled magnetic environments, two well-resolved peaks coalesce into a single broad peak from which rate data can be estimated. Further heating narrows the single peak as the dynamic system undergoes fast exchange on an NMR timescale. Higher quality data can be derived from the modelling of NMR spectra to understand the mechanism of reaction that connects the two magnetic environments and also to extract rate data.[38–42]

We have synthesised two novel and stable spirobicyclic zwitterionic Janovsky anionic σ-complexes via an efficient and 100% atom economic route. The present study characterises the dynamic behaviour observed by ^{1}H NMR spectra in 1D and 2D experiments for spirohydantoin Janovsky complexes.

Experimental

Compounds **1** and **2** were synthesised from 2,4-dinitrobenzoic acid (**1**) or 4-nitrobenzoic acid (**2**) (1 mmole) in dichloromethane (4 ml) and diisopropylcarbodiimide (1 mmole) in the presence of diisopropylethylamine (1 mmole) with stirring at room temperature (20 °C) overnight. The intensely coloured compounds were purified by preparative silica gel thin layer chromatography (1 mm; SiliCycle, Canada) using a 9 : 1 (v/v) dichloromethane : methanol mobile phase. A larger library of spirocyclic dearomatised hydantoins has been prepared for biological activity assessment and a manuscript is in preparation.

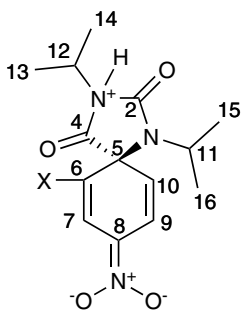
All NMR experiments on the spirohydantoin Janovsky complexes (Fig. 1) were acquired on a Jeol JNM GSX-270 spectrometer using Jeol Delta NMR 4.3.5 software operating at 270 MHz for ^{1}H or a Varian MercuryPlus spectrometer operating at 200 MHz for ^{1}H. ^{1}H NMR spectra were acquired as d_3-acetonitrile or d_6-dimethyl sulfoxide (DMSO) solutions, whereas ^{13}C NMR spectra (50 MHz) were collected as d_4-methanol solutions. All solutions had a concentration of 10−20 mg ml^{-1}. Variable temperature experiments were recorded at 270 MHz at 17 °C, 40 , 60 and 75 °C for **1** and **2** in d_3-acetonitrile and additionally at 61, 62 and 65 for **2** in the same solvent and at 25, 75, 100 and 150 °C for **1** in d_6-DMSO using the variable temperature unit on the Jeol NMR spectrometer. All 1D NMR spectra were acquired using a 45° tip angle and a 4-s relaxation delay and were referenced to tetramethylsilane at 0 ppm. Gradient-COSY-45 2D spectra were acquired on the Varian instrument with one FID for each t_1 increment, acquisition time of 128 ms and relaxation delay of 1.0 s over a 2000 Hz spectral width with 128 increments. ^{13}C DEPT-45, DEPT-90 and DEPT-135 spectra were performed on the Varian instrument using standard parameters including a spectral width of 12.53 kHz, acquisition time of 1.51 s and a recycle delay of 1.00 s. ^{13}C/^{1}H HETCOR spectra were acquired on the Varian instrument using standard parameters including spectral widths of 12.5 kHz (^{13}C) and 2.00 kHz (^{1}H), acquisition time of 82 ms, recycle delay of 1.00 s for four repetitions and 128 increments. NOESY and EXSY spectra were recorded using a standard NOESY pulse sequence on the Varian instrument with a relaxation delay = 2.0 s and mixing time = 1.0 s. NMR spectral assignments are given in Table 1.

UV/visible measurements were collected with a Molecular Devices SpectraPlus 384 and electrospray mass spectra were collected with an Agilent VL1100MSD single quadrupole instrument.

Compound **1**: Red, λ_1, 522 nm (21 980 l mol^{-1} cm^{-1}), λ_2, 348 nm (12 150 l mol^{-1} cm^{-1}) in acetonitrile; *m/z* (ESI negative ion) 337 (M−H), 252 (M−H-isopropyl isocyanate), 167 (M−H-two isopropyl isocyanates). Found M−H 337. $C_{14}H_{18}N_4O_6$ requires M 338.12.

Compound **2**: Yellow, λ_1, 382 nm (21 210 l mol^{-1} cm^{-1}), λ_2, 294 nm (31 360 l mol^{-1} cm^{-1}) in acetonitrile; *m/z* (ESI negative ion) 229 (M−H), 207 (M−H-isopropyl isocyanate), 122 (M−H-two isopropyl isocyanates). Found M−H 292. $C_{14}H_{19}N_3O_4$ requires M 293.14.

NMR spectra modelling simulations were performed with Qsim,[43,44] a software tool for pulse sequence design and testing.



X = NO_2 (1), H (2)

Figure 1. Structures of spirohydantoin Janovsky complexes 1 and 2.

Table 1. ^{1}H and ^{13}C (50.3 MHz) NMR data for **1** (200 MHz) and **2**[a] (270 MHz)

	1	**1**	**2**
Atom[b]	δ_H (ppm)[c], *J* (Hz)	δ_c (ppm)[d]	δ_H (ppm)[c], *J* (Hz)
2	–	174.3	–
4	–	171.8	–
5	–	67.7	–
6	–	154.2	5.99, d, 12.5
7	8.62, d, 2.2	130.0	7.94, d, 12.5
8	–	154.2	–
9	7.12, dd, 10.0/2.2	123.2	–
10	5.10, dd, 10.0	116.4	–
11	3.26, septet, 6.8	43.7	3.76, septet, 6.7
12	4.26, septet, 6.8	45.7	4.13, septet, 6.7
13	1.38, d, 6.8	18.3	1.25, d, 6.7
14	1.39, d, 6.8	18.6	–
15	1.28, d, 6.8	20.2	1.26,d, 6.7
16	1.13, d, 6.8	22.4	–

[a] Assignments derived from ^{1}H, ^{13}C, ^{1}H saturation transfer, COSY, ^{1}H/^{13}C HETCOR, DEPT and NOESY spectra.
[b] Atom numbering and molecular structures given in Fig. 1.
[c] Recorded in d_3-acetonitrile.
[d] Recorded in d_4-methanol.

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Results and Discussion

The structures of spirohydantoin Janovsky complexes are given in Fig. 1 and their ^{1}H and ^{13}C NMR assignments are listed in Table 1; the observed 1D ^{1}H NMR peak shapes for compounds **1** and **2** as a function of temperature are shown in Fig. 2 and Fig. 3. 2D EXSY spectra of compounds **1** and **2** are shown in Fig. 4; the two proposed mechanisms connecting the two distinct magnetic environments are delineated in Scheme 1 and the modelled NMR spectra illustrating these two mechanisms are shown in Fig. 5. This is our first report where we will be attempting to investigate spirocyclic molecular architectures that may be approached via thermodynamically stable Janovsky complexes. The purified compounds **1** and **2** were characterised by 1D and 2D NMR methods (^{1}H and ^{13}C NMR assignments: Table 1) as well as mass spectrometry and UV/visible spectrophotometry (Experimental section). The observed spectroscopic behaviour conformed to that expected for anionic σ-complexes[29,30] and was consistent with the structures assigned (Fig. 1).

Compound **2**, lacking the *ortho*-nitro group to the spiro-junction, showed chemical exchange behaviour (Fig. 2 with structures shown in Fig. 1) whereas **1**, with an *ortho*-nitro group, did not show any chemical exchange behaviour up to 150 °C (Fig. 3). Compound **2** is an example of exchange between two equally populated non-coupled magnetic environments.[45–48] We observed that the two well-resolved peaks of the isopropyl methine protons of the hydantoin ring coalesce into a single broad peak as the temperature was increased above room temperature. Importantly, we did not observe any change in other resonances assigned to the structure. Coalescence was observed to occur at $T_{coalescence} = 62$ °C (335 K) in d_3-acetonitrile. Using this value of $T_{coalescence}$, we were able to calculate the free energy of activation for the exchange, $\Delta G^{\ddagger}$ using the equation:[49]

$$\Delta G^{\ddagger} = RT_{coalescence}[23 + \ln(T_{coalescence}/\Delta\upsilon)] \quad (1)$$

where R is the gas constant and $\Delta\upsilon$ is the frequency difference between the exchanging peaks. In the case of **2**, $\Delta\upsilon = 100$ Hz at

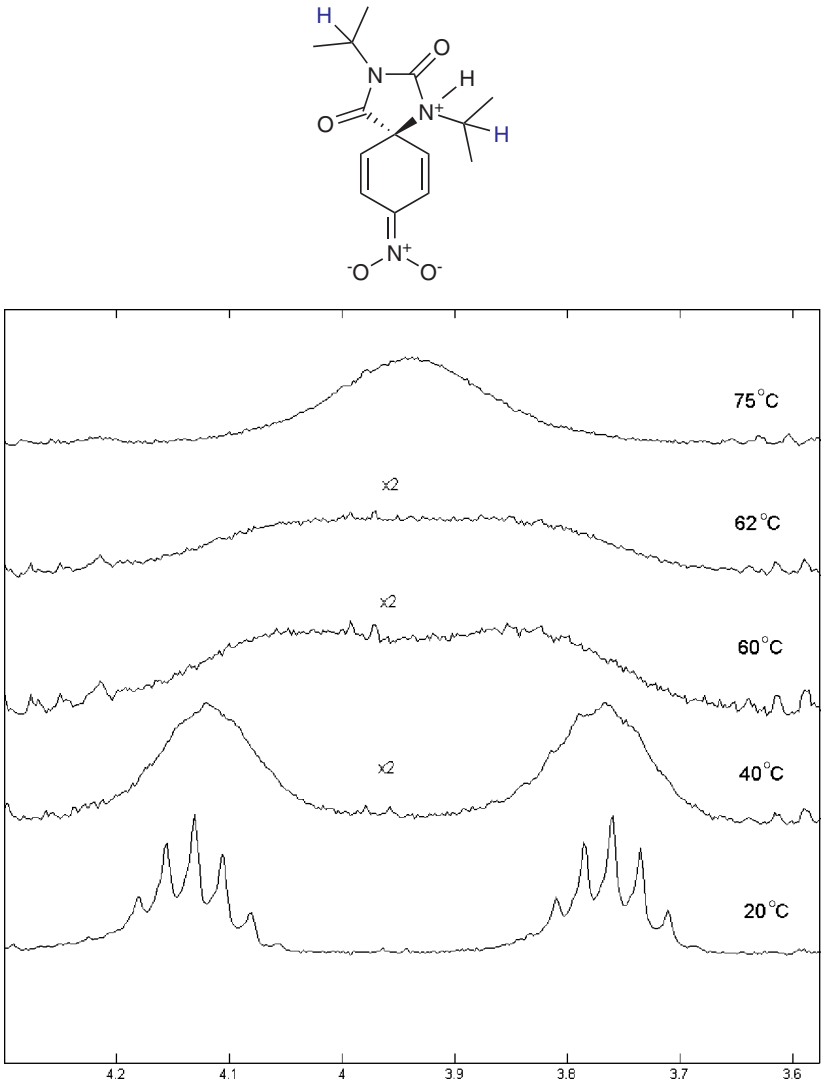

Figure 2. 1D variable temperature ^{1}H NMR of the isopropyl methine protons in compound **2**, showing the behaviour of a classic exchange between two equally populated non-coupled magnetic environments. The coalescence temperature was experimentally determined to be 62 °C (335 K); $k_{coalescence} = 220$ Hz, free energy of activation, $\Delta G^{\ddagger} = +67$ kJ mol^{-1} with an equilibrium constant, $K_{eqm} = 0.98$. All spectra were recorded as solutions in d_3-acetonitrile.

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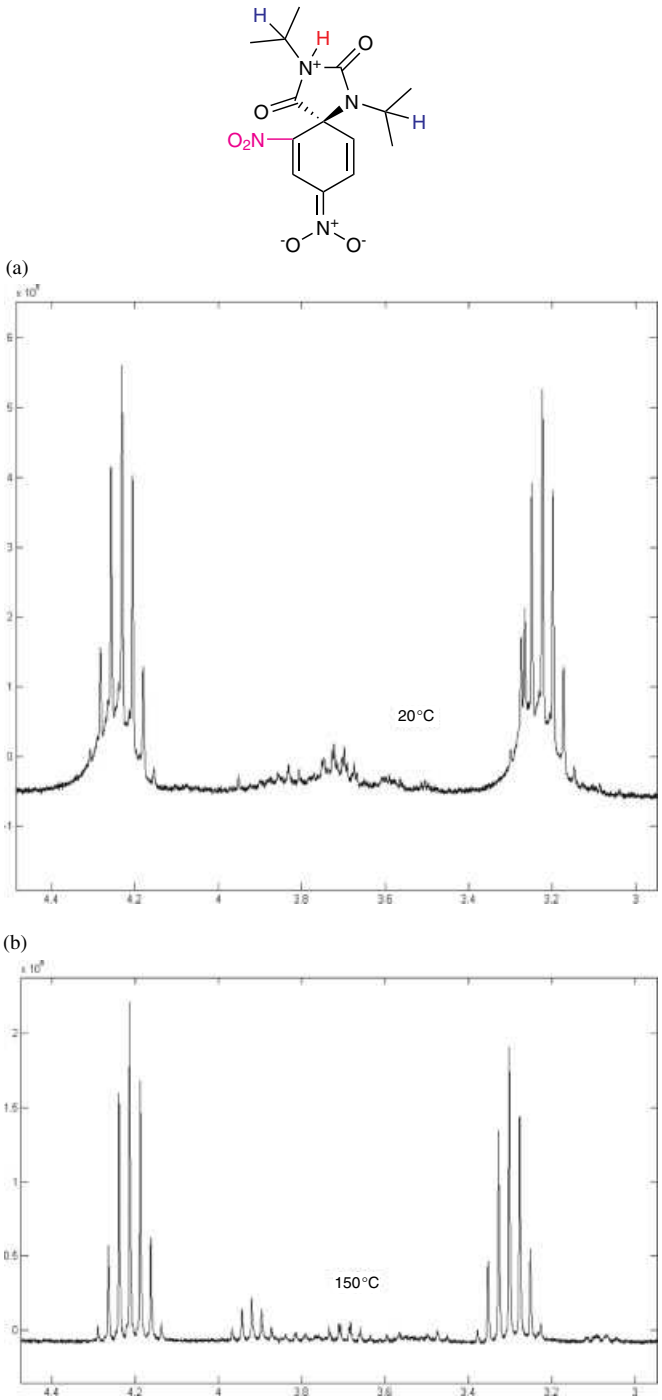

Figure 3. 1D variable temperature ^{1}H NMR of the isopropyl methine protons in compound **1**. No evidence of chemical exchange was observed experimentally up to 150 °C (423 K). Top spectrum (a) was recorded as a solution in d_3-acetonitrile at 20 °C while the lower spectrum (b) used d_6-DMSO at 150 °C. Signal at 3.9 ppm (b) indicates the possible thermal degradation of compound **1**, possibly via the ring-opening mechanism illustrated in Scheme 1a.

6.34 Tesla or 270 MHz for ^{1}H giving $\Delta G^{\ddagger} = +67$ kJ mole^{-1}. This falls within the accepted range observable by NMR ($\Delta G^{\ddagger} = 20 - 100$ kJ mole^{-1}).[47] From the following equation:[49]

$$k_{\text{coalescence}} = [\pi(\upsilon_A - \upsilon_B)]/\sqrt{2} \qquad (2)$$

we obtained a value for the rate of exchange at the point of coalescence, $k_{\text{coalescence}} = 220\,\text{s}^{-1}$. Furthermore, we obtained a value for the equilibrium constant, $K_{\text{eqm}} = 0.98$ from the equation:[49]

$$\Delta G^{\ddagger} = -RT_{\text{coalescence}} \ln K_{\text{eqm}} \qquad (3)$$

An equilibrium value close to unity implies that both forward and reverse reactions occur at identical, or very similar, rates, k_1 and k_{-1}, respectively. On a molecular basis this further implies that both reaction mechanisms are essentially the same.

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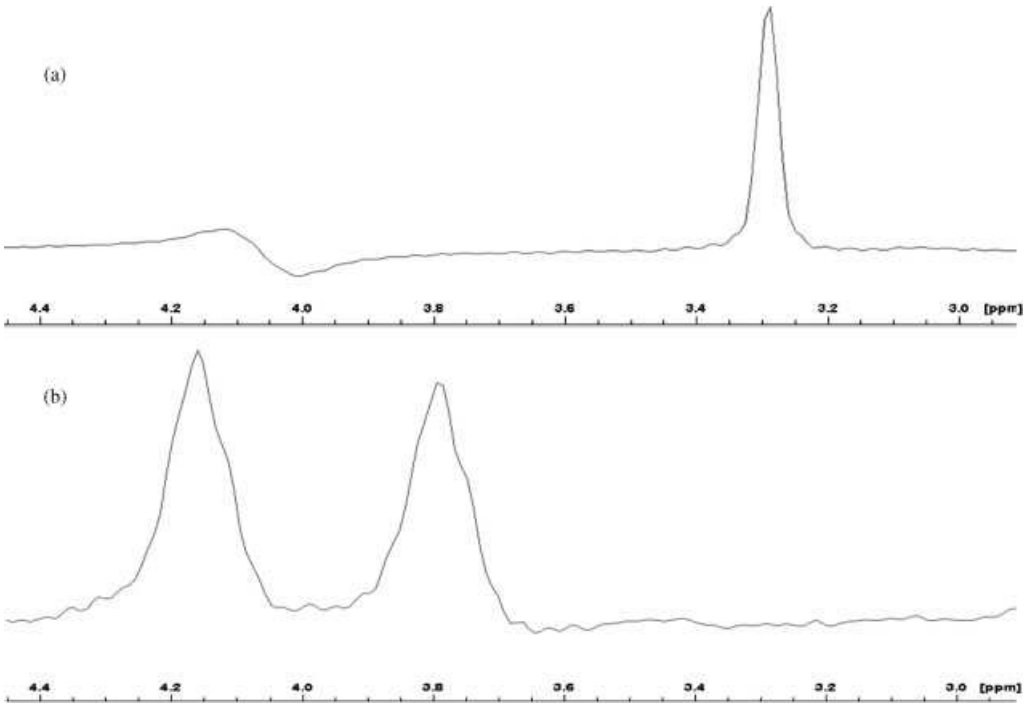
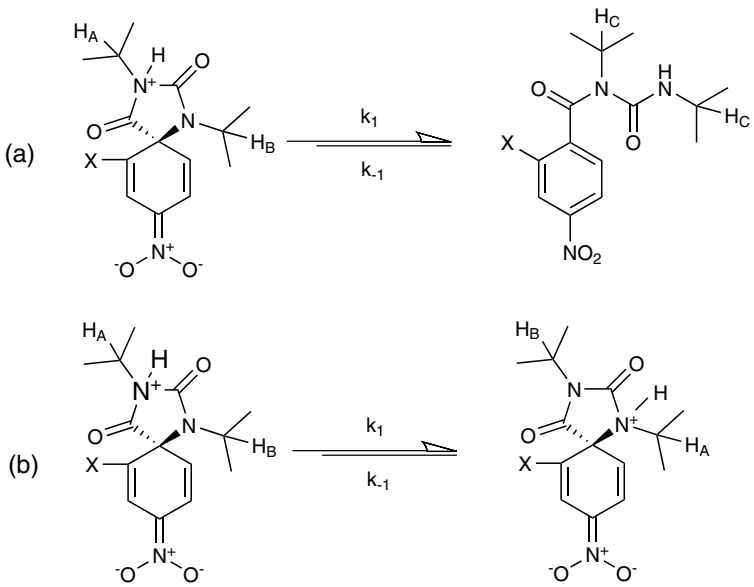


Figure 4. (a) 1D plot taken from a 2D EXSY spectrum of compound **1** in d_3-acetonitrile at 20 °C at 3.3 ppm (signal for H-11). No exchange cross-peak was observed, indicating the absence of an exchange mechanism between the two isopropyl methine protons (H-11 and H-12). Mixing time, $\tau_m = 1$ s. (b) 1D plot taken from a 2D EXSY spectrum of compound **2** in d_3-acetonitrile at 20 °C at 3.8 ppm (signal for H-11). A cross-peak of the same phase as the diagonal peak was observed (shown here at 4.2 ppm), indicating an exchange mechanism between the two isopropyl methine protons, H-11 and H-12. Mixing time, $\tau_m = 1$ s.



Scheme 1. Proposed mechanisms to connect the two magnetic environments. (a) Reversible ring opening of the Janovsky complex to give a substituted benzenoid structure where protons H_C reside in identical magnetic environments.

$$H_AH_B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_BH_A$$

(b) Simple proton exchange between the two nitrogen sites of the hydantoin ring resulting in re-hybridization of these two sites from trigonal to tetrahedral

$$H_AH_B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2H_c$$

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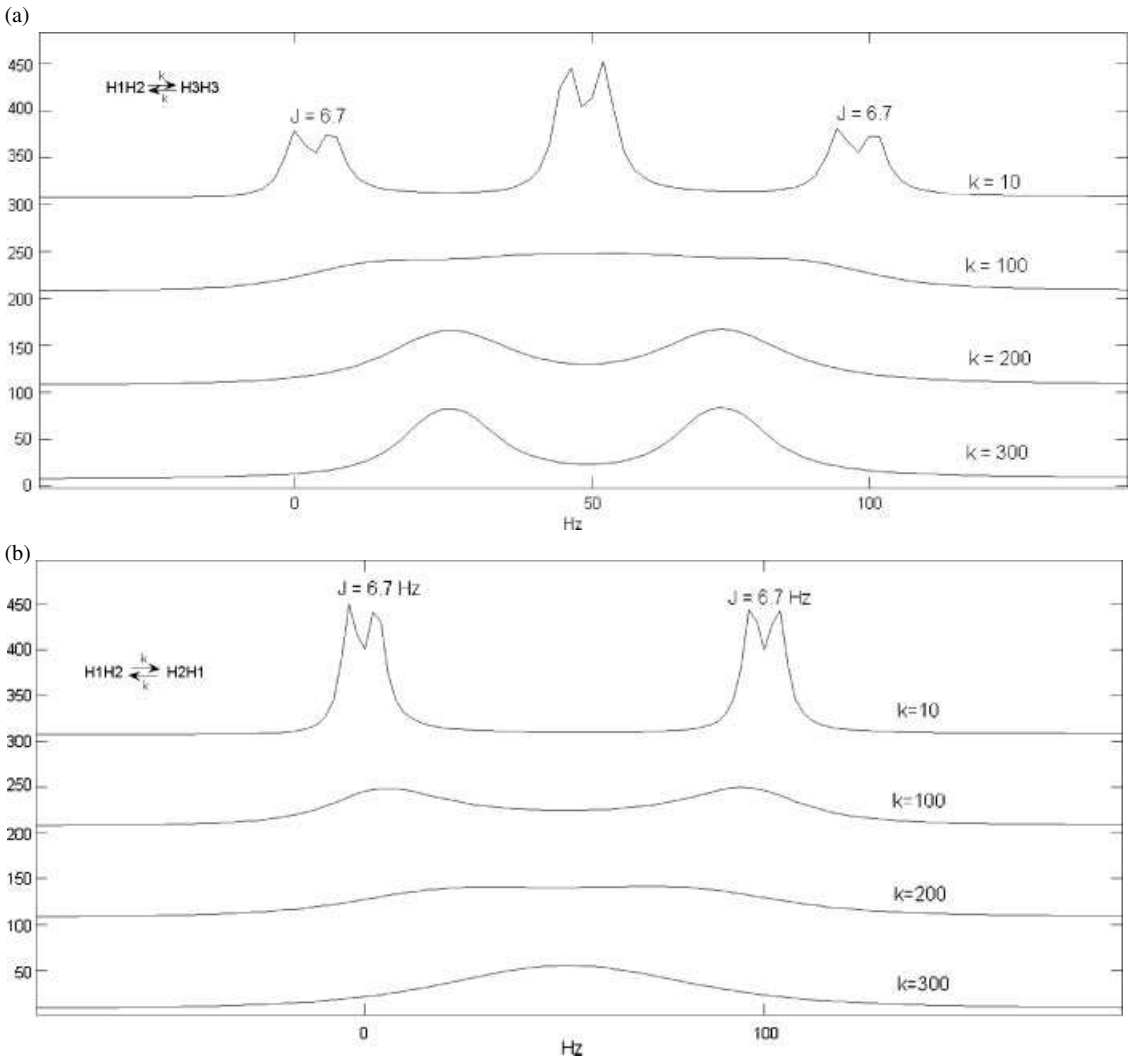

Figure 5. (a) NMR model spectrum corresponding to the ring-opening mechanism, Scheme 1a. (b) NMR model spectrum corresponding to the simple proton exchange mechanism, Scheme 1b, was able to replicate the experimentally observed spectra shown in Fig. 2. All spectra were simulated using QSim software.[43,44] Rates of exchange, *k*, are denoted next to each spectrum and cover the range representing the slow exchange limit ($k = 10$ Hz) to the fast exchange limit ($k = 300$ Hz).

These data derived from 1D ^{1}H NMR are supported by the observed 2D EXSY spectra (Fig. 4). For small molecules chemical exchange and NOE effects have opposite phases and can be distinguished. Chemical exchange cross-peaks will have the same phase as the diagonal peaks, whereas NOESY cross-peaks will have opposite phase.[36] Exchange cross-peaks were absent in the EXSY spectrum of **1** (Fig. 4a), whereas an exchange cross-peak was observed for **2** (Fig. 4b).

We envisaged two possible mechanisms to account for the chemical exchange behaviour of **2** that would be inaccessible or less likely to occur for **1** (Scheme 1). The first mechanism describes simple proton exchange between the two nitrogen sites of the hydantoin ring that does not involve the rupture of the spirocyclic junction (Scheme 1b). This is similar to well-known proton exchange of backbone NH protons in proteins. The second describes a ring-opening mechanism whereby the Janovsky complex degrades to a benzenoid structure (Scheme 1a). This mechanism was considered likely given the numerous reports of anionic σ-complex instability[25] leading to the attainment of a stable aromatic ring system. In order to consider these mechanistic choices we reduced the spin systems to only those spins involved in the exchange process, arriving at the spin equilibria shown in Scheme 1.

Using the value of 100 Hz resonance separation, the expected NMR spectra were modelled with QSim[43,44] and the results are shown in Fig. 5. Only the proton exchange mechanism was able to convey modelled NMR spectra (Fig. 5b) that reflected our experimental results (Fig. 2). It is possible that H_A is removed by a water molecule before returning from water to become H_B on the hydantoin ring. More complex intermediary NMR spectra would have been observed for the ring-opening mechanism even if H_C resonances were not coincident, yet potentially yielding similar slow and fast exchange limit NMR spectra to those experimentally observed. Furthermore, aromatization of the nitrated ring would result in resonance position changes for H-6, H-7, H-9 and H-10 that was not observed experimentally. Thus, we conclude that the chemical exchange observed in **2** is due to simple proton exchange between nitrogen sites of the spirohydantoin ring.

The exchange mechanism inferred for **2** necessitates the exchange of both nitrogens from three-bond trigonal amide

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or imide environments to four-bond tetrahedral ammonium environments (Scheme 1b). Qualitative molecular modelling MM2 calculations (Chem3D Pro, CambridgeSoft) for both **1** and **2** suggested that there would be a steric collision between the *ortho*-nitro group and the isopropyl substituent attached to N-1 of **1** when in a tetrahedral ammonium environment. This was not the case for **2** where both methyl pairs, H-13/H-14 and H-15/H-16 have resonances that are averaged by rapid rotation about the N-1–C-11 and N-3–C-12 bonds, respectively. Experimental evidence for the conformational rigidity for the spirohydantoin in **1** was observed for the ^{1}H NMR signals for isopropyl methyl groups H-13–H-16 (Table 1). Even at 150 °C, the four signals are well resolved. Consequently, we infer that there is no rotation about the N-1–C-11 or the N-3–C-12 bond and that the resonances for H-16 is shifted upfield due to their presence in the shielding cone of an adjacent π-bond system.

Conclusions

We have described two thermodynamically stable spirohydantoin Janovsky zwitterionic σ-complexes, that structurally differ by a nitro group *ortho* to the spiro-junction. The compound lacking this *ortho*-nitro group undergoes proton exchange between the ring nitrogens of the hydantoin ring, whereas the compound with this substituent is a stable and unique entity up to 150 °C. NMR modelling and qualitative molecular modelling have been able to support these observations.

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