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Polymeric and polymer-ligated spirobicyclic zwitterionic Janovsky complexes

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ABSTRACT

A novel approach to the synthesis of spirobicyclic Janovsky complexes is described. The complexes were prepared on silica and polystyrene polymeric supports as well as on a solution-borne poly(carbodiimide) polymer with 100% atom economy. A carbon-centered intramolecular de-aromatizing nucleophilic aromatic substitution ipso-cyclization mechanism describes the synthesis of these spirobicyclics. The molecules were characterized by solution and solid-state ¹H and ¹³C NMR, IR, and MS.

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1-Azaspiro[4.5]decane^{1a} (Fig. 1; **1**) and 2-azaspiro[4.5]decane (**2**) skeletons are distinguishing structural features in natural products.^{1b–d}

One structure that possesses both heteroatom substitutions is the hydantoin **3**.^{2a–c} Biologically active natural products with a hydantoin moiety include the indoleamine-2,3-dioxygenase inhibitor, Exiguame A^{3a,b}, apoptotic Pyrrospiroenes A and B^{3c–e}, and phenylmethylenhydantoins.^{3f} With such a diverse biological activity, the (spiro)hydantoin system has been a goal of numerous synthetic efforts. Some recent examples include the reaction of 3-methylene-2-pyridones with nitrile oxides affording a range of interesting oxadiazaspiro[4.5]dienes;^{4a} spirohydantoins derived from dihydrothieno[2,3-*b*]naphtho-4,9-diones^{4b}, and spiro-piperidine iminohydantoins.^{4c} Spirohydantoins have also been made using a seven-step solid-phase synthesis via a cyclic α,α -disubstituted α -aminoester intermediate that is condensed with an isocyanate and ring-closed under basic conditions to afford the spiro-product.^{4d}

We are interested in utilizing the intramolecular *ipso*-nucleophilic addition reaction to electron-poor aromatics as a synthetic strategy to 1- and 2-azaspiro[4.5]decane skeletons via anionic sigma complex formation: Figure 2. These are considered to be the intermediates in the S_NAr mechanism.^{5a,b}

Of the two main types of anionic sigma complexes (Meisenheimer^{5c,d} or Janovsky^{5e}), our attention was drawn to the more thermodynamically stable Janovsky (variant spelling Yanovsky or Yanovskii).^{5f,g} Synthetically, this approach can be viewed in general terms as a spiro-dearomatization method. Several recent reports have used this as a key step in the preparation of spirobicyclics: the N-triflylate-activated de-aromatization of N-arylisonicotinamides in the presence of nitrogen bases^{6a} and the *ipso*-nucleophilic aromatic addition route of Pigge and Dalvi.^{6b}

Figure 1.

Figure 2. Spirocyclic Janovsky complex. X = O, S, N, C. EWG = electron-withdrawing group.

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The approach that we describe herein involves the tertiary amine base-catalyzed, 100% atom economic, *ipso*-nucleophilic addition of an intramolecular nucleophile derived from *N,N'*-dialkylcarbodiimide to an electron-poor aromatic ring yielding stable spiro[4.5]decane zwitterionic Janovsky complexes bearing a spiro-hydantoin ring.

We reasoned that in order to facilitate library preparation of spirocyclic Janovsky complexes for screening purposes (including on-resin),⁷ it would be advantageous to utilize solid-phase chemistry.⁸ The need for chromatographic purification would be circumvented as by-products and reagents can be efficiently separated by filtration and solvent washing. Following from our previous synthesis of Janovsky complexes in solution phase,⁹ we proposed to move to organic (polystyrene, PS) and inorganic (silica, Si) supported carbodiimide resins to effect synthesis of the targeted Janovsky complexes by solid-phase methods.

The syntheses of red Si-Janovsky, PS-Janovsky, and poly-Janovsky are summarized in Scheme 1.

NMR spectroscopy has been an incredible stimulus for the study of anionic sigma complexes with ^1H ^{10a,b}, ^{13}C ^{10c} and ^{17}O NMR^{10d} being reported; some spectral assignments being reviewed by Crampton^{10e} and Strauss.^{10f} Solid-state ^{13}C cross-polarization (CP)/magic angle spinning (MAS) NMR experiments were conducted at various spinning rates and Hartmann–Hahn contact times to assist in spectral assignments.¹¹ The ^{13}C CP/MAS solid-state NMR of PS-Janovsky was confounded by the position and strength of the underlying polystyrene resin making signal assignment unreliable. However, the ^{13}C CP/MAS NMR spectral signals of Si-Janovsky were well resolved (Fig. 3).

The most distinctive feature is the appearance of new signals from the reaction in the chemical shift range δ 115–160 ppm (Fig. 3B), of which the most prominent occurs at δ 159 ppm (see Supplementary data). Simulation¹² predicts a resonance with a chemical shift around δ 159 ppm for the urea-like carbonyl (C4)

Figure 3. Solid-state ^{13}C CP/MAS NMR spectra of (A) Si-carbodiimide (Silicycle Inc.); (B) Si-Janovsky and (C) 2,4-dinitrobenzoic acid (DNB) were acquired at 100.65 MHz with TPPM proton decoupling optimized on glycine. Typically, 2048 scans were acquired for the polymers.

in the hydantoin ring and this peak is also close to that observed experimentally for **4** in acetonitrile- d_3 (δ 154.4 ppm; Fig. 4). We interpret new signals in the chemical shift range δ 115–145 ppm as originating from the 2,4-dinitrocyclohexadienyl ring in the Si-Janovsky complex (Fig. 3B). These signals are notably absent in the Si-carbodiimide starting material (Fig. 3A). Most peaks in the aliphatic region are easily assigned to the anchoring side chain and the cyclohexane ring (Scheme 1). We attribute the ^{13}C NMR signal at δ 42.6 ppm for Si-Janovsky to the polymer linker methylene group next to nitrogen (C3) based on its CP behavior and chemical shift predictions.¹² The corresponding signal in Si-carbodiimide appears at δ 49.0 ppm. Finally, lineshape deconvolutions of the peak at δ 51 ppm taken with different CP contact times show that it is composed of two components: One component at δ 55 ppm stems from the methine carbon (C5) of the Si-Janovsky

Scheme 1. Synthetic route for polymer-ligated and polymeric zwitterionic spirobicyclic Janovsky complexes. Atom numbers refer to spectral assignments.

Figure 4. Solution phase ^1H NMR spectra in $\text{DMSO}-d_6$ of (A) the precursor poly-carbodiimide polymer; (B) the cyclohexadienyl region of poly-Janovsky showing the distinctive 1/2/3 proton signal pattern of the de-aromatized dinitrophenyl ring; (C) discrete zwitterionic spirobicyclic hydantoin Janovsky complex **4** displaying signals at similar chemical shifts to poly-Janovsky (B). Molecular structure of **4** was consistent with ^1H , ^{13}C , COSY, $^1\text{H}-^{13}\text{C}$ HSQC, DEPTQ, $^1\text{H}-^{13}\text{C}$ HMBC, $^1\text{H}-^{15}\text{N}$ HMBC, and $^1\text{H}-^1\text{H}$ NOESY analyses.

complex (Scheme 1); the other component at δ 51 ppm follows the CP contact time behavior of a quaternary carbon and we believe it to be from the spirojunction carbon C9 (Scheme 1). Its chemical shift does not agree closely with simulations suggesting shifts of δ 65.0 ppm¹² or the range of δ 64.1–65.4 ppm that has recently been reported for similar C_3N_1 spirojunctions in CDCl_3 .¹³ The corresponding spirojunction carbon of **4** was observed at δ 68.3 ppm in CD_3CN . The solid-state NMR spectra of Si-Janovsky (Fig. 3B) do not show any signals in this chemical shift region. We believe that the discrepancy is due to packing in the solid state.¹⁴ The chemical shift of the quaternary heterocumulene sp-carbon of carbodiimides is reported to be in the range of δ 135–140 ppm.¹⁵ Only a hint of a signal was observed in this range for Si-carbodiimide (Fig. 3A) possibly due to the absence of close protons. 2,4-Dinitrobenzoic acid, the other starting material in the reaction, has carbonyl (at δ 172.4 ppm) and quaternary carbon chemical shifts (at δ 144.6 and δ 149.4 ppm) that straddle the prominent new signal observed for Si-Janovsky (Fig. 3C). Hence, it is unlikely that the red Si-Janovsky product occurs as a non-covalent species, especially since the solid-phase resin was subjected to a rigorous washing regime (see Supplementary data).

Key distinctive solution ^1H NMR chemical shifts for poly-Janovsky in $\text{DMSO}-d_6$ are easily discernible at δ 8.5, 7.1, and 5.0 ppm (Fig. 4B). Similarly shifted peaks are absent for the poly-carbodiimide starting material (Fig. 4A), yet they are mirrored in the spectrum of the discrete molecule **4** where they are assigned to the 2,4-dinitro-cyclohexadienyl ring following the extensive application of 2D NMR techniques (Fig. 4C).⁹ The broad nature of these signals (Fig. 4B) may be due to a lack of molecular mobility or the possibility of a composite of two or more molecular environments for the poly-Janovsky complex in this polymeric system (Scheme 1).

Mass spectrometry gave, as expected, an ESI+ response for poly-carbodiimide $(\text{R}-\text{N}=\text{C}=\text{N})_n-\text{R}'$ whereas poly-Janovsky was detected in ESI- mode, as previously demonstrated with other anionic sigma complexes.^{9,16}

IR spectroscopy is an extremely useful spectroscopic tool in identifying functional group type, particularly those with polarized chemical bonds. Bands corresponding to N–O stretching vibrations^{17a} have been reported for nitro-substituted Janovsky^{10f,17b} and Meisenheimer^{17c,d} complexes. However, due to the polymeric

nature of the chemicals under study in this work and given that the reported diagnostic nitro IR bands occur in the crowded fingerprint region, band assignment is unreliable.^{17e} We therefore turned to the carbonyl stretching band region of the IR spectrum (1550–1900 cm^{-1}) to assign the hydantoin portion of the Janovsky complexes (Table 1).

IR spectra were collected under non-hydrogen bonding conditions and were compared to the starting materials. The carbonyl stretching vibration for all Janovsky complexes was observed close to 1700 cm^{-1} . Hydantoin (1700 cm^{-1}) and two oxazolidinedione heterocycles were measured as model comparators (Table 1). It was observed that the IR bands for the starting materials lie to higher frequency in comparison to the products whereas the mechanistically feasible oxazolidinedione structures straddle the observed bands that coincide with the hydantoin and Janovsky complexes (Table 1). The IR data support the presence of a hydantoin ring in the Janovsky structures. Poly-Janovsky exhibited a two maxima UV–visible spectrum, typical of anionic sigma complexes.^{10f}

The reaction of carboxylic acids with carbodiimides as a dehydration reagent is well known.¹⁸ The electrophilically activated

Table 1

IR carbonyl absorption data for novel polymer-ligated and polymeric spirobicyclic Janovsky compounds compared to representative structures

Compound	$\nu(\text{C}=\text{O})/\text{cm}^{-1}$
PS-Janovsky ^a	1600–1720 br
Si-Janovsky ^a	1700
Poly-Janovsky ^c	1703
Hydantoin (Glycolylurea) ^d	1776 (m) ^e , 1700 (s)
2,5-Oxazolidinedione ^b	1752 (w), 1684 (m), 1633 (s)
5,5-Dimethyl-2,4-oxazolidinedione ^b	1817 (m), 1739 (s)
2,4-Dinitrobenzoic acid ^b	1722
PS-carbodiimide ^b	2120
Si-carbodiimide ^b	2120
Poly-carbodiimide ^d	2120

^a Nujol mull between NaCl plates.

^b KBr disc.

^c Dichloromethane solution between NaCl plates.

^d Neat film between NaCl plates.

^e w = weak; m = medium; s = strong signal intensity.

Scheme 2.

O-acylisourea intermediate formed usually reacts intermolecularly with available nucleophiles, typically amines, yielding amides.^{18,19} However, intramolecular migration of the acyl group from the O-atom to N yields the N-acylurea. The extent of migration is partially dictated by solvent type being reported to be high in THF and non-existent in tetrachloromethane with tertiary amines catalyzing the rearrangement.^{19b,20,21}

The nucleophilic aromatic substitution (S_NAr) mechanism is synthetically extremely useful^{22a–f} and is finding many applications in modern medicinal chemistry.^{22g,h} We propose an intramolecular *ipso*-spirocyclization de-aromatization mechanism, catalyzed by a tertiary amine base, as the mechanistic route to the zwitterionic spirobicyclic Janovsky complexes in this work as outlined in Scheme 2. The mechanism involves an intramolecular transfer from O-acylurea to N-acylurea prior to sigma complex ring closure.^{19b,23} The spiro[4.5]decane skeletons so derived have been shown to be stable as analogous Meisenheimer complexes^{24a} and amply illustrated with a typical X-ray structure of Borbulevych.^{24b}

In summary, for the first time, we have prepared zwitterionic spirocyclic Janovsky complexes on soluble and solid-phase polymeric systems with 100% atom economy and moderate yield (52% for poly-Janovsky). These new materials were characterized by NMR, IR, and MS techniques and a mechanism for their preparation has been proposed.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.136.

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