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The first dipolar spirocycle based on 10-(benzylamino)colchicine

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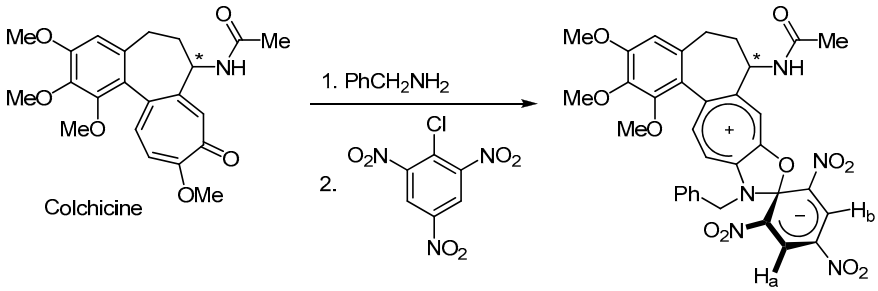


We have synthesized the first dipolar spirocyclic σ-complex of Meisenheimer type from 10-(benzylamino)colchicine and trinitrobenzene. The chirality of colchicine moiety resulted in magnetic non-equivalence of protons in the trinitrophenyl ring, enabling their use as diastereotopic markers. The kinetic and activation parameters for the reversible degenerate recyclization of spirocycle were determined by a dynamic NMR method.

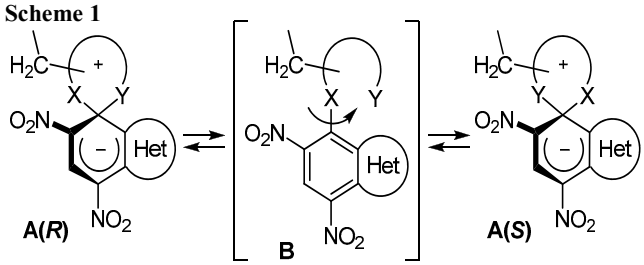
Keywords: colchicine, dipolar spirocycle, nucleophilic aromatic substitution, stereodynamics.

Dipolar spirocyclic σ-complexes of type **A(*R*)** are stable, preparatively isolable intermediates of intramolecular nucleophilic aromatic substitution reactions. In contrast to the widely known anionic Meisenheimer σ-complexes, dipolar σ-complexes require much higher capability of negative and positive charge delocalization in electrophilic and nucleophilic fragments, respectively. In the case if the dipolar spirocycle is chiral, it is possible to determine the energy barrier to enantiomerization **A(*R*)** ⇄ **A(*S*)** by dynamic NMR methods, using temperature-dependent evolution of the signal from a diastereotopic CH_2 group located near the chiral center (Scheme 1).[1–4] A similar classical approach to the study of enantiomerization occurring *via* bond dissociation and recombination at the stereocenters has been successfully used earlier not only for carbon atoms,[5,6] but also for atoms of other elements.[7,8]

This method for measuring the kinetic stability of spirocycle does not require a previous separation of enantiomers, but is obviously applicable only to asymmetric nitrohetarenes, such as dinitrobenzofuroxan,[2] dinitrobenzofurazan,[4] or dinitrobenzo[*e*][1,2,3,4]tetrazine 1,3-dioxide,[9] and is not suitable for symmetric electrophiles, for example, trinitrobenzene.

The use of chiral nucleophilic moiety allows to avoid these limitations. In the current work, a natural alkaloid was used and here we report the synthesis and

Scheme 1

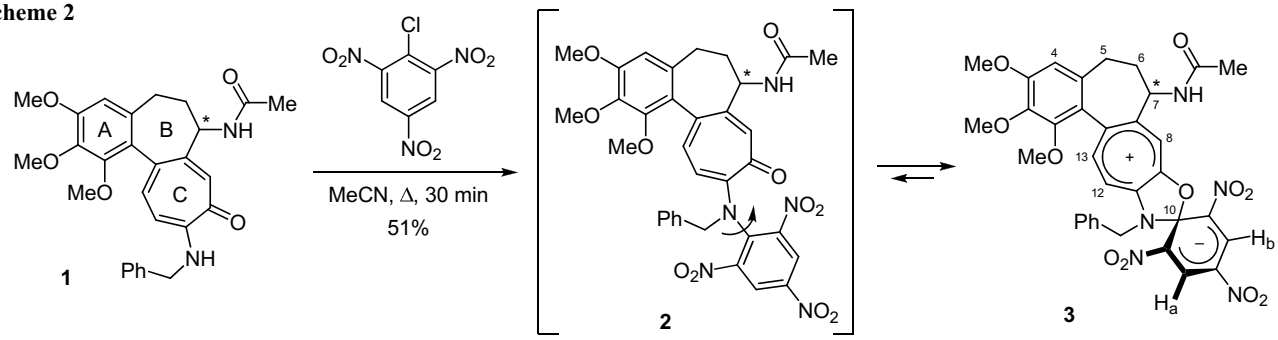


stereodynamics of the first dipolar spirocycle, a colchicine derivative.

The interaction of 10-(benzylamino)colchicine (**1**)[10] with picryl chloride likely involves the formation of a metastable 10-picrylamino derivative **2**. This assumption is supported by the fact that the reaction of *N*-alkylaminotropones with 2-chloro-3,5-dinitropyridine and 2,4,6-trichloro-1,3,5-triazine forms exclusively *N*-arylation products that can be isolated preparatively, while no *O*-aryl derivatives have been detected.[11] Picrylaminocolchicine **2** undergoes an intramolecular nucleophilic attack, resulting in the formation of stable dipolar spirocyclic σ-complex **3**, isolated from the reaction medium as red crystals with a high melting point (Scheme 2).

The spirocyclic structure of picryl derivative **3** was confirmed by ^1H and ^{13}C NMR spectroscopy. Compared to 10-(benzylamino)colchicine (**1**), the signal of the H-12

Scheme 2



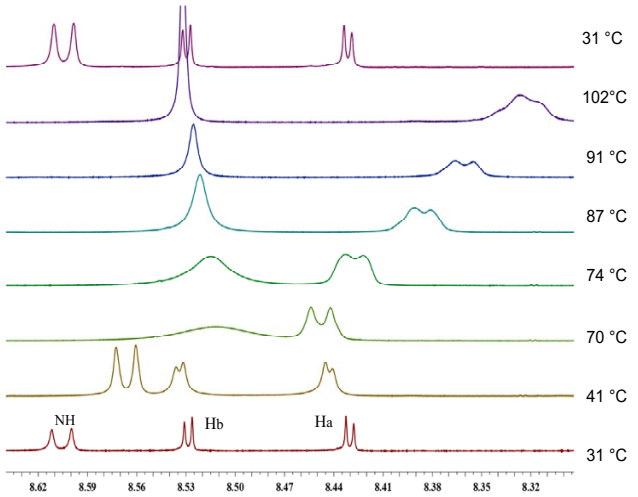


Figure 1. The temperature-dependent evolution of proton signals from the picryl moiety in spirocycle **3**.

proton in the ^{1}H NMR spectrum of the spirocycle **3** was shifted downfield by 1.42 ppm, the signal of the H-13 proton – by 1.05 ppm, while the signal of the H-8 proton – by 0.45 ppm. Proton deshielding in the electron-donating part of the molecule indicated a significant degree of charge transfer.[4,12] The spirocyclic carbon atom appeared in the spectrum at 105.6 ppm, which is also characteristic for dipolar spirocyclic σ-complexes.[4] The principal difference from all previously investigated open-chain or spirocyclic derivatives of trinitrobenzene was the magnetic non-equivalence of H_a and H_b protons, which appeared not as two-proton singlets, but rather as two one-proton doublets at 8.43 and 8.53 ppm. The presence of a chiral center at position 7 means that the plane containing A, B, and C rings is diastereofacial. Thus, the H_a and H_b protons, which are located in the spirocycle at different sides of this plane, become diastereofacially differentiated and can be used as diastereotopic markers.

Heating a DMSO-d_6 solution of spirocycle **3** resulted in broadening of the H_a and H_b proton signals (~40°C), followed by coalescence (~70°C) and further transformation into a two-proton singlet (~100°C). Cooling of the solution to room temperature fully restored the spectrum, without any traces of degradation in the spirocyclic structure (Fig. 1).

The computational modeling of temperature-dependent NMR spectra and calculation of rate constants was performed with the gNMR 5.1 software.[13] The obtained set of temperature-dependent experimental spectra was converted with the gCVT program (included in the gNMR software suite) to a set of .spg files compatible with gNMR. For the spectrum acquired at room temperature, theoretical modeling of proton signal shape from the indicator groups was performed, by using a least squares method to match the experimentally observed signal shape in .spg file with a computer model that included variation of chemical shift, width at half height, and spin-spin coupling constant. The calculated spectrum was compared *via* the computer model to a set of other temperature-dependent spectra, while varying the exchange rate constant. As a result, the rate constant was determined for each spectrum and for the respective temperature. The Gibbs free energy value ($\Delta G^{\neq}$) was calculated by Arrhenius equation for each rate constant. A least squares linearization with a correlation coefficient of no less than 0.98 allowed to find the activation entalphy ($\Delta H^{\neq}$) and enthropy ($\Delta S^{\neq}$). Based on literature data,[14] we estimate that the error in determining k did not exceed 15%, $\Delta G^{\neq}$ – 0.6 kJ/mol, $\Delta H^{\neq}$ – 2 kJ/mol, $\Delta S^{\neq}$ – 8 J/mol·K. Thus, the kinetic and activation parameters for rearrangement involving the exchange of H_a and H_b protons, obtained by full analysis of indicator proton signal shape, are the following: k_{298} = 0.19 s^{-1}, $\Delta G^{\neq}_{298}$ = 77.0 kJ/mol, $\Delta H^{\neq}$ = 126 kJ/mol, $\Delta S^{\neq}$ = 163 J/mol·K.

The reason for exchange of H_a and H_b proton positions apparently is degenerate recyclization, involving the cleavage of C_{spiro}–O bond, torsion rotation around the C–N bond in the metastable open-chain isomer **2**, and subsequent spirocyclization. The observed inversion of configuration can be formally linked also to the cleavage and formation of C_{spiro}–N bond. We should note that none of the possible "open" forms were experimentally observed. However, the previously studied set of kinetic and activation parameters for the tautomerism and stereodynamics of several nitroaryl and nitrohetaryl derivatives of aminotropone, thiotropone, and troponimine[1] allows to consider a C_{spiro}–O bond cleavage mechanism as the most likely scenario.

Thus, the interaction of 10-(alkylamino)colchicine with aromatic electophiles allowed to synthesize new derivatives of colchicine, an alkaloid known for its broad spectrum of biological activity,[15] while the use of natural chirally pure synthetic precursors enables new approaches to the study of stereodynamics in molecules with flexible structure and variable stereo configuration.

Experimental

^{1}H and ^{13}C NMR spectra (600 and 150 MHz, respectively) were acquired on a Bruker Avance-600 spectrometer in DMSO-d_6, with TMS as internal standard. The assignment of ^{1}H and ^{13}C NMR signals was based on the data of COSY, NOESY, HSQC, and HMBC 2D NMR experiments. High-resolution mass spectra were recorded on a Bruker micrOTOF II instrument, electrospray ionization, positive ion mode (capillary voltage 4500 V). The mass scanning range was 50–3000 Da. Melting points were determined in glass capillaries on a PTP apparatus. Merck Silicagel 60 (36–71 μm) was used for column chromatography. Picryl chloride[16] was synthesized according to a published procedure. Benzylaminocolchicine was synthesized from commercially available colchicine (Alfa Aesar) and benzylamine (Fluka) following a modified literature procedure.[10]

10-(Benzylamino)colchicine (1). Benzylamine (0.25 ml, 2.3 mmol) was added to colchicine (200 mg, 0.5 mmol), the mixture was stirred and maintained at room temperature for 3 days. The reaction mixture was separated chromatographically on silica gel, eluent $CHCl_3$–EtOH (20:1). Yield 190 mg (80%), bright-yellow powder, mp 165–166°C (mp 166–168°C (EtOAc–cyclohexane)[6]).

7-(Acetylamino)-11-benzyl-1,2,3-trimethoxy-2',4',6'-trinitro-5,6,7,11-tetrahydro-8a*H*-spiro[benzo[6,7]heptaleno[3,2-*d*][1,3-*d*]oxazol-8a-ylium-10,1'-cyclohexa[2,4]dien[6]-ide] (3). Picryl chloride (23 mg, 0.09 mmol) was added to a solution of 10-(benzylamino)colchicine (**1**) (41 mg, 0.09 mmol) in acetonitrile (2 ml); the reaction mixture was refluxed with stirring for 30 min, then evaporated under air stream. The residue was purified two times by chromatography on silica gel, eluent $CHCl_3$–Me_2CO (10:1). Yield 31 mg (51%), bright-red crystals, which decomposed at 180–185°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.85 (3H, s, $COCH_3$); 2.04–2.10 (1H, m) and 2.19–2.26 (1H, m, 6-CH_2); 2.15 (1H, dd, *J* = 13.0, *J* = 6.8) and 2.67 (1H, dd, *J* = 13.0, *J* = 6.4, 5-CH_2); 3.67 (3H, s, OCH_3); 3.83 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 4.45 (1H, dt, *J* = 12.3, *J* = 7.1, 7-CH); 4.85 (1H, d, *J* = 15.8) and 5.02 (1H, d, *J* = 15.8, NCH_2Ph); 6.89 (1H, s, H-4); 7.10 (2H, d, *J* = 7.6, H-2,6 Ph); 7.19–7.24 (2H, m, H-3,5 Ph); 7.26–7.30 (1H, m, H-4 Ph); 7.59 (1H, s, H-8); 8.01 (1H, d, *J* = 11.8, H-12); 8.14 (1H, d, *J* = 11.8, H-13); 8.43 (1H, d, *J* = 2.7, H_a); 8.53 (1H, d, *J* = 2.7, H_b); 8.60 (1H, d, *J* = 7.1, NH). ^{13}C NMR spectrum, δ, ppm: 22.4 ($CO\underline{C}H_3$); 28.9 (C-5); 37.7 (C-6); 47.7 ($\underline{C}H_2$Ph); 52.4 (C-7); 56.0 (3-$O\underline{C}H_3$); 60.7 (2-$O\underline{C}H_3$); 61.1 (1-$O\underline{C}H_3$); 105.6 (C-10); 108.0 (C-4); 115.3 (C-8); 117.1 (C-12); 120.6 (C-4'); 123.8 (C-2'); 124.1 (C-6'); 124.3 (C-13b); 127.4 (C-3'); 127.8 (C-5'); 128.2 (C-2,6 Ph); 128.4 (C-3,4,5 Ph); 132.7 (C-1 Ph); 135.0 (C-4a); 139.5 (C-13a); 140.6 (C-2); 149.9 (C-1); 151.2 (C-13); 154.2 (C-3); 154.3 (C-11a); 159.4 (C-7a); 161.7 (C-8a); 169.1 ($\underline{C}OCH_3$). Found, *m*/*z*: 708.1911 $[M+Na]^+$. $C_{34}H_{31}N_5NaO_{11}$. Calculated, *m*/*z*: 708.1912.

The Supplementary information file containing ^{1}H and ^{13}C NMR spectra of 10-(benzylamino)colchicine (**1**) is available online at http://link.springer.com/journal/10593.

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