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On the 100th anniversary of V.V. Perekalin

Reactions of 1-Nitrocyclohexene with Alicyclic Amines

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Abstract—The interaction of 1-nitrocyclohexene with alicyclic amines can proceed via nucleophilic addition at the carbon–carbon double bond (morpholine, piperazine) to form aza-Michael products or as deprotonation (piperidine, azepane) to give ammonium salts, 2-cyclohexene-1-nitronates. The preferred reaction pathway is determined by the amine basicity.

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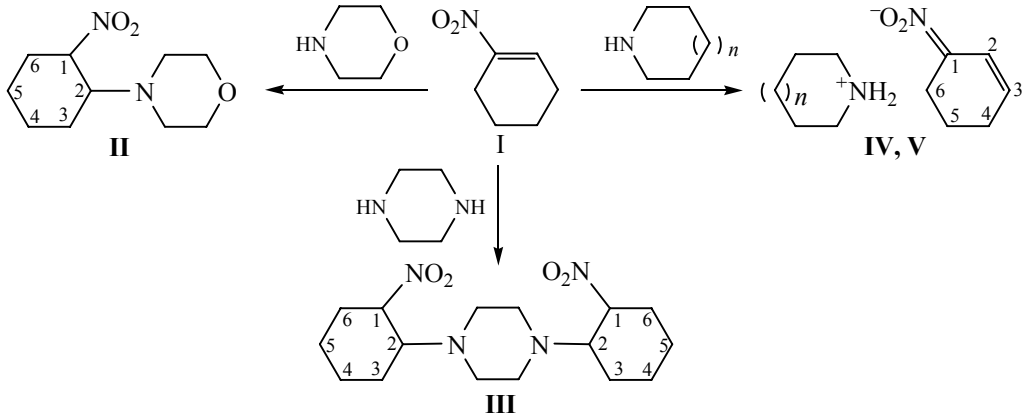
Reactions involving *N*-nucleophiles form an important part of the unsaturated nitro compounds chemistry [1, 2], however, understanding of their products in the case of carbocyclic nitroalkenes is not straightforward. For example, the interaction of 1-nitrocyclohexene with substituted pyrrolidine and piperidine may result in the products of nucleophilic addition or salt formation [3]. According to the authors of [3], the reaction pathway is determined by spatial structure of the nucleophile.

We investigated the interaction of 1-nitrocyclohexene **I** with some sterically similar secondary alicyclic amines of different basicity (pK_a of HB^+ values were taken from [7]). The experiments performed at room temperature in bulk proved that the amine basicity determined the preferred reaction pathway: either nucleophilic addition or deprotonation of the carbocycle allyl methylene group.

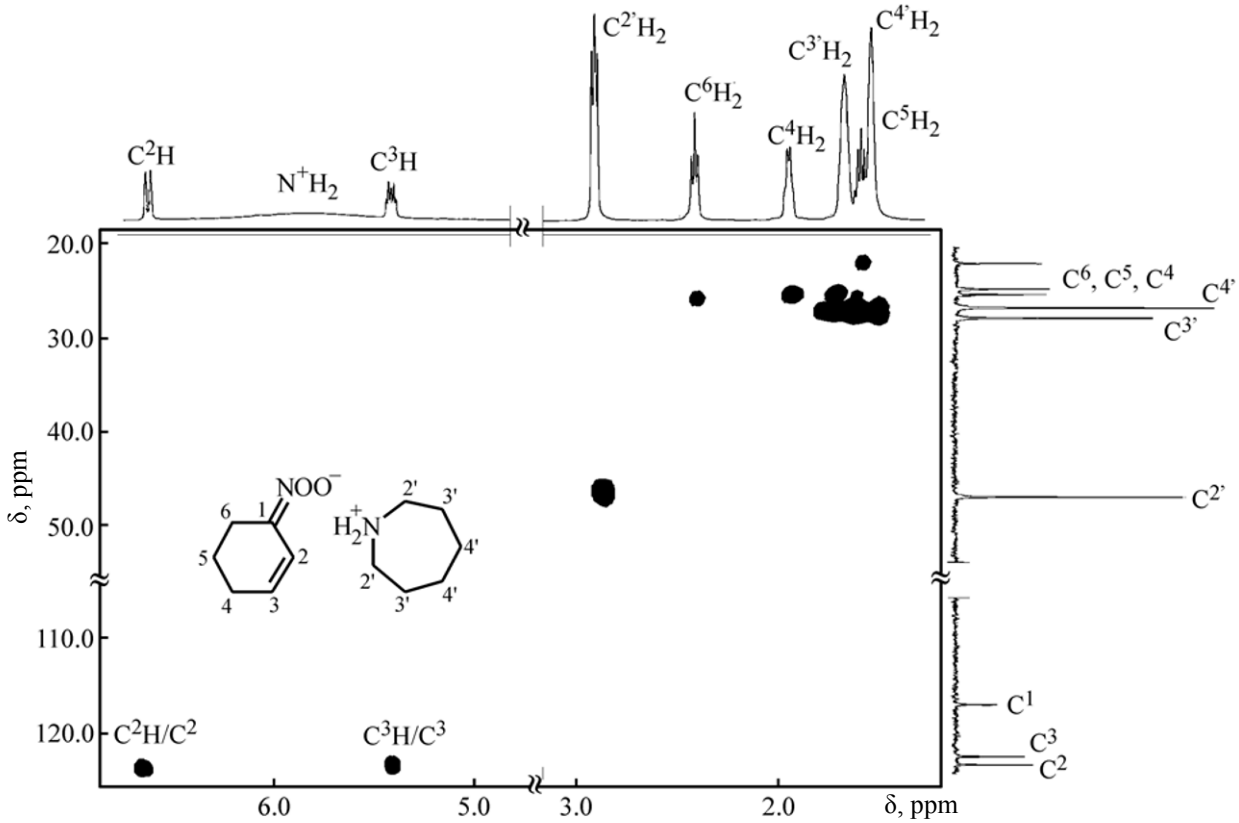
For example, the reactions with morpholine (pK_a HB^+ 8.97) and piperazine (pK_a HB^+ 9.90) occurred within 24 h to give the products of mono-addition (**II**) and bis-addition (**III**).

In the reaction of nitroalkene **I** with the more basic piperidine and azepane (pK_a or HB^+ was 11.12 and 11.24, respectively) the CH-acidic properties of C^3H_2 methylene group of nitrocyclohexene were more pronounced. The reaction resulted in ammonium 2-cyclohexene-1-nitronates **IV** and **V**, easily isolated by treating the reaction mixture with diethyl ether.

Obtained compounds **II**–**V** were stable crystalline substances; their structure was elucidated by ^{1}H NMR, ^{13}C NMR, ^{1}H–^{13}C HMQC, IR, and UV spectroscopy methods. The structurally similar salts of nitrocyclohexene obtained in [3] were not characterized and described as individual substances.



n = 1 (**IV**), 2 (**V**).



^{1}H–^{13}C HMQC NMR spectrum of **V** in DMSO-d_6.

In the IR spectra of aminonitrocyclohexanes **II** and **III,** the absorption bands of non-conjugated nitro group (1550–1553, 1377–1378 cm^{-1}) were observed. In the ^{1}H NMR spectra of those adducts the proton signals of all structural fragments were identified. The signals of methylene protons of the cyclohexane ring and those of heterocyclic amines appeared as strongly coupled multispin systems in the range of 1.20–3.45 ppm. The spectra contained complex multiplets of nitromethine (4.56–4.72 ppm) and aminomethine (2.76–2.84 ppm) protons as well. The chemical shifts of those groups were close to those of the known vicinal aminonitrocyclohexanes [4, 6].

Parameters of the nitronates **IV** and **V** electronic spectra (absorption maximum at 285–287 nm, ε = 12300–14200) were close to those reported in the literature for the corresponding nitrocyclohexene salts (λ_{max} = 278 nm, ε = 16100, [8]). The IR spectra of those compounds contained vibrational bands of the ionized nitro group (1354, 1216–1221, 1154–1160, and 1063–1064 cm^{-1}), of C=C and C=N$^+$ double bonds (1624–1626, 1551–1596, and 1534–1537 cm^{-1}), and of the ammonium groups N–H bonds (2318–2736 cm^{-1}).

^{1}H and ^{13}C NMR spectra were important to confirm the structures of **IV** and **V**. The ^{1}H NMR spectra of **IV** and **V** contained the signals of olefinic protons C^{3}H (multiplet, 5.41–5.44 ppm) and of C^{2}H (doublet, 6.60–6.62 ppm), along with the signals assigned to methylene groups protons of heterocyclic ammonium cation and to carbocyclic anion.

The ^{13}C NMR spectra of **IV** and **V** contained the downfield signals of sp^2 carbon atoms (C^1, C^2, and C^3) of cyclohexene nitronate anion in the range of 117.37–123.88 ppm; they were assigned on the basis of ^{1}H–^{13}C HMQC data. For example, the absence of any cross-peaks of the 117.55 ppm signal in the spectrum of **V** allowed its assignment to C^1 (see figure). Then, the correlation of the signals at 123.07 and 123.43 ppm with the signals of olefinic protons (multiplet of C^{3}H and doublet of C^{2}H) allowed their assignment to C^3 and C^2, respectively.

To conclude, the study of model reactions with alicyclic amines demonstrated that the pathway of 1-nitrocyclohexene **I** interaction depended on the nucleophilic reagent basicity: the aza-Michael adducts were formed in the case of amines with pK_a(HB$^+$) less

than 11.12 (morpholine, piperazine). When more basic reagents were used, the nitrocyclohexene system was acting as a CH-acid to give corresponding conjugated 2-cyclohexene-1-nitronates.

EXPERIMENTAL

The 1H, ^{13}C–{1H}, and ^{1}H–^{13}C HMQC NMR spectra were recorded with Jeol ECX400A spectrometer [399.78 (^{1}H), 100.525 (^{13}C) MHz] in DMSO-d_6, the residual non-deuterated solvent signals were used as internal reference. The IR spectra were registered with Shimadzu IRPrestige-21 Fourier spectrometer in KBr pellets. The electronic absorption spectra were recorded with Shimadzu UV2401PC spectrophotometer in quartz cuvettes (l = 0.1 cm, $c = 1.0\times10^{-3}$ mol l^{-1} in ethanol). Elemental analysis was performed with Eurovector EA 3000 (CHN Dual mode) analyzer.

1-Nitrocyclohexene (I) was synthesized by nitromercurization method [9], which was modified to avoid direct contact with the highly toxic reagent, mercury(II) chloride. A suspension of 40.00 g (180 mmol) of mercury(II) oxide in 20 ml of distilled water was added to 150 ml of 10% hydrochloric acid (d = 1.05 g cm^{-3}). After 5 min, 25.20 g (360 mmol) of sodium nitrite and 14.76 g (18.22 ml, 180 mmol) of cyclohexene were added to the mixture. The resulting mixture was incubated for 72 h at room temperature. (2-Nitrocyclohexyl)mercury chloride was filtered off (37.59 g, 110 mmol, 61%), dissolved in 200 ml of dichloromethane, and mixed with 44 ml of 2.5 M sodium hydroxide solution (110 mmol). The reaction mixture was stirred for 5 min, and then 40.15 ml of 10% hydrochloric acid (110 mmol) was added. The inorganic residue was filtered off; the mother liquor was separated in a separating funnel. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was distilled in vacuum. Yield 10.83 g (47%), pale yellow oil, bp 72–74°C (4 mm Hg), n_D^{20} 1.5052 {bp 71.5°C (3 mm Hg), n_D^{20} 1.5051 [10]}. Inorganic residue containing mercury and soluble salts (NaCl, $HgCl_2$) was treated with diluted nitric acid.

2-Morpholino-1-nitrocyclohexane (II). 0.35 g (0.35 ml, 4 mmol) of morpholine was added to 0.50 g (4 mmol) of 1-nitrocyclohexene **I**. After 24 h incubation, the reaction mixture was treated with 2 ml of anhydrous ether. The resulting precipitate was filtered off, washed with cold diethyl ether, and dried in air. Yield 0.64 g (75%), mp 62–64ºC. IR spectrum (KBr), ν, cm^{-1}: 1553, 1378 (NO_2). ^{1}H NMR spectrum, δ_H, ppm: 1.20–1.29 m, 1.67–1.79 m (6H, C^3H_2, C^4H_2, C^5H_2), 1.82–2.05 m (2H, C^6H_2), 2.29–2.62 m (4H, CH_2N), 3.36–3.49 m (4H, CH_2O), 2.78–2.85 m (1H, C^2H), 4.68–4.75 m (1H, C^1H). ^{13}C NMR spectrum, δ_C, ppm: 86.77 (C^1), 66.07 (C^2), 24.56, 22.67, 23.82, 31.56 (C^3, C^4, C^5, C^6), 48.85 (2C, CH_2N), 67.19 (2C, CH_2O). Found N, %: 12.97. $C_{10}H_{18}N_2O_3$. Calculated N, %: 13.07.

1,4-Bis(2-nitrocyclohexyl)piperazine (III). 0.32 g (4 mmol) of piperazine was added to 1.00 g (8 mmol) of 1-nitrocyclohexene **I**. After 24 h incubation, the resulting precipitate was filtered off and washed with cold diethyl ether. Yield 0.29 g (22%), mp 153–155ºC. IR spectrum (KBr), ν, cm^{-1}: 1550, 1373 (NO_2). ^{1}H NMR spectrum, δ_H, ppm: 1.21–1.29 m, 1.69–1.82 m and 2.05–2.25 m (16H, C^3H_2, C^4H_2, C^5H_2, C^6H_2), 2.59–2.61 m (8H, CH_2N), 2.76–2.84 m (2H, C^2H), 4.56–4.65 m (2H, C^1H). Found N, %: 16.54. $C_{16}H_{28}N_4O_4$. Calculated N, %: 16.46.

Piperidinium 2-cyclohexene-1-nitronate (IV). 0.34 g (0.39 ml, 4 mmol) of piperidine was added to 0.50 g (4 mmol) of 1-nitrocyclohexene **I**. After 24 h of incubation, the reaction mixture was treated with 2 ml of anhydrous ether. The resulting precipitate was filtered off, washed with cold diethyl ether, and dried in air. Yield 0.77 g (91%), mp 68–70ºC. IR spectrum (KBr), ν, cm^{-1}: 1354, 1221, 1154, 1063 (NO_2^-), 1626, 1551, 1537 (C=C, C=N$^+$), 2318–2736 (NH_2^+). UV spectrum, λ_{max}, nm (ε): 287 (12300). ^{1}H NMR spectrum, δ_H, ppm: 1.51–1.53 m, 1.61–1.64 m and 2.82–2.84 m [10H, $(CH_2)_5$], 1.55–1.60 m, 1.96–2.00 m, 2.40–2.44 m (6H, C^4H_2, C^5H_2, C^6H_2), 5.41–5.64 m (1H, C^1H), 6.60 d (1H, C^2H, J 10.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 122.85 (C^3), 123.88 (C^2), 117.37 (C^1), 22.30, 25.56, 25.00, 24.72 [6C, C^4, C^5, C^6, $(CH_2)_3$], 44.23 (2C, CH_2N). Found N, %: 13.48. $C_{11}H_{20}N_2O_2$. Calculated N, %: 13.20.

Azepanium 2-cyclohexene-1-nitronate (V) was prepared similarly. Yield 50%, mp 49–50ºC. IR spectrum (KBr), ν, cm^{-1}: 1354, 1216, 1160, 1064 (NO_2^-), 1624, 1596, 1534 (C=C, C=N$^+$), 2396–2727 (NH_2^+). UV spectrum, λ_{max}, nm (ε): 285 (14200). ^{1}H NMR spectrum, δ_H, ppm: 1.50–1.52 m, 1.63–1.67 m, 2.89–2.92 m [12H, $(CH_2)_6$], 1.55–1.58 m, 1.94–1.96 m, 2.40–2.43 m (6H, C^4H_2, C^5H_2, C^6H_2), 5.40–5.42 m (1H, C^1H), 6.62 d (1H, C^2H, J 10.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 123.07 (C^3), 123.43 (C^2), 117.55 (C^1), 22.29, 25.56, 25.00, 26.95, 28.05 [7C, C^4, C^5, C^6, $(CH_2)_4$], 46.04 (2C, CH_2N). Found N, %: 11.99. $C_{12}H_{22}N_2O_2$. Calculated N, %: 12.38.

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