New type of ring-chain tautomerism. Direct evidence from ^{1}H NMR spectroscopy*

M. V. Zlokazov, A. V. Lozanova, and V. V. Veselovsky★

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: ves@ioc.ac.ru

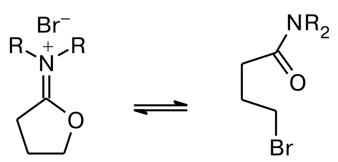
A new type of ring-chain tautomerism consisting in the reversible transformation of 4-(5-)haloalkanecarboxylic acid dialkylamides into dialkyl(tetrahydrofuran-2-ylidene)- and dialkyl(tetrahydropyran-2-ylidene)ammonium halides, respectively, was found and studied by ^{1}H NMR spectroscopy.

Key words: γ-halobutyric acid dialkylamides, δ-bromopentanoic acid diisopropylamide, dialkyl(tetrahydrofuran-2-ylidene)ammonium halides, diisopropyl(tetrahydropyran-2-ylidene)ammonium bromide, ring-chain tautomerism, temperature effect, solvent effect, ^{1}H NMR spectroscopy.

Examples of ring-chain tautomeric transformations were described for a wide variety of organic compounds. An effort to classify reversible transformations of this type has been made earlier.[2] However, Jones reasoned[2] that in a rigorous treatment of tautomerism, one should consider exclusively examples for which the presence of both ring and chain tautomers as well as their rapid interconversion were proved. However, these cases are scarce. In the present study, we describe a new type of ring-chain tautomerism belonging (in the light of Jones's statement[2]) to a rare case, where the presence of the cyclic and linear forms and their interconversion are observable by ^{1}H NMR spectroscopy.

Earlier, it has been reported[3] that the reaction of γ-bromobutyric acid chloride with dimethylamine afforded crystalline dimethyl(tetrahydrofuran-2-ylidene)ammonium bromide (**1**). When performing this reaction and identifying the reaction product by ^{1}H NMR spectroscopy, we unexpectedly found that in a $CDCl_3$ solution the latter occurs in equilibrium with γ-bromobutyric acid dimethylamide **2**. More thorough investigation demonstrated that this fact is a consequence of the reversible interconversion (tautomerism) between "ring" form **1** and "chain" form **2** (Scheme 1). The ratio between the components involved in this equilibrium was found to depend on the concentration of the sample under study. For example, the **1** : **2** ratio changes from 24 : 76 to 53 : 47 as the concentration of the solution was increased from 0.02 to 0.2 mol L^{-1} (^{1}H NMR spectroscopic data, $CDCl_3$, 303 K). Accumulation of more polar form **1** with increasing concentration is, apparently, favored by the possibility of formation of ion-pair aggregates. This situation has been noted earlier for solutions of salt-like organic compounds in nonpolar solvents.[4]

Scheme 1



1, **3** **2**, **4**

R = Me (**1**, **2**) Prⁱ (**3**, **4**)

As expected, the equilibrium under consideration is substantially affected by the temperature conditions. Thus, heating of a solution leads to an increase in the percentage of "chain" form **2**, whereas cooling of the solution to the initial temperature restores the system to its original state (Table 1). It should be noted that in the interpreta-

Table 1. Temperature dependence of the ratios between tautomers **1** : **2**, **3** : **4**, and **5** : **6** (^{1}H NMR spectroscopic data for 0.1 *M* solutions in $CDCl_3$)

T/K	**1** : **2** (%)	**3** : **4** (%)	**5** : **6** (%)
293	—	—	73 : 27
303	42 : 58	92 : 8	67 : 33
318	20 : 80	84 : 16	43 : 57
333	10 : 90	70 : 30	25 : 75

---

* For the preliminary communication, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 521—524, March, 2004.

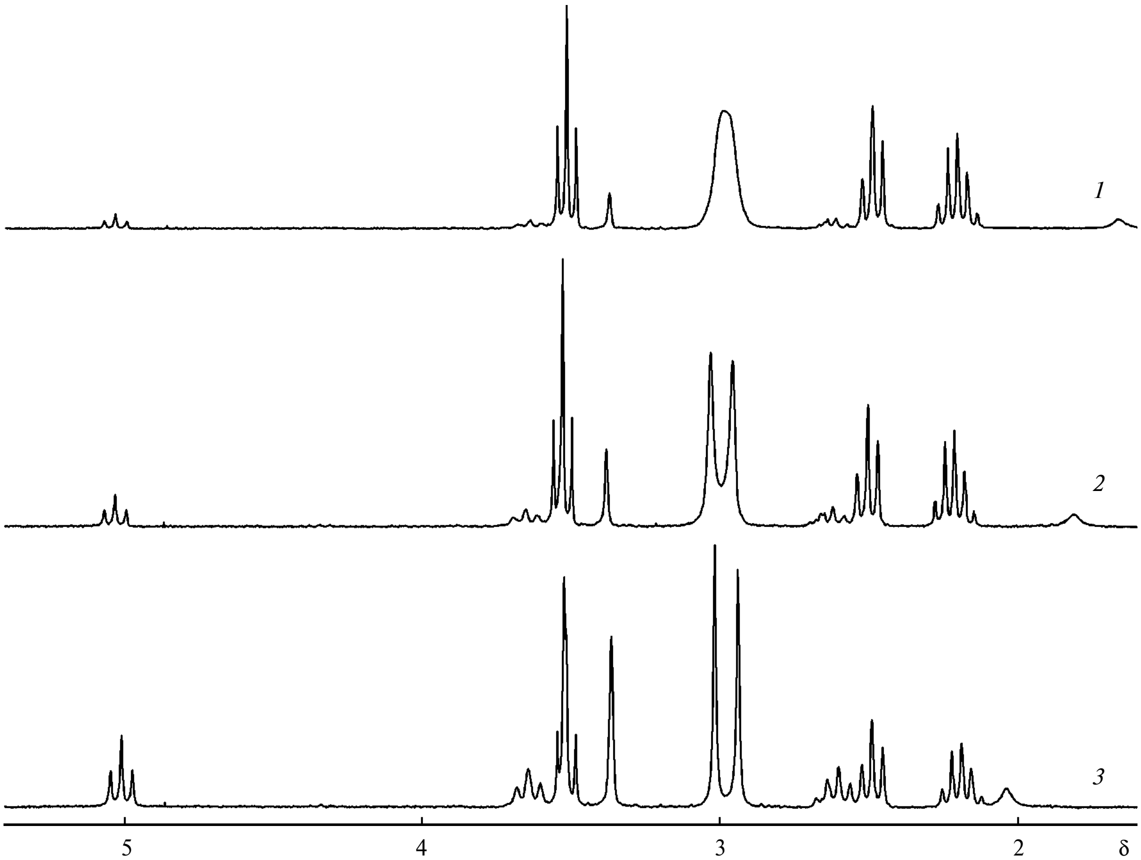


Fig. 1. ^{1}H NMR spectra of a mixture of tautomers **1** and **2** (a 0.1 *M* solution in $CDCl_3$) at different temperatures: 333 (*1*), 318 (*2*), and 303 K (*3*).

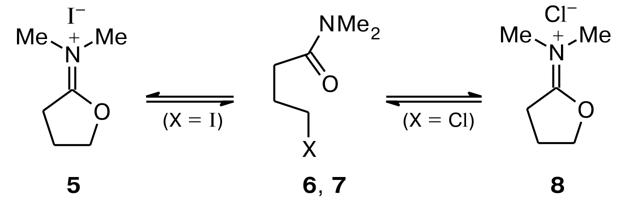
tion of the observed temperature effect, dissociation of ion-pair aggregates (the possibility of their formation was discussed above) at high temperature must be taken into account. Analysis of the changes in the ^{1}H NMR spectra of a mixture of **1** and **2** (Fig. 1) shows that heating of the sample leads to the disappearance of the nonequivalence of the methyl groups of amide **2**, which is associated with a substantial barrier to rotation about the C—N bond typical of alkylamides.

An analogous behavior was observed for a previously unknown diisopropylamine derivative **3**. In solutions of this compound, tautomeric forms **3** and **4** are present in different ratios depending on the temperature.

The transformations under consideration would also be expected to depend substantially on the polarity of the solvent used. In both cases, the equilibrium in D_2O solutions is actually completely shifted to cyclic forms **1** and **3**, as evidenced by ^{1}H NMR spectroscopy. The same effect was observed for salt **3** in DMSO-d_6. In the same solvent, the ratio between tautomers **1** and **2** is 50 : 1 (in both cases, the NMR spectra were recorded at 303 K).

After the replacement of the bromide anion in compound **1** with the iodide anion (Scheme 2), the ratio between cyclic form **5** and linear form **6** in a $CDCl_3$ solution is shifted toward the former tautomer (67 : 33, ^{1}H NMR spectroscopic data at 303 K). By contrast, the ^{1}H NMR spectrum of γ-chlorobutyric acid dimethylamide **7** (which is a liquid)^5 in $CDCl_3$ at the same temperature shows the presence of only traces of salt **8**, whose diagnostic signal at δ 5.0 virtually disappears upon heating of the solution to 333 K. In a DMSO-d_6 solution, the ratio between the cyclic (**8**) and linear (**7**) forms is 14 : 86 and 11 : 89 at 303 and 333 K, respectively. Upon dissolution in D_2O, the ^{1}H NMR spectroscopic study revealed exclusively cyclic tautomer **8**. It should be noted that chloride **7** is poorly soluble in D_2O. However, stirring of an emulsion of **7** in D_2O at 20 °C for 20 h led to its

Scheme 2

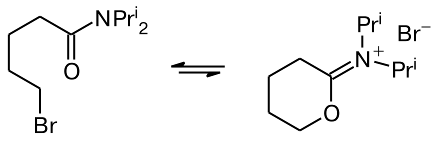


X = I (**6**), Cl (**7**)

complete homogenization followed by the formation of salt **8**. The transformation was accompanied by rather rapid hydrolysis giving rise to γ-butyrolactone.

For 5-bromopentanoic acid diisopropylamide (**9**), we also observed a process related to the above-described tautomeric transformations. However, a solution of **9** in $CDCl_3$ (T = 298 K), unlike those of bromides **1** and **3**, contains only ~3% of cyclic isomer **10** (Scheme 3). Dissolution of amide **9** in DMSO-d_6 results in an increase in the percentage of cyclic form **10** (**9**/**10** is 1 : 1 at 298 K and 6 : 5 at 340 K) in the equilibrium mixture. Finally, this equilibrium in a D_2O solution* is completely shifted to immonium salt **10**.

Scheme 3



9 **10**

Previously unknown compounds **3** and **9** were characterized by NMR spectroscopy and elemental analysis. Cyclic tautomers **2**, **4**, **5**, **8**, and **10** were identified in the ^1H NMR spectra based on the spectroscopic data for related compounds published in the literature.[6,7] In particular, tetrahydrofuran derivatives are characterized by the presence of a low-field signal at δ ~5 (CH_2O). This signal has similar positions in the spectra of compounds **2**, **4**, **5**, and **8** and, hence, it is virtually independent of the nature of the halogen atom. The latter is also true for the signals of the CH_2O group (δ ~80) in the ^{13}C NMR spectra of these immonium salts.

Experimental

The IR spectra were recorded on a Specord M-80 instrument. The ^1H NMR (200.13 MHz) and ^{13}C NMR (50.03 MHz) spectra were measured on a Bruker AC-200 spectrometer relative to the signals of the solvent. The compositions of tautomeric mixtures were determined by comparing the integral intensities of nonoverlapping signals of the protons, in particular of the CH_2O groups of the cyclic forms and the $H_2C(3)$ groups of the linear forms.

Solvents were purified according to standard procedures. 4-Bromobutanoic and 5-bromopentanoic acid chlorides, Me_2NH, and Pr^i_2NH were purchased from Aldrich.

Dimethyl(tetrahydrofuran-2-ylidene)ammonium bromide (**1**)[3] and 4-chlorobutanoic acid dimethylamide (**7**)[4] were prepared according to procedures described earlier.

Mixture of bromide **1** and 4-bromobutanoic acid dimethylamide **2** (**1** : **2** = 42 : 58). ^1H NMR ($CDCl_3$, 303 K), δ: bromide **1**: 2.60 (m, 2 H, $H_2C(4)$); 3.36 and 3.52 (both s, 3 H each, Me); 3.64 (t, 2 H, $H_2C(3)$, J = 7.8 Hz); 5.01 (t, 2 H, $H_2C(5)$, J = 7.5 Hz); compound **2**: 2.19 (m, 2 H, $H_2C(3)$); 2.49 (t, 2 H, $H_2C(2)$, J = 6.8 Hz); 2.94 and 3.02 (both s, 3 H each, Me); 3.51 (t, 2 H, $H_2C(4)$, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$, 298 K), δ: bromide **1**: 21.8 and 31.2 (2 CH_2); 39.1 and 41.8 (2 Me); 78.5 (CH_2O); 180.5 (C=N); compound **2**: 27.2, 30.2, and 32.7 (3 CH_2); 33.6 and 36.2 (2 Me); 170.4 (C=O).

Amide 7. ^1H NMR ($CDCl_3$, 298 K), δ: 2.12 (m, 2 H, $H_2C(3)$); 2.49 (t, 2 H, $H_2C(2)$, J = 6.9 Hz); 2.95 and 3.02 (both s, 3 H each, Me); 3.64 (t, 2 H, $H_2C(4)$, J = 6.2 Hz).

Dimethyl(tetrahydrofuran-2-ylidene)ammonium chloride (8). ^1H NMR (D_2O, 333 K), δ: 2.40 (m, 2 H, $H_2C(4)$); 3.17 (t, 2 H, $H_2C(3)$; J = 8.3 Hz); 3.24 and 3.29 (both s, 3 H each, Me); 4.85 (t, 2 H, $H_2C(5)$, J = 7.4 Hz).

Diisopropyl(tetrahydrofuran-2-ylidene)ammonium bromide (3). A solution of Pr^i_2NH (3.03 g, 30.0 mmol) in $MeOBu^t$ (10 mL) was added to a stirred solution of γ-bromobutyric acid chloride 2.79 (g, 15.0 mmol) in $MeOBu^t$ (20 mL) at –5 °C (Ar) for 20 min. The reaction mixture was kept for 15 min. The precipitate that formed was filtered off and washed on a filter with $MeOBu^t$. The combined filtrates were concentrated *in vacuo*. The powdered residue was washed with $MeOBu^t$ (2×5 mL). The supernatant was decanted and the residue was dried *in vacuo*. Bromide **3** was obtained in a yield of 2.83 g (75%), m.p. 173—174 °C ($CHCl_3$—$MeOBu^t$). IR (ν/cm^{-1}, in KBr pellets): 668, 776, 824, 916, 956, 1052, 1140, 1204, 1280, 1328, 1380, 1436, 1464, 1668 (C=N), 2980. Found (%): C, 47.76; H, 7.95; Br, 32.00; N, 5.60. $C_{10}H_{20}BrNO$. Calculated (%): C, 48.01; H, 8.06; Br, 31.94; N, 5.60.

A mixture of bromide **3** and 4-bromobutanoic acid diisopropylamide (**4**). ^1H NMR ($CDCl_3$, 303 K), δ: bromide **3**: 1.46 (d, 6 H, 2 Me, J = 6.6 Hz); 1.47 (d, 6 H, 2 Me, J = 6.9 Hz); 2.56 (m, 2 H, $H_2C(4)$); 3.83 (t, 2 H, $H_2C(3)$, J = 8.1 Hz); 3.91 (sept, 1 H, $\underline{H}CMe_2$, J = 6.9 Hz); 4.32 (sept, 1 H, $\underline{H}CMe_2$, J = 6.6 Hz); 5.05 (t, 2 H, $H_2C(5)$, J = 7.4 Hz); compound **4**: 1.18 (d, 6 H, 2 Me, J = 7.0 Hz); 1.33 (d, 6 H, 2 Me, J = 6.4 Hz); 2.15 (m, 2 H, $H_2C(3)$); 2.44 (t, 2 H, $H_2C(2)$, J = 7.2 Hz); 3.49 (t, 2 H, H(4), J = 6.2 Hz); the signals of the protons of $\underline{H}CMe_2$ in the region of δ 3.5—4.1 overlap with other signals. ^{13}C NMR ($CDCl_3$—CCl_4, ~1 : 1, 297 K), δ: bromide **3**: 19.8 and 20.0 (4 Me); 21.8 and 33.7 (2 CH_2); 50.6 and 57.2 (2 CH); 79.4 (C(5)); 180.4 (C=N); compound **4**: 20.6 and 20.9 (4 Me); 27.9, 32.5, and 33.8 (3 CH_2); 45.5 and 47.9 (2 CH); 169.6 (C=O).

Dimethyl(tetrahydrofuran-2-ylidene)ammonium iodide (5). A suspension of NaI (2.70 g, 18.0 mmol) in MeCN (12 mL) containing bromide **1** (1.16 g, 6.0 mmol) was stirred at 20 °C (Ar) for 1 h and then filtered. The filtrate was concentrated *in vacuo*. The residue was triturated with CH_2Cl_2. The portion, which remained undissolved, was filtered off and washed on a filter with CH_2Cl_2. The combined filtrates were concentrated *in vacuo* to prepare crude product **5** (^1H NMR spectroscopic data) in a yield of 1.45 g. The latter was crystallized three times from an MeCN—$MeOBu^t$ mixture (it should be noted that the solution of iodide **5** turned red-brown even upon moderate heating) to prepare the pure product in a yield of 0.58 g (40%) as colorless crystals, m.p. 147—149 °C. IR (ν/cm^{-1}, in KBr pellets): 792, 856, 908, 980, 1032, 1240, 1292, 1336, 1380, 1408, 1432, 1460, 1708 (C=N), 2948.

A mixture of iodide **5** and 4-iodobutanoic acid dimethylamide (**6**) (**5** : **6** = 67 : 33). ^1H NMR ($CDCl_3$, 303 K), δ:

---

* Dissolution of amide **9** in D_2O proceeded analogously to that described above for compound **7**.

iodide **5**: 2.63 (m, 2 H, $H_2C(4)$), 3.36 and 3.50 (both s, 3 H each, Me); 3.61 (br.t, 2 H, $H_2C(3)$, *J* = 8.1 Hz); 5.02 (t, 2 H, $H_2C(5)$, *J* = 7.4 Hz); compound **6**: 2.14 (m, 2 H, $H_2C(3)$); 2.44 (t, 2 H, $H_2C(2)$, *J* = 6.9 Hz); 2.94 and 3.02 (both s, 3 H each, Me); 3.30 (t, 2 H, $H_2C(4)$, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 293 K), δ: iodide **5**: 22.7 and 33.0 (2 CH_2); 40.6 and 43.2 (2 Me); 79.5 (C(5)); 181.2 (C=N); compound **6**: 7.6 (CH_2I); 28.6 and 33.5 (2 CH_2); 35.4 and 37.2 (2 Me); 171.4 (C=O).

5-Bromopentanoic acid diisopropylamide (9). A solution of Pr^i_2NH (3.03 g, 30.0 mmol) in $MeOBu^t$ (10 mL) was added to a stirred solution of 5-bromopentanoic acid chloride (2.99 g, 15.0 mmol) in $MeOBu^t$ (20 mL) at −5 °C (Ar) for 20 min. The reaction mixture was kept for 15 min. The precipitate that formed was filtered off and washed on a filter with $MeOBu^t$. The combined filtrates were washed with a 10% $NaHCO_3$ brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was distilled off *in vacuo* to give compound **9** in a yield of 3.77 g (95%) as a viscous liquid, b.p. 89—92 °C ($8 \cdot 10^{-2}$ Torr), n_D^{20} 1.4835. IR (ν/cm^{-1}, film): 608, 648, 748, 888, 940, 1044, 1136, 1156, 1216, 1252, 1308, 1344, 1368, 1440, 1476, 1540, 1560, 1640, 2872, 2932, 3000. Found (%): C, 49.95; H, 8.54; Br, 30.75; N, 5.58. $C_{11}H_{22}BrNO$. Calculated (%): C, 50.01; H, 8.39; Br, 30.24; N, 5.30. ^1H NMR ($CDCl_3$, 298 K), δ: 1.19 and 1.36 (both d, 6 H each, 4 Me, *J* = 6.6 Hz); 1.68—1.98 (m, 4 H, 2 CH_2); 2.30 (t, 2 H, $H_2C(2)$, *J* = 7.2 Hz); 3.43 (t, 2 H, $H_2C(5)$, *J* = 6.6 Hz); 3.46 (m, 1 H, $HCMe_2$); 3.95 (sept, 1 H, $HCMe_2$, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 312 K), δ: 20.3 and 20.6 (4 Me); 23.6, 32.0, 33.2, and 33.7 (4 CH_2); 45.2 and 47.9 (2 CH); 170.61 (C=O).

Mixture of amide **9** and diisopropyl(tetrahydropyran-2-ylidene)ammonium bromide (**10**). ^1H NMR (DMSO-d_6, 298 K), δ: amide **9**: 1.12 (d, 6 H, 2 Me, *J* = 6.6 Hz); 1.28 (d, 6 H, 2 Me, *J* = 6.6 Hz); 1.57 (quintet, 2 H, $H_2C(3)$, *J* = 7.6 Hz); 1.75—1.94 (m, 2 H, $CH_2(4)$); 2.27 (t, 2 H, $H_2C(2)$, *J* = 7.2 Hz); 3.54 (t, 2 H, $H_2C(5)$, *J* = 6.9 Hz); 3.44 (m, 1 H, CH); 3.97 (sept, 1 H, CH, *J* = 6.6 Hz); compound **10**: 1.28 (d, 6 H, 2 Me, *J* = 6.7 Hz); 1.32 (d, 6 H, 2 Me, *J* = 6.4 Hz); 1.75—1.94 (m, 4 H, 2 CH_2); 2.99 (t, 2 H, $H_2C(3)$, *J* = 7.2 Hz); 4.03 and 4.36 (both sept, 1 H each, 2 $HCMe_2$, *J* = 6.6 Hz); 4.66 (t, 2 H, $H_2C(6)$, *J* = 5.5 Hz).

^{13}C NMR of cyclic isomer **10** (D_2O, 307 K), δ: 15.4, 19.7, and 24.7 (3 CH_2); 17.5 and 18.3 (4 Me); 49.5 and 51.5 (CH); 72.6 (CH_2O); 173.6 (C=N).

This study was financially supported by the Grant from the President of the Russian Federation (the Program "Leading Scientific Schools," Project No. NSh--1802.2003.3).

References

1. M. V. Zlokazov, A. V. Lozanova, and V. V. Veselovsky, *Mendeleev Commun.*, 2003, 242.
2. P. R. Jones, *Chem. Rev.*, 1963, **69**, 461.
3. D. E. Ames and P. J. Islip, *J. Chem. Soc.*, 1963, 4363.
4. J. March, *Advanced Organic Chemistry. Reactions, Mechanisms and Structrure*, 3rd Ed., J. Wiley and Sons, New York, 1985.
5. J. P. Begue and D. Bonnet-Delpon, *Org. Magn. Reson.*, 1980, **14**, 349.
6. R. A. Stokbroekx, J. Vandenberk, A. H. M. T. van Heertum, G. M. L. W van Laar, M. J. M. C. van der Aa, W. F. M. Van Bever, and P. A. J. Janssen, *J. Med. Chem.*, 1973, **16**, 782.
7. O. Kitagawa, T. Hanano, T. Hirata, T. Inoue, and T. Taguchi, *Tetrahedron Lett.*, 1992, **33**, 1299.

Received December 23, 2003;
in revised form January 15, 2004