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Structure and tautomerism of 2-benzimidazolylthioureas

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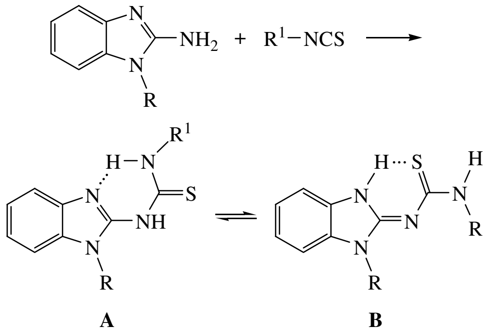
The results of quantum-chemical, ^{1}H NMR and X-ray studies demonstrated that *N*-2-benzimidazolylthioureas exist in 1,3-dihydrobenzimidazolinylidene tautomeric forms.

2-Benzimidazolylthioureas[1–5] derived from primary 2-aminobenzimidazoles are potentially tautomeric owing to the presence of an amidine fragment and may exhibit prototropic N→N tautomerism (Scheme 1). Nevertheless, the structure of ‘genuine’ thioureas was *a priori* ascribed[1–5] to these compounds that is in agreement with thiourea form determined for 2-pyridylthioureas by X-ray diffraction.[6–9]

However, quantum-chemical calculations of benzimidazolylthioureas **1** and **2** by the DFT method (B3LYP/6-31G**) have shown that their ylidenethiourea tautomers **B** possess lower total energy E_{tot} and total free energy in EtOH, G^0_{tot} (PCM/B3LYP/6-31G**), than thiourea forms **A** [$\Delta E^{\mathrm{tot}}_{\mathbf{A,B}}(G^0_{\mathbf{A,B}})$ for two pairs of tautomers are –2.4 (–0.9) and –5.0 (–4.0) kcal mol^{-1}, respectively].[†] Four examined tautomers are stabilised by strong intramolecular H-bond (NH···N or NH···S) and characterised by the close calculated dipole moments ($4.3 < \mu_{\mathrm{calc}} < 5.0$ D). Tautomers **1A**,**B** and **2A** possess an almost planar nonhydrogen framework, whereas in tautomer **2B** the phenyl group is noncoplanar to the plane of the benzimidazolydenethiourea moiety (rotation angle is ~30°) because of repulsion from the methyl group.



1–3

1 R = H, R^1 = Me
2 R = Me, R^1 = Ph
3 R = PhOCH$_2$CH$_2$, R^1 = Ph

Scheme 1

The above data suggest that the structure of ylidenethiourea **B** is more favourable to benzimidazolydenethioureas especially to those containing N′-phenyl group both in the presence and absence of intermolecular interaction and that this tautomer is likely to dominate in solutions. The latter is confirmed by the results of ^{1}H NMR spectral investigations of compounds **2** and **3**.[‡] The ^{1}H NMR spectra, in both weakly polar CDCl$_3$ and polar [^{2}H$_6$]DMSO, indicate the existence of only one form with considerably different chemical shifts of the signals of protons of non-chelated ($\delta \approx 8$ ppm) and chelated ($\delta > 13$ ppm) NH group; this form is characterised by the significant deshielding of the phenyl *o*-protons ($\delta^{o\text{-H}}$ 7.59 and 7.56 ppm; CDCl$_3$).

Affiliation of these spectral characteristics with tautomeric form **B** follows from the comparison of experimental chemical shifts of compound **2** with those of calculated ones for tautomers **2A** and **2B** by the SOS-DFT-IGLO method[12,13] (PW91/IGLO-II//PW91/6-31G**).[§] Analysis of the calculation results has shown that protons of the above tautomers possess noncharacteristic chemical shifts from the point of view of their identification. They are either too close (CH protons) or highly variable (NH protons) depending on the conditions of the

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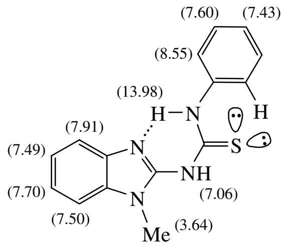
[†] Density functional theory (DFT) optimization of geometries and calculations of the energies were performed using the PC GAMESS program.[10] A hybrid density functional B3LYP was used with 6-31G** basis set. For all stationary points obtained, numerical Hessians were calculated. All tautomer structures had zero negative Hessian eigenvalues. E_{tot} values were calculated taking into account the correction on the vibration energy (ZPE). PCM calculations were performed in a single-point regimen without geometry optimization.

[‡] N-*(1,3-Dihydrobenzimidazol-2-ylиден)*-N′-*phenylthioureas* **2**, **3**: a solution of 10 mmol of 1-methyl- or 1-(β-phenoxyethyl)-2-aminobenzimidazole[11] and 1.67 g (11 mmol) of PhNCS in 15 ml of acetonitrile was refluxed for 4 h; then, the reaction mixture was cooled, and the product of reaction was filtered. Yields 85% (**2**) and 78% (**3**), mp 199–200 °C (MeNO$_2$) and 166–167 °C (MeCN), respectively.

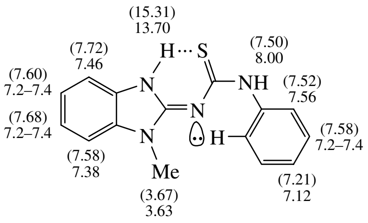
For **2**: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.63 (s, 3H, Me), 7.12 (t, 1H, *p*-H$_{\mathrm{Ph}}$, *J* 7.3 Hz), 7.20–7.42 (m, 6H, *m*-H$_{\mathrm{Ph}}$, 4,5,6,7-H), 7.59 (d, 2H, *o*-H$_{\mathrm{Ph}}$, *J* 7.9 Hz), 8.00 (br. s, 1H, N*H*Ph), 13.72 (br. s, 1H, NH). ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 3.62 (s, 3H, Me), 6.97 (t, 1H, *p*-H$_{\mathrm{Ph}}$, *J* 7.4 Hz), 7.06–7.31 (m, 4H, *m*-H$_{\mathrm{Ph}}$, 5,6-H), 7.39 (d, 1H, 7-H, *J* 8.3 Hz), 7.59 (d, 1H, 4-H, *J* 8.0 Hz), 7.71 (d, 2H, *o*-H$_{\mathrm{Ph}}$, *J* 8.1 Hz), 9.71 (s, 1H, N*H*Ph), 13.44 (s, 1H, NH). Found (%): C, 63.57; H, 5.27; N, 20.03. Calc. for C$_{15}$H$_{14}$N$_4$S (%): C, 63.81; H, 5.00; N, 19.84.

For **3**: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.27 (t, 2H, CH$_2$, *J* 5.3 Hz), 4.47 (t, 2H, CH$_2$, *J* 5.3 Hz), 6.79 (d, 2H, *o*-H$_{\mathrm{OPh}}$, *J* 7.9 Hz), 6.94 (t, 1H, *p*-H$_{\mathrm{OPh}}$, *J* 7.3 Hz), 7.11 (t, 1H, *p*-H$_{\mathrm{NPh}}$, *J* 7.2 Hz), 7.19–7.35 (m, 7H, *m*-H$_{2\mathrm{Ph}}$, 5,6,7-H), 7.44 (d, 1H, 4-H, *J* 7.3 Hz), 7.56 (d, 2H, *o*-H$_{\mathrm{NPh}}$, *J* 7.6 Hz), 8.00 (br. s, 1H, N*H*Ph), 13.69 [br. s, 1H, N(3)H]. ^{1}H NMR (300 MHz, [^{2}H$_6$]DMSO) δ: 4.25 (t, 2H, CH$_2$), 4.31 (t, 2H, CH$_2$), 6.78–6.90 (m, 3H, *o*,*p*-H$_{\mathrm{OPh}}$), 6.95 (t, 1H, *p*-H$_{\mathrm{NPh}}$, *J* 7.6 Hz), 7.09–7.32 (m, 4H, *m*-H$_{\mathrm{OPh}}$, 5,6-H), 7.49 (d, 1H, 4-H or 5-H, *J* 8.2 Hz), 7.57 (d, 1H, 5-H or 4-H, *J* 7.6 Hz), 7.65 (d, 2H, *o*-H$_{\mathrm{NPh}}$, *J* 7.4 Hz), 9.78 (s, 1H, NH), 13.42 (s, 1H, NH). Found (%): C, 67.63; H, 5.38; N, 14.33. Calc. for C$_{22}$H$_{20}$N$_4$OS (%): C, 68.02; H, 5.19; N, 14.42.

[§] Calculation was performed using the program complex DeMon 1.0.4.[14]



2A



2B

Figure 1 Molecular structures of tautomeric forms **2A**, **2B** and chemical shifts of their protons in $CDCl_3$ and calculated ones (in parentheses) in the absence of solvation.

spectra measurement (Figure 1). The *o*-protons of N-phenyl group are the only exclusion. For tautomer **2B**, the calculated chemical shift of these protons is close to the experimental one for compound **2**, whereas for tautomer **2A** it is much greater [$\delta^{o\text{-H}}_{\text{calc}}$ (**2A**), $\delta^{o\text{-H}}_{\text{calc}}$ (**2B**) and $\delta^{o\text{-H}}_{\text{exp}}$ (**2**) in $CDCl_3$ are 8.55, 7.52 and 7.59, respectively]. Note that the values of δ_{calc} for other protons of form **2B** (of course, except for the protons of NH groups) sufficiently agree with experimental shifts observed for **2**. For the aromatic protons, calculated δ values are somewhat overestimated as compared to the experimental ones (Figure 1) that is apparently caused by insufficient accuracy of the calculation, as well as by a disturbing influence of solvation. As calculation shows, the increased deshielding of *o*-protons of N-phenyl group in tautomers **A** and **B** is caused by the influence of lone electron pairs of neighbour heteroatoms (Figure 1). Thus, a significantly greater value of $\delta^{o\text{-H}}$ for tautomer **2A**, as compared with tautomer **2B**, is caused by about two times stronger deshielding influence of the sulfur atom than of nitrogen atom having a lower number of such electron pairs.

The preference of ylidenethiourea form **B** in the solid state was shown for thiourea **3** by X-ray analysis (XRD).[¶]

According to XRD, **3** crystallises in tautomeric form **B** (Figure 2) possessing the *E*-configuration relatively to C=N bond with the formation of N–H···S bonded six-membered ring, that is in a good agreement with results of calculations. Note that the N–H···S bond in **3** is rather strong [N(2)···S(1) 2.945(2) Å, H(2N)···S(1) 2.29 Å, ∠NSH 133°] for such a type of proton donor and acceptor and according to estimation for similar system (2*Z*)-2-cyano-2-quinolin-2(1*H*)-ylideneethanethioamide [N···S 2.9617(5) Å] can be characterised by an energy of *ca.* 9 kcal mol^{-1}.[15(*a*)]

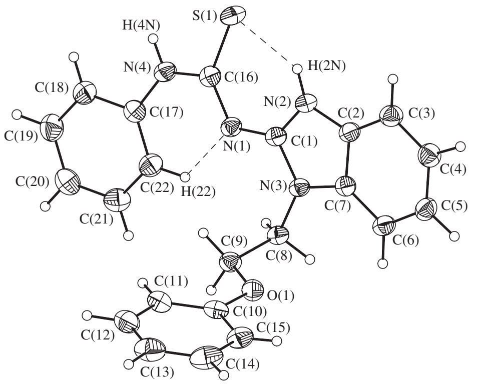


Figure 2 X-ray structure of compound **3** representing atoms as thermal ellipsoids (p = 50%). Selected bond lengths (Å): S(1)–C(16) 1.7251(16), O(1)–C(10) 1.3787(19), O(1)–C(9) 1.4349(19), N(1)–C(1) 1.335(2), N(1)–C(16) 1.341(2), N(2)–C(1) 1.350(2), N(2)–C(2) 1.384(2), N(3)–C(1) 1.367(2), N(3)–C(7) 1.396(2), N(3)–C(8) 1.458(2), N(4)–C(16) 1.364(2), N(4)–C(17) 1.417(2).

Phenylthiourea and benzimidazolyl fragments in **3** are coplanar while a substituent at the N(3) atom is perpendicular to the above plane. Note that, in addition to the N–H···S bond, the planarity of a central fragment leads to the formation of a weak C(22)–H(22A)···N(1) contact [H···N 2.28 Å, C(1)···N(1) 2.895(2) Å, ∠CHN 122°], which can further stabilise the above tautomer.

Analysis of crystal packing revelead that, in addition to intramolecular interactions, a molecule of **3** also participates in the formation of a number of weak interactions such as intermolecular N–H···S bond [N···S 3.465(2) Å, ∠NHS 163°, H···S 2.63 Å], C–H···S (H···S 2.98 Å), stacking (C···C 3.38–3.48 Å) and finally C–H···π contacts (H···C 2.54 Å) interlinking molecules into a three-dimensional framework (Figure 3). Taking into account that such N–H···S and C–H···S contacts generally result in the weakening of intramolecular H-bonds,[15(*b*)] we can assume that in the isolated molecule of **3** the energy of N–H···S H-bond and thus its contribution to tautomer **B** stabilization will be even greater.

Thus, quantum-chemical calculations, ^{1}H NMR and X-ray analysis cooperatively point to the preference of ylidenthiourea **B** for the 2-benzimidazolylthioureas studied.

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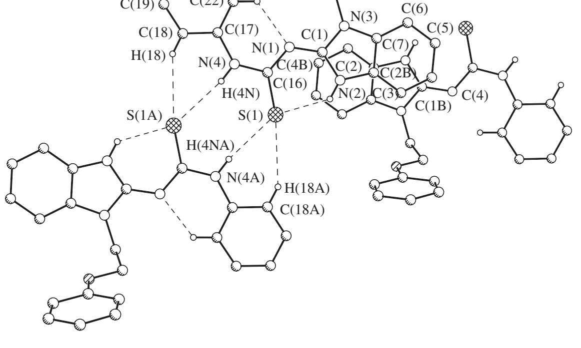

Figure 3 Intermolecular N–H···S, C–H···S and stacking interactions in a crystal of **3**.

[¶] *X-ray diffraction analysis*: at 120(2) K crystals of **3** ($C_{22}H_{20}N_4OS$) are monoclinic, space group $P2_1/n$, a = 10.6160(6), b = 8.4902(5) and c = 22.3817(12) Å, α = 90°, β = 103.627(5)°, V = 1960.52(19) Å^3, Z = 4, (Z' = 1), M = 388.48, d_{calc} = 1.316 g cm^{-3}, μ(MoKα) = 1.210 cm^{-1}, F(000) = = 816. Intensities of 16496 reflections were measured with a Smart 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, $1.87 < \theta < 28.00°$], and 4713 independent reflections (R_{int} = 0.0254) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atoms were located from the Fourier density synthesis. The refinement converged to wR_2 = 0.1032 and GOF = 1.000 for all independent reflections [R_1 = 0.0440 was calculated against F for 3503 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 649845 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2007.

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