STABILITY OF THE DIMERS OF *AZA* ANALOGS OF 2-FORMYLPYRROLE. CONJUGATION VERSUS HYDROGEN BONDING

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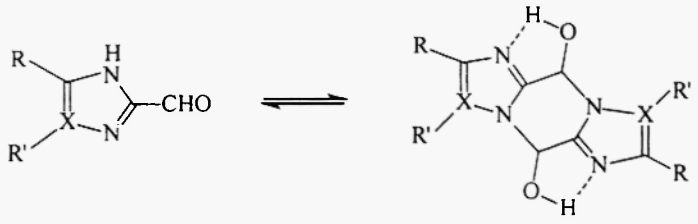
Abstract: The calculated (MP2/6-31G**//HF and B3LYP /6-31G**) energies show that some dimers of 1*H*-benzimidazole-2-carboxaldehyde are more stable than aldehyde itself (monomer). This is in agreement with the literature reports on spontaneous dimerization of 1*H*-benzimidazole-2-carboxaldehyde resulting in formation of 6*H*,13*H*-bis(benzo[4,5]imidazo)[1,2-*a*;1',2'-*d*]pyrazine. Although the calculated hydrogen bond length in this compound is 265.79 pm, position of the signal of hydroxy proton in the ^{1}H NMR spectrum proves that the OH...N bond in the dimer is strong. Discussion shows that formation of the hydrogen bonds in the molecule of 6*H*,13*H*-bis(benzo[4,5]imidazo)[1,2-*a*;1',2'-*d*]pyrazine is responsible for its spontaneous formation from 1*H*-benzimidazole-2-carboxaldehyde.

Introduction

1*H*-Imidazole-2-carboxaldehyde is both an aromatic aldehyde and C-formylamidine. Although it is stable as the monomer (1-5), some other *aza* analogs of 2-formylpyrrole dimerize spontaneously. In crystal state and partly in solution 1*H*-benzimidazole-2-carboxaldehyde is known to have the hemiaminale dimeric form {6*H*,13*H*-bis-(benzo-[4,5]imidazo)[1,2-a;1',2'-d]pyrazine; 5*H*,11*H*-4b,6,10b,12-tetraaza-indeno[1,2-b]fluorene-5,11-diol} (6,7). It was also found to be the case for 5-aryl-1*H*-[1,2,4]triazole-3-carboxaldehydes, **1**, which are transformed into hemiaminals **2** {2,7-diaryl-5*H*,10*H*-bis[1,2,3]triazolo[1,5-a;1',5'-d]pyrazine-5,10-diols; 2,6-diaryl-4*H*,8*H*-1,3,3a,5,7,7a-hexaaza-s-indacene-4,8-diols} (7) (Scheme 1). IR spectra show that the crystal contains only the molecules of the dimer **2** which are stabilized by the intramolecular hydrogen bonds (7).

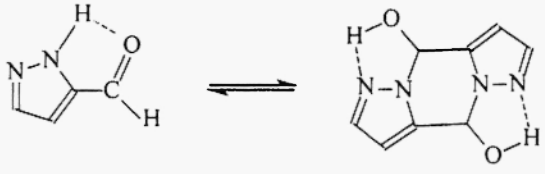
^{1}H NMR and IR spectra indicate that monomeric 5-aryl-1*H*-[1,2,4]triazole-3-carboxaldehydes are present in solution, the dimers being reformed on removal of the solvent (7). Hemiaminals that carry non-aromatic substituents in position 5 are less stable. This shows that extension of the conjugation into aromatic substituents favors dimerization. Benzo annulation of the imidazole moiety seems to have similar effect on stability of the monomeric 1*H*-imidazole-2-carboxaldehydes. These observations show that formation of the strong intramolecular hydrogen bond can be the most important reason for the aldehyde to dimerize.



1	XR' = N; R = Ar	**2**	XR' = N; R = Ar
3	X = C; R = R' =H	**4**	X = C; R = R' =H
5	X = C; R,R' = benzo	**6**	X = C; R,R' = benzo

Scheme 1

1*H*-[1,2,4]Triazole-3-carbaldehyde itself exists predominantly in the carbonyl monomer form (7). 1*H*-Imidazole-4-carboxaldehyde is also stable as the monomer (3). 1(2)*H*-Pyrazole-3-carboxaldehyde also dimerizes (Scheme 2). It is noteworthy, however, that the dimer formed from this aldehyde is of different type. It was found that solution of this aldehyde in DMSO-d_6 contains 10 % of the monomer and 90 % of the dimer **8** {4*H*,9*H*-di-pyrazolo[1,5-



7 **8**

Scheme 2

a;1',5'-d]pyrazine-4,9-diol} (5). The IR spectra (KBr disc and Nujol mull) did not show a strong absorption band which can be assigned to the C=O stretching vibration (8). This would prove that conjugation is less important reason of dimerization than the type of intramolecular hydrogen bond formed in the molecule of the dimer (the N...HO hydrogen bond is stronger than the NH...O one).

Instability of the compound results in its spontaneous transformation into more stable product. It is known that in crystal state 1*H*-benzimidazole-2-carboxaldehyde has the hemiaminale dimeric form (6,7). There is a question why this aldehyde dimerizes so spontaneously. Is this a result of the extent of conjugation in the molecule of the dimer or, perhaps, the specific type of the intramolecular hydrogen bond present in the molecule is responsible for this behaviour? One should keep in mind that some other effects, *e.g.* steric interaction, may also contribute.

Experimental

Known procedure (9) was used to prepare 1*H*-benzimidazole-2-carboxaldehyde.

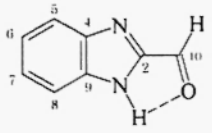
All NMR spectra were recorded for the saturated solution in DMSO-d_6 at 303 K with a Bruker Avance DRX 500 FT NMR spectrometer equipped with an inverse detection 5 mm diameter broad band probehead and z-gradient

working at 500.13 MHz for proton and 125.76 MHz for carbon-15, respectively. The ^{1}H NMR chemical shifts are referenced to the (trace) signal of $CHCl_3$ (δ = 7.26 from int. TMS) and the ^{13}C NMR chemical shifts to the signal of solvent $CDCl_3$ (δ = 77.00 from int. TMS), respectively. 2 D pulsed field z-gradient (PFG) selected $^{1}H,^{13}C$ HMQC (10,11) and $^{1}H,^{13}C$ HMBC (12) experiments were run to assign reliably the ^{13}C NMR spectra. Other experimental details are available in our recent paper (13).

Ab initio calculations were carried out with the GAUSSIAN 98 (14) program using the 6-31G** basis set at the RHF and MP2 levels. All calculations were performed with the PCM model of solvation (5,16).

Results and discussion

There is usually more than one reaction product that can be obtained from the definite starting material. In addition to **6** (6*H*,13*H*-bis(benzo[4,5]imidazo)[1,2-*a*;1',2'-*d*]pyrazine, 5*H*,11*H*-4b,6,10b,12-tetraaza-indeno[1,2-*b*]-fluorene-5,11-diol), there are other dimers of **5**. 1,2-Bis(1*H*-benzimidazol-2-yl)-2-hydroxyethanone and its tautomer, **9** [1,2-bis(1*H*-benz-imidazol-2-yl)ethane-1,2-diol], is the bezoin condensation product of this aldehyde (6) Further, at least two more different dimeric forms **9** and **10** should be taken into account. It is noteworthy that the molecule of 1,2-enediol **9** is stabilized by two intramolecular hydrogen bonds and by the very effective π-electron delocalization (6). In



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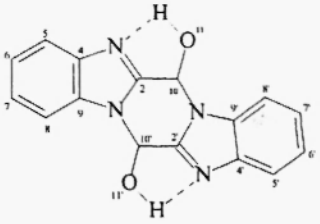

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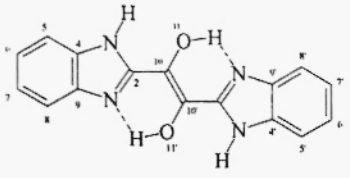

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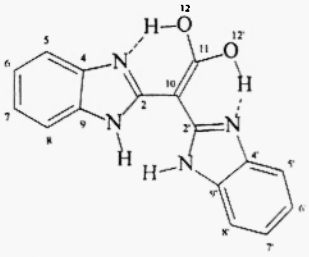

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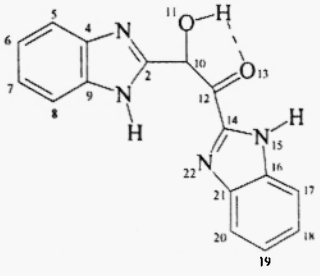

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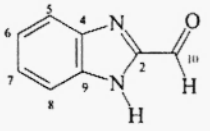

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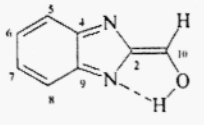

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Scheme 3

contrast with these in **6**, the hydrogen bonds both in **9** and in 1,1-enediol **10** (17) are of RAHB (Resonance Assisted Hydrogen Bond) type (18). There is no resonance interaction between different parts of the molecule **6**. Even though some dimers were not synthesized earlier, it is possible to learn about them by use of the theoretical methods that have proved to be highly reliable to compare stability of other compounds (19). In addition to **5** and its dimers, the rotamer **12** and tautomer **13** (Scheme 3) are also included in this consideration.

The calculated relative energies for 1*H*-benzimidazole-2-carboxaldehyde and its dimers are shown in Table 1. In order to draw the credible conclusions, half of the energy for dimers was compared to the energy for monomers. Irrespective of the method used 1,1-enediol **10** was found to be the most stable both *in vacuum* and in solution. The

Table 1. Calculated relative energies (kJ/mol) for 1*H*-benzimidazole-2-carboxaldehyde and its dimers[a]

	MP2/6-31G**// HF/6-31G** *in vacuum*	MP2/6-31G**// HF/6-31G** PCM in DMSO	MP2/6-31G**// B3LYP/6-31G** *in vacuum*	MP2/6-31G**// B3LYP/6-31G** PCM in DMSO
10	0.00	0.00	0.00	0.00
9	28.90	33.80	26.96	33.10
11	36.20	37.84	33.42	34.96
6	40.17	39.84	40.47	46.20
5	75.56	73.79	70.95	70.57
12	104.58	87.55	100.23	84.73
13	190.68	186.97	177.35	176.77
b	-491.7836196	-491.7884023	-491.7879076	-491.79306

[a] Half of the energy for dimers was compared to the energy for monomers. [b] Total energy (hartree) of the most stable tautomer/rotamer/dimer.

hydrogen bond in its molecule is of the RAHB type. This is also true for the dimer 9. On the other hand, that bond in the less stable dimers 6 and **11** has different nature. Difference in energy between **5** and **12** is a result of the presence or absence of the intramolecular hydrogen bond in these compounds. The mutual steric orientation of the electron orbitals at the carbonyl oxygen atom and N3 seems also to affect the energy of **12**. The extent of conjugation in the molecule is responsible for different stability of **5** and **6**. It includes the benzene and imidazole rings and carbonyl group in **5**. On the other hand, only benzene and imidazole rings are conjugated in 6.

The geometrical parameters for the species considered, calculated at the RHF/6-31G** level (PCM solvation model, DMSO), seem worthy to be discussed. Since the O11–H1 distance in **5** is equal to 266.56 pm, one may see that there is no intramolecular N1H1...O11 hydrogen bond in this compound. The N3–H3 length in **6** is 265.79 pm, which shows that the respective intramolecular N3...H3O11 hydrogen bond is also weak. On the other hand, the intramolecular N1...H11O11 hydrogen bond ($d_{N1...H11}$ = 213.48 pm) in 9 is strong. It can be seen from the N1C2C10N1' (-4.70 deg), C2C10N1'C2' (5.02 deg) and C10N1'C2'C10' dihedral angles (-5.62 deg) that the central six membered ring in 6 is only slightly folded. Carbons 10 and 10' in its molecule have the R and S configurations, respectively.

The N3–H12 distance in **10** is equal to 173.00 pm. Thus, the intramolecular hydrogen bond in this 1,1-enediol is strong. Some steric interaction can be expected to take place between H1 and H1' ($d_{H1-H1'}$ = 220.27 pm). This causes some twist in that molecule: ∠ N1C2C10C2' = -16.71 deg, ∠ C2C10C11O12 = 6.07 deg, ∠ C10C11O12H12 = 2.90 deg. The absolute configuration of both N1 and N1' is R.

Important geometrical parameters for **11** are as follows: $d_{H11...O13}$ = 230.08 pm (O11–H11...O13), ∠ N1C2C10O11 = 32.08 deg, ∠ C2C10O11H11 = 78.14 deg, ∠ C2C10C12O13 = -90.01 deg, ∠ C10C12C14N15 = -175.83 deg, ∠ O13C12C14N15 = 6.23 deg and ∠ O11C10C12O13 = 31.81 deg. The distance between N1...H11 (N1...H11–O11 hydrogen bond) in **13** is equal to 238.18 pm.

Due to very weak solubility of the monomer and dimer in DMSO the S/N in the NMR spectra was not that good as it could be. Unfortunately, for that reason also PFG $^{1}H,^{15}N$ HMBC experiments gave only the signal of the reference. The experimental NMR chemical shifts (δ) are: ^{1}H; 13.45 (broad, O**H**, dimer), 9.95 (C**H**O, monomer), 7-8 (aromatic H + H10), 3.25 (broad, N**H**, monomer); ^{13}C; 184.65, 147.94, 147.84, 143.12, 142.88, 133.04, 132.94, 124.65, 123.12, 122.98, 122.86, 119.50, 119.45, 112.61, 111.71, 72.61, 71.60. By comparison of the experimental chemical shifts with these theoretically calculated (Table 2) one can see that the solution studied contains a mixture of the

Table 2. Calculated (GIAO) ^{13}C NMR chemical shifts (δ) for the compounds studied

atom	**5**	6	**9**	**10**	**11**[a]	**12**	**13**
2	145.82	144.09	143.82	149.89	150.61	144.18	158.17
4	145.73	144.66	134.59	141.49	145.05	145.42	158.44
5	125.44	121.83	110.81	118.81	122.12	126.20	127.38
6	124.55	125.07	125.25	124.76	122.67	124.80	130.73
7	129.16	126.60	123.86	123.85	124.88	128.93	133.04
8	111.18	114.23	121.29	109.08	109.68	110.66	125.42
9	133.23	135.70	143.04	132.26	132.93	133.07	154.14
10	186.90	72.45	128.79	72.99	68.55	178.49	164.24
11	-	-	-	176.00	194.66	-	-

[a] The chemical shifts of residual carbon atoms: 144.75 (C12), 134.00 (C13), 111.28 (C14), 129.30 (C15), 124.61 (C16), 125.21 (C17), 145.16 ppm (C18).

aldehyde **5** and its dimer 6. The presence of two high-field signals in the ^{13}C NMR spectrum may suggest some nonequivalence between C10 and C10' in the molecule of the dimer 6. Moreover, the chemical shift of the amine proton of the dimer (3.25 ppm) shows there is no NH...O intramolecular hydrogen bond in the monomeric aldehyde. On the other hand, although the calculated N3–H3 length in 6 is 265.79 pm, position of the signal of hydroxy proton (13.45 ppm) proves the OH...N bond in the dimer is strong.

Conclusions

Formation of the hydrogen bonds in the molecule of 6*H*,13*H*-bis(benzo[4,5]imidazo)[1,2-*a*;1',2'-*d*]pyrazine is responsible for its spontaneous formation from 1*H*-benzimidazole-2-carboxaldehyde. Both *ab initio* calculations and experimental NMR spectra prove that the OH...N bond in the dimer is strong.

Acknowledgment

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