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Ring-chain tautomerism with participation of pyridine nitrogen: The intramolecular cyclization of 2-pyridinecarboxaldehyde–indandione adducts in acidic medium

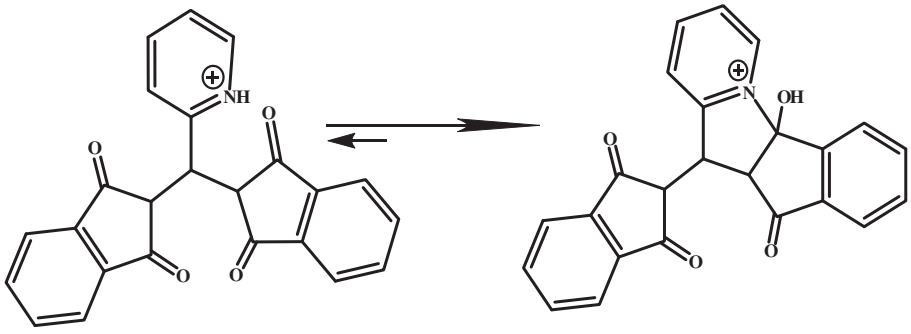
Mark V. Sigalov *

Department of Chemistry, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel

HIGHLIGHTS

- 2-Pyridine-carbaldehyde derivatives of 1,3-indandiones in acidic medium were studied.
- Prototropic ring-chain tautomerism with participation of pyridine nitrogen is found.
- A good agreement is found between experimental (NMR) and theoretical (DFT) results.
- Tautomerization mechanism is suggested.

GRAPHICAL ABSTRACT



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ABSTRACT

Keto-enol tautomerism of 2-pyridine carboxaldehyde adducts with ring-substituted 1,3-indandione derivatives observed in neutral solutions, in the presence of trifluoroacetic acid (TFA) is changed by the previously unknown prototropic ring-chain tautomerism with reversible quaternization of pyridine nitrogen. The proposed mechanism of tautomerization includes intramolecular proton transfer from the protonated nitrogen to indandione carbonyl oxygen, with subsequent cyclization of the unstable O-protonated intermediate. Neutralization of TFA leads to recovery of the keto-enol tautomers.

Introduction

Cyclic β-diketones are an important class of organic compound. Among them, 1,3-indandione (1H-indene-1,3(2H)-dione) has attracted the interest of researchers as a valuable synthetic precursor. 1,3-Indandione and its derivatives have been employed in the synthesis of drugs [1], dyes and pigments [2], and semi-conductors and photo-semi-conductors [3], and in forensic chemistry for fingerprint detection [4]. Keto-enol equilibrium, one of the main structural features of 1,3-diketones, is of a great importance for chemical and biological processes including the important role of prototropic rearrangements within DNA base pairs in the determination of the genetic code [5] and understanding of acid-base and structure–reactivity relationships [6]. On other hand, 1,3-diketones are important ligands in various metal complexes, and the keto-enol tautomerism also plays the determining role in coordination chemistry [7–9]. The keto-enol equilibrium is governed both by

* Tel.: +972 8 6479322.
E-mail address: msigalov@bgu.ac.il

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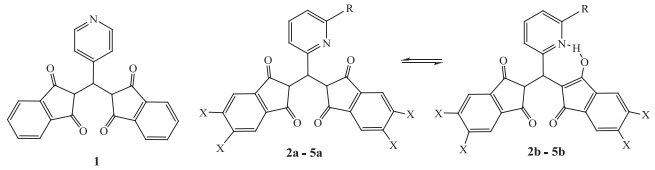
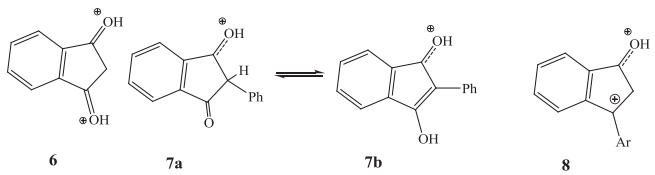
the molecular structure of the compounds and by the properties of the reaction medium. The main factor stabilizing the enol form is hydrogen bond: in acyclic 1,3-diketones the intramolecular hydrogen bond formation leads to a planar chelate *cis*-enol structure [10–15], whereas for cyclic 1,3-diketones the W-shaped geometry of O=C–C–C=O moiety prevents formation of such a bond. In this case, the enol form is stabilized by intermolecular hydrogen-bonded dimers [16–18] or hydrogen bonding with the basic solvent molecules [19]. In the solid state, dimedone exists as the enol tautomer stabilized by intermolecular hydrogen bonded network [20]. Sometimes, the presence of an additional (besides the 2 carbonyl oxygen atoms) basic atom in the molecule leads to formation of intramolecular hydrogen bonding [21,22]. Recently, we described 2:1 adducts of substituted 1,3-indandiones with pyridine aldehydes [21]. We showed that for the 4-pyridinecarbaldehyde derivative **1** in solvents such as dichloromethane the all-keto form is the sole tautomer, whereas for the 2-pyridinecarbaldehyde derivative **2,** the all-keto form (**a**) exists in equilibrium with the keto-enol (**b**) form, the latter being stabilized by an intramolecular hydrogen bond. For the aryl-substituted analogs **3** and **4**, the equilibrium is completely shifted to the all-keto (**3a**) and keto-enol (**4b**) forms, respectively.



We posit that the rupture of the hydrogen bond shifts the keto-enol equilibrium towards the all-keto form. The simplest way for this shift to take place is, at a first glance, protonation of the pyridine nitrogen. This paper reports a study of the interaction of compounds **1–5** with trifluoroacetic acid (TFA); the reactions were followed by NMR spectral methods, supported by quantum–mechanical calculations.

1,3-Diketones are weak bases, and their protonation will take place only in a strongly acidic medium. For instance, the dication of 2,4-pentandione was observed in FSO_3H–SbF_5–SO_2 (magic acid), whereas under the same conditions 1,3-cyclohexanedione formed the monoprotonated species exclusively [23]. 1,3-Indandione dissolved in magic acid transforms to dication **6** [24]. According to UV spectroscopic data, 2-phenyl-1,3-indandione in concentrated sulfuric acid gives monocation **7,** which exists as an equilibrium mixture of the O-protonated diketo (**7a**) and the keto-enol (**7b**) forms [25]. 3-Arylindenones, the close analogs of the enol form of 1,3-indandione, undergo to double protonation in super acid medium, both at the carbonyl oxygen and at C-2, to give dication **8** [26]:



To the best of our knowledge, this study is the first report of protonation of 1,3-diketones both in their diketo and keto-enol forms by a less strong acid, such as TFA.

Results and discussion

NMR spectral data

The addition of excess TFA to a solution of **1** in CD_2Cl_2 resulted, as expected, in protonation of the pyridine nitrogen atom to give 2-(bis(1,3-dioxo-2,3-dihydro-1H-inden-2-yl)methyl)-pyridinium trifluoroacetate **1H$^+$**, as may be seen in the NMR spectrum (Fig. 1). The spectrum showed an N^+H signal at 14.75 ppm. Both signals of the pyridine ring protons were shifted downfield relative to their positions in the nonprotonated molecule, and the common signal of H-3 and H-5 was split into a triplet due to additional spin–spin coupling with the N^+H proton. The three aliphatic protons remained unchanged, but their spin system changed from A_2X in neutral **1** into A_2B in **1-H$^+$**, because the signal of the bridge proton moved to the low field.

Quite a different spectral pattern was observed for the 2-pyridine derivative **2**, indicating the presence of two species (Fig. 2) at a ratio of 15:1 at 260 K. The minor species was the one N-protonated form **2-H$^+$**, which was similar to the 4-pyridine derivative **1-H$^+$**. Proof of its structure is provided by the broad singlet of NH^+ at 14.64 ppm, the triplet at 4.53 ppm, and the doublet at 4.05 ppm (J = 7.0 Hz) belonging to the A_2X spin system of alkyl CH protons, and the triplet of pyridine H-6 at 8.96 ppm. The major component – according to ^{1}H NMR, ^{13}C NMR, COSY, HMQC and HMBC spectra (Figs. S1–S4) – was the cyclic product 10-(1,3-dioxo-2,3-dihydro-1H-inden-2-yl)-2b-Hydroxy-11-oxo-4b,10,10a,11-tetrahydroindeno[2,1-b] indolizinium trifluoroacetate (**2H$^+$-cycle**, Scheme 1).

The characteristic signals that indicate the structure of **2H$^+$-cycle** are H^a (5.12 ppm, J = 3.1 Hz and 2.0 Hz), H^b (4.48 ppm, J = 3.1 Hz) and H^c (4.09 ppm, J = 2.0 Hz). Unlike similar protons of **2H$^+$**, these protons are non-equivalent and form the spin system AMX. Low-field doublet (δ = 9.10 ppm, J = 6.0 Hz) was assigned to the pyridine proton H-6, and its chemical shift indicates that the adjacent nitrogen atom is quaternized but not protonated (otherwise the spectrum would have shown a triplet splitting, similarly to **1H$^+$**). The one-bond spin–spin coupling value for this proton and its bearing carbon, $^1J(^{13}CH)$ = 190 Hz, also proved the presence of a positively charged nitrogen in proximity to the carbon atom [27].

The signal of the quaternary carbon at 106.4 ppm plays a key role in the **2H$^+$-cycle** structure assignment. Its chemical shift is characteristic of a carbon bearing two electronegative atoms or of a carbon at double bond. In the 2D HMBC spectrum (Fig. 3), this signal has six cross-peaks, indicating the existence of long-range spin–spin coupling ^{13}C–^1H over two, three and four bonds, with signals at 9.10d (pyridine H-6), 8.35d, 8.08t, 7.96d, 5.14t and 4.09d (see Scheme 2 for the assignment of the other signals). This finding unambiguously proves the structure of the major product as **2H$^+$-cycle**. The relatively small vicinal spin–spin coupling constant $^3J(H_a, H_c)$ = 2.0 Hz indicates *cis*-fusion of five-membered cycles and agrees well with calculated dihedral angle H_a–C–C–H_c value of 101.5°. The alternative diastereoisomer with trans-fusion is by 21.5 kcal/mol less stable.

The cyclization is reversible: upon neutralization of the acid with 1,8-diazabicyclo[5.4.0]-undec-7-ene, (DBU), starting compound **2** is recovered (Fig. S5). Thus, the keto-enol tautomerism observed for these adducts in neutral solutions [21] changes to ring-chain tautomerism in acid media. To the best of our knowledge, this type of tautomerism involving pyridine nitrogen is observed for the first time. The closest analog found in literature is the prototropic tautomerism in oxoalkyl-pyridone derivatives [28]: