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New Type of Prototropic Tautomerism Involving Carbon, Hydrogen, and Oxygen Atoms

**A. G. Filimoshkin[1], V. F. Kosolapova[2], T. V. Petrenko[2],
V. S. Aksenov[3], and O. Kh. Poleshchuk[4]**

[1] *Tomsk State University, pr. Lenina 36, Tomsk, 634050 Russia*
e-mail: poly@ipc.tsc.ru

[2] *Institute of Petroleum Chemistry, Siberian Division, Russian Academy of Sciences, Tomsk, Russia*

[3] *Kursk State Technical University, Kursk, Russia*

[4] *Tomsk Pedagogical University, Tomsk, Russia*

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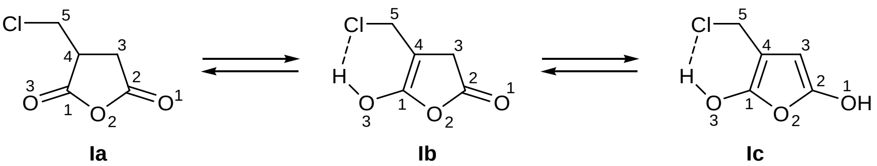
Abstract—A low-molecular weight analog of the vinyl chloride–maleic anhydride copolymer, chloromethylsuccinic anhydride gives rise to a new type of prototropic tautomerism, cyclic anhydride–enol, with formation of quasiaromatic enol and dienol derivatives. The ratio of the anhydride and enol tautomers in solution at room temperature is 7 : 1.

While studying the properties of vinyl chloride–maleic anhydride copolymer, we have revealed and described a new type of prototropic reactions, namely cyclic anhydride–enol tautomerism, which spontaneously occurs in the macromolecules in organic solvents [1]. By physical and chemical methods we have found that the copolymer molecules in the condensed state consist of 67 mol % of alternating monomer units and 33 mol % of the corresponding enol tautomers [2]. Just the presence of such tautomeric ensembles in the polymeric chains is responsible for the anomalous reactivity of the copolymer [3]. It was important to elucidate whether the observed pattern originates from conformation–configuration effects in the macromolecules or it is also intrinsic to the respective low-molecular analogs. Therefore, the goal of the present study was to synthesize chloromethylsuccinic anhydride (**I**) as a low-molecular model of the regular unit of the vinyl chloride–maleic anhydride copolymer and examine its ability to undergo prototropic tautomerism of the above type.

We presumed that, like vinyl chloride–maleic anhydride copolymer [4], compound **I** in solution gives rise to cyclic anhydride–enol tautomerism and that the tautomeric equilibrium involves anhydride form **Ia**, enol **Ib**, and dienol **Ic**, as shown in Scheme 1. Tautomers **Ib** and **Ic** are stabilized via intramolecular hydrogen bond O–H···Cl. The second O^1–H group in tautomers **Ic** is involved in intermolecular hydrogen bond with the solvent molecules.

In order to estimate the possibility for such tautomeric equilibrium, we performed quantum-chemical calculations of the geometric structure and energies of formation of tautomers **Ia**–**Ic** (see table). The results showed that the formation of tautomers **Ib** and **Ic** is accompanied by reduction of the electronic energy by 9 kJ/mol, which corresponds to the energy of stabilization due to intramolecular hydrogen bonding H···Cl. The H···Cl distances in **Ib** and **Ic** conform to the structural criterion for closure of such bonds [5]: these distances are shorter than the sum of the corresponding van der Waals radii (0.30 nm) [6].

Scheme 1.



It is known that H-chelate ring in enol forms of β-diketones is a quasiaromatic system [7]. We believe that tautomer **Ib** contains such six-membered quasi-aromatic chelate ring which involves two π-electrons of the $C^1=C^4$ bond, four *p*-electrons on the O^3 and Cl atoms, and two electron holes (O^3–H proton and C^5). For example, delocalization of electron density in tropone and tropolone involves the carbonyl group and is enhanced due to intramolecular hydrogen bonding, while in the tropylium cation electron hole participates in the delocalization [8]. The ten-electron system in tautomer **Ic** is delocalized over a combination of five- and six-membered rings.

The total energies E_{tot} of all tautomers are approximately similar. We cannot estimate the thermodynamic stability of anhydride **Ia** relative to tautomers **Ib** and **Ic** on the basis of their enthalpies of formation ΔH_f, for the corresponding entropies should differ considerably due to negative contribution of intramolecular hydrogen bonding. Moreover, the energy of stabilization via electron density delocalization over the six-membered H-chelate ring may be comparable with the energy of conjugation between *p*- and π-electrons in the O=C–O–C=O fragment in anhydride **Ia** (26 kcal/mol in acetic anhydride [9]). However, the heat of formation of tautomer **Ic** is lower by 52.8 kJ/mol than that of **Ib**; this difference is likely to reflect the energy gain due to conjugation in the ten-electron system.

Let us consider structural criteria of aromaticity. The contiguous five- and six-membered rings in tautomers **Ib** and **Ic** are coplanar, the angle C^4C^5Cl is equal to ~114°, and the C^5 atom has trigonal rather than tetragonal configuration ($sp^{2.15}$), ensuring coplanar arrangement of the rings. The furan ring is characterized by leveled bond lengths and bond angles. The $C^1=C^4$ bond in enol **Ib** is slightly longer, while the C^4–C^5 and C^1–C^3 bonds are slightly shorter than might be expected [6]. An analogous pattern is observed for dienol **Ic** where intramolecular hydrogen bond is somewhat weaker than in enol **Ib**, but the $C^1=C^4$ bond is even longer than in **Ib**, indicating a stronger conjugation.

Thus, the results of *ab initio* calculations performed for the isolated molecules support our assumption that enol (**Ib**) and dienol (**Ic**) tautomers can be formed from anhydride **Ia**. Obviously, in going to real systems interaction with the solvent should be taken into account, specifically formation of intermolecular hydrogen bonds. Therefore, solvated enol tautomers should be fairly stable. Below are given experimental proofs for the existence of anhydride–enol tautomerism for compound **I**.

Calculated energy parameters, bond lengths *d*, and bond angles ω of tautomers **Ia**–**Ic**

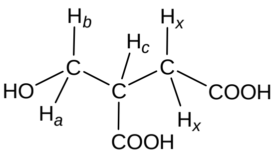
Parameter	**Ia**	**Ib**	**Ic**
$-E_{tot}$, kJ/mol	355.6333	354.2576	371.0927
ΔH_f, kJ/mol	912.7036	1644.7220	1591.9433
$-E_{El}$, kJ/mol	1327.1355	1336.2227	1335.3282
Bond	*d*, nm		
C^1–O^2	0.1394	0.1380	0.1369
O^2–C^2	0.1390	0.1389	0.1369
C^1–C^4	0.1531	0.1356	0.1362
C^4–C^3	0.1537	0.1509	0.1458
C^3–C^2	0.1520	0.1526	0.1352
C^1–O^3	0.1194	0.1332	0.1345
C^4–C^5	0.1529	0.1491	0.1494
C^5–Cl	0.1806	0.1832	0.1833
O^3–H^1	–	0.0976	0.0974
H^1–Cl	–	0.2318	0.2352
Angle	ω, deg		
$C^1O^2C^2$	111.4372	108.1631	106.5096
$O^2C^2C^3$	108.7871	107.9509	111.2770
$C^2C^3C^4$	104.0270	102.7158	105.7285
$C^3C^4C^1$	102.6853	106.7805	105.7292
$C^4C^1O^2$	108.7884	114.3896	110.7557
$C^4C^1O^3$	129.6182	134.6774	136.6700
$C^1C^4C^5$	114.1254	132.1701	131.3158
C^4C^5Cl	110.6927	114.2746	113.9925
C^5ClH^1	–	88.8462	89.8251
ClH^1O^3	–	141.9191	140.8491
$H^1O^3C^1$	–	108.1126	107.3475

Identification of particular tautomers by spectral methods is often difficult because of their low concentration. For example, acetylacetone (which is a classical compound capable of keto–enol tautomerism) exists as a 4 : 1 mixture of the ketone and enol forms [10]. As applied to compound **I**, IR and ^1H NMR spectra turned out to be informative. The IR spectrum of **I** (see Experimental) contains absorption bands due to stretching vibrations of three energetically non-equivalent C=O groups and also from O–H and C=C bonds, indicating the presence of enol tautomers.

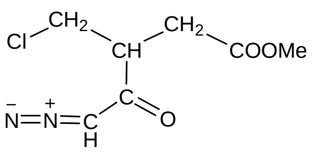
Apart from signals belonging to anhydride structure **Ia**, compound **I** shows in the ^1H NMR spectrum a narrow singlet whose position depends on the concentration. Obviously, this signal corresponds to an acidic proton. The spectral pattern is complex, and overlapped signals of tautomers **Ia** and **Ib** can be divided into three groups: (1) $ClCH_2$ in **Ia** and **Ib**, (2) CH in **Ia** and CH_2 in **Ib**, and (3) CH_2 in **Ia**. The intensity ratio of these signals is 2.28:1.28:2. No signals were present in the region typical of olefinic protons (δ 4.5–7.0 ppm), presumably due to low concentration of dienol **Ic**. Thus the ratio of anhydride tautomer **Ia** and enol form **Ib** is 7:1. It is interesting that signals from the $ClCH_2$ protons of tautomers **Ia** and **Ib** overlap each other, though the signal from enol **Ib** should appear in a weaker field due to effect of the double C=C bond in the α-position. Presumably, the $ClCH_2$ protons in enol **Ib** are arranged at angle of 120° with respect to the six-membered quasiaromatic ring, so that they suffer its shielding effect.

We also performed hydrolysis of anhydride **I** in aqueous solution at 40°C (reaction time 5 days). The hydrolysis product was hydroxymethylsuccinic acid (**II**), which showed the following signals in the ^1H NMR spectrum, δ, ppm: 4.36 q (H_a, $J_{ab} = 9$, $J_{ac} = 8.5$ Hz), 4.46 q (H_b, $J_{ab} = 9$, $J_{bc} = 5.5$ Hz), 2.7 d (H_x, $J_{xc} = 8$ Hz), 3.54 t (H_c, $J_{xc} = 8$, $J_{ac} = 8.5$, $J_{bc} = 5.5$ Hz), 9 s (OH). As in the spectrum of initial anhydride **I**, the $HOCH_2$ protons in acid **II** give rise to *AB* part of an *ABC* spin system, while the CH_2 protons (former H_x) become magnetically equivalent. The signal from the hydroxy protons is broader and more diffuse than the OH signal in the spectrum of **I**. This means that the OH groups in **I**, identified by the IR and ^1H NMR spectra, cannot be assigned to carboxy groups.

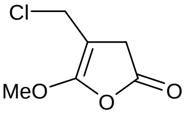
Treatment of compound **I** with diazomethane according to the procedure described in [11] at 0°C afforded a mixture of methyl ester **III** and methyl ether **IV**. The intensities of the methyl proton signals (δ 3.56 and 3.62 ppm for **III** and **IV**, respectively) indicate approximately equimolar amounts of the products. In the ^1H NMR spectrum of the product obtained at 40°C we also observed signals from dimethyl ether **V** whose fraction did not exceed 10%. Probably, the etherification is faster than esterification, and the tautomeric equilibrium is displaced to the right. This displacement is also favored by elevated temperature.



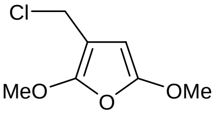
II



III



IV

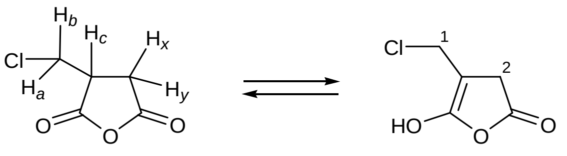


V

Compound **I** also undergoes other chemical transformations which are not typical of anhydride form **Ia**. Dissolution of compound **I** in water at room temperature is accompanied by evolution of HCl (4.4 mol % in 5 min and 21.6 mol % in 24 h after dissolution) as a result of S_N reaction at the CH_2Cl group. It is known that dissociation of the C–Cl bond in alkyl halides requires a lot of energy (400–600 kJ/mol). The ease of HCl evolution implies that the C–Cl bond is cleaved in the enol form **Ib** which gives rise to hydrogen bond H···Cl. Presumably, the reaction involves transition state with a low energy of activation, as in the dehydrochlorination of 2-chloroethanol where the chlorine atom is more labile than in common alkyl halides [12].

In addition, solutions of compound **I** in DMF and DMSO, as well as solutions of mixtures of equimolar amounts of compound **I** and NaN_3, $NaNO_2$, and KCNO, are red–brown. Their electron absorption spectra contain new overlapping bands belonging to molecular complexes between the enol (**Ib**) and dienol forms (**Ic**) and the above reagents, λ_{max} 376, 395, 415, and 467 nm. Analogous complexes with the same reagents are formed by the vinyl chloride–maleic anhydride copolymer [3]. After storage for more than 6 months, compound **I** no longer forms such complexes because of spontaneous dehydrochlorination. Finally, we failed to effect esterification of compound **I** with methanol under standard conditions for esterification of succinic anhydride and its derivatives [13].

Our results led us to conclude that chloromethylsuccinic anhydride is capable of prototropic tautomerism involving the C, H, and O atoms, which we called cyclic anhydride–enol tautomerism.



EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord M-80 instrument. The ^{1}H NMR spectra of solutions in acetone-d_6 were obtained on a Tesla BS-491 spectrometer (100 MHz, HMDS, 24°C). *Ab initio* quantum-chemical calculations were performed with the aid of GAUSSIAN 98W software [14]. The geometric parameters were optimized, and the electronic structure parameters were calculated, in terms of the density functional theory B3LYP/6-31G(*d*) with the Becke B3 exchange functional [15] and Lee–Yang–Parr correlation functional [16]. Carbon atom hybridizations were calculated in terms of the natural bond orbital approximation [17].

Chloromethylsuccinic anhydride (I) was synthesized by hydrochlorination of itaconic anhydride (contrary to the Markownikoff rule [18]). A solution of 30 g (0.23 mol) of itaconic acid in 45 ml (0.48 mol) of acetic anhydride containing 3 drops of concentrated hydrochloric acid was heated for 1 h at 40°C. The solvent was removed at room temperature, and the residue was washed with carbon tetrachloride, recrystallized from chloroform, and dried under reduced pressure over P_2O_5. Yield of itaconic anhydride 23.727 g (92%); colorless needles, mp 69–70°C [18]. IR spectrum, ν, cm^{-1}: 2935 (CH_2); 3120 (=C–H); 1780, 1850 (C=O); 1660 (C=C); 1240 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 3.66 d.d (2H, J = 2.5, 2.75 Hz), 5.88 t (1H, J = 2.5 Hz), 6.16 t (1H, J = 2.75 Hz).

A stream of thoroughly dried (concentrated sulfuric acid, anhydrone) hydrogen chloride [19] was passed over a period of 4 h through a solution of 13 g (0.117 mol) of itaconic anhydride in 100 ml of dry chloroform, maintained at –5 to –10°C, and the reaction flask was capped and left to stand for 12 h at room temperature. This procedure was repeated three times, and the mixture was kept for 24 h at –18°C until it divided into layers. The yellow oily liquid was separated and was kept under reduced pressure over P_2O_5. The colorless crystals were thoroughly washed with carbon tetrachloride, recrystallized from diethyl ether, and dried under reduced pressure over P_2O_5. Yield 8.247 g (48%), mp 126–130°C. IR spectrum, ν, cm^{-1}: 3220–2800 br (O–H); 1850 w, 1776 m, 1708 s (C=O); 1640 (C=C); 1240 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 3.89 q (H_b, $J_{ab} = -17$, $J_{bc} = 5.9$ Hz), 3.82 q (H_a, $J_{ab} = -17$, $J_{ac} = 7.1$ Hz), 2.79 q (H_y, $J_{xy} = -17$, $J_{bc} = 5.9$ Hz), 2.58 q (H_x, $J_{xy} = -17$, $J_{xc} = 7.1$ Hz), 3.19 m (H_c, $J_{ac} = 7.1$, $J_{bc} = 5.9$ Hz), 3.39 (C^2H_2), 3.87 (C^1H_2), 9.97 s (OH). Found, %: C 40.32; H 3.21. $C_5H_5ClO_3$. Calculated, %: C 40.40; H 3.37.

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