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Ring–Chain Tautomerism in 2-(2,2-Dicyano-1-methylethenyl)benzoic Acid and Related Compounds

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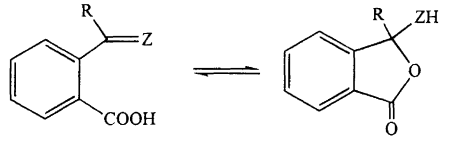
Ring–chain tautomerism with slow interconversion (compared with the NMR timescale) was observed in solutions of 2-(2,2-dicyano-1-methylethenyl)benzoic acid (**3e**), obtained by Knoevenagel condensation of 2-acetylbenzoic acid with malononitrile, forming the ring tautomer 3-dicyanomethyl-3-methylphthalide (**4e**) in admixture with **3e**. Similar condensations of 2-formylbenzoic acid with methyl cyanoacetate or malononitrile give 2-(2-cyano-2-methoxycarbonylethenyl)benzoic acid (**3b**) and 2-(2,2-dicyanoethenyl)benzoic acid (**3d**), respectively, which in solution also exhibit the same tautomerism to give the ring tautomers, 3-(cyanomethoxycarbonylmethyl)phthalide (**4b**) and 3-(dicyanomethyl)phthalide (**4d**), respectively. Condensation of 2-formylbenzoic acid with dimethyl malonate gave only the ring compound, 3-(dimethoxycarbonylmethyl)-phthalide (**4a**). Attempts to synthezise 2-(2-cyano-2-methoxycarbonyl-1-methylethenyl)benzoic acid (**3c**) by methylation of the trimethyl silylester of **3b** with diazomethane led to the ring form of **3c**, viz. 3-cyanomethoxycarbonylmethyl-3-methylphthalide (**4c**) as an equimolar mixture of two diastereomers. No tautomerism was observed when the benzene ring was replaced by a thiophene ring (**7a**, **7b** and **8**) or an aliphatic double bond (**9**). Solid state spectra (IR and NMR) indicated that all compounds carrying two cyano groups at the double bond, except the aliphatic compound **9**, were in the open-chain form, while all the others were in the ring form. Equilibrium studies for compound (**3e** ⇌ **4e**) indicated increased stability for the chain form **4e** with increasing solvent polarity. Determination of the free energy change, ΔG°, and of the free energy of activation, $\Delta G^\ddagger$, for the tautomerization in deuteriochloroform (using ^{1}H NMR spectroscopy) indicated that, in this solvent, a concerted process from the starting material **3e** to the anion of **4e** is taking place. It is also postulated that a similar reaction path is followed in the other solvents used in this investigation, all belonging to the solvent class 'protophobic dipolar aprotic solvents'.

Examples of ring–chain tautomerism in *ortho*-substituted benzoic acids are numerous when Z is oxygen (acyl) or NH (imines) and are extensively reviewed in a monograph (Scheme 1).[1] On the other hand, similar tautomerism involving olefinic systems ($Z=CR_2$) has been observed only in the product formed by condensation of 2-formylbenzoic acid with nitromethane (Scheme 2).[2,3]



Scheme 1. Ring–chain tautomerization in 2-substituted benzoic acid.

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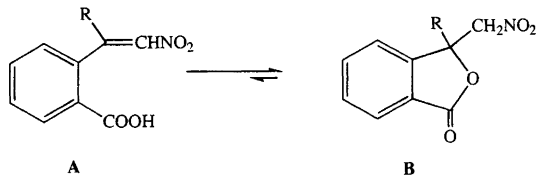
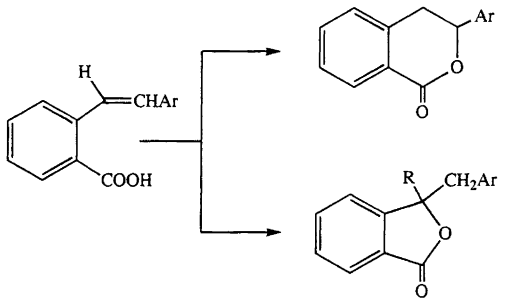


Scheme 2. Ring–chain tautomerization in 2-(2-nitroethenyl)-benzoic acid.

The equilibrium constant ($K_T=[B]/[A]$) at pH 6 was found to be about 10 using UV spectroscopy.[3] The forward reaction, i.e. chain–ring transformation, was observed as 2-(2-arylethenyl)benzoic acid lactonized to give the regioisomeric isocoumarins [Ar = phenyl, naphthyl (1- and 2-), 3-thienyl, 3-indolyl and 3-pyridyl] and phthalide (Ar = 4-pyridyl).[4] However, tautomerism has not been observed in this case (Scheme 3). We now



Scheme 3.

report the syntheses of a series of compounds where Z in Scheme 1 is CXY with X and Y having electron-withdrawing functions, especially cyano or ester groups. These compounds show all the characteristics of ring–chain tautomerism.

Syntheses

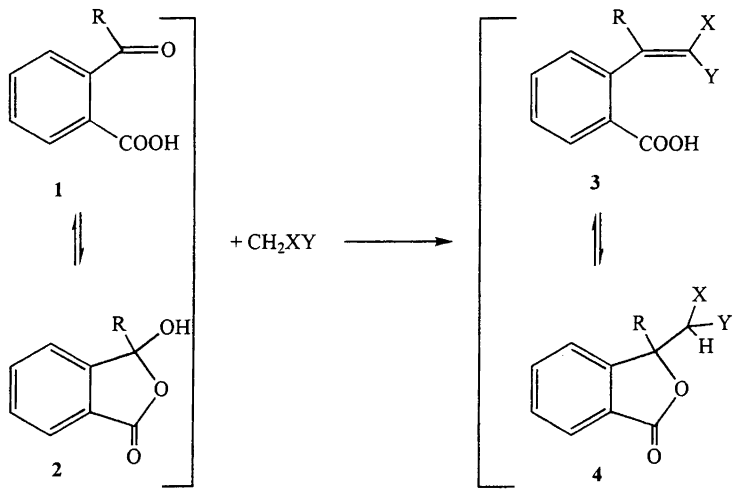
When 2-formylbenzoic acid [Scheme 4, R = H (**1** ⇌ **2**)] was subjected to Knoevenagel condensation with methyl cyanoacetate or malononitrile, products were formed clearly indicating the presence of ring–chain tautomerism with slow interconversion (compared with the NMR timescale) of the isomers [Scheme 4 (**3** ⇌ **4**)]. On the other hand, the condensation with dimethyl malonate gave only the ring product 3-(dimethoxycarbonylmethyl)phthalide (**4a**), as shown by ^{1}H NMR spectroscopy.

As described in Experimental, the condensation of 2-formylbenzoic acid with methyl cyanoacetate gave a mixture of small amounts of **3b** and a 1:1 mixture of the two diastereoisomers of **4b** as demonstrated by ^{1}H NMR spectroscopy. Upon slow evaporation of a chloroform solution one of the diastereoisomers crystallized out in very pure form and in nearly quantitative yield, shown by ^{1}H NMR to be diastereoisomer I (Tables 1 and 2). An X-ray crystal structure determination showed that this diastereomer had the (*RS,SR*)-configuration, both enantiomers being present in the centrosymmetric unit cell.[5]

Knoevenagel condensation of 2-acetylbenzoic acid was successful only with malononitrile and ring–chain tautomerism was also observed by ^{1}H NMR spectroscopy. The failure of 2-acetylbenzoic acid to react with methyl cyanoacetate was circumvented by the reaction sequence outlined in Scheme 5 using hexamethyldisilazane (HMDS) as silylating agent.* Both the silylation step and the methylation step[6] were essentially quantitative, but attempts to purify the silylated ester **5** by column chromatography (SiO_2) resulted in complete desilylation. The whole sequence in Scheme 5 gave an overall yield of close to 85%. However, after desilylation of **6** it was disclosed by NMR spectroscopy that the product obtained was the ring form, 3-cyanomethoxycarbonylmethyl-3-methylphthalide **4c**.

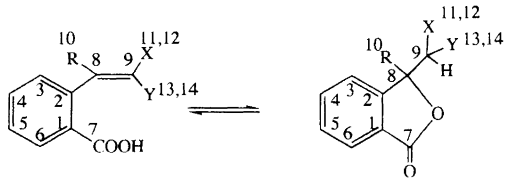
It is interesting to note that (see Experimental) that the ^{13}C NMR spectrum of **6** shows two sets of resonance signals which only can be interpreted as the result of atropisomerism where the torsion angles for the two isomers differ *both* in sign *and* in magnitude, i.e., the isomers are not enantiomers, but diastereoisomers. A similar observation was made in the crystal structure of **3e** (and its solid-state ^{13}C NMR spectrum), but this was interpreted as a result of the dimerization of the acid function, resulting in different rotational restriction around the pivotal bond for the two monomers.[7] The reason for such behavior in the present case is not quite clear. Since atropisomerism was not observed for compound **5**, introduction of the methyl group at the double bond is the prime reason for the atropisomerism, cf., discussion of the UV spectra in Ref. 7. A surprising

* Atom numbers in the NMR spectra discussed above and in the corresponding part of the Experimental section refer to the corresponding atoms in formulae **3** or **4** (Tables 1 or 2).



Scheme 4. Condensation products of 2-acylbenzoic acid with dimethyl malonate, methyl cyanoacetate or malononitrile: a, R = H, X = Y = CO_2Me; b, R = H, X = CO_2Me, Y = CN; c, R = Me, X = CO_2Me, Y = CN; d, R = H, X = Y = CN; e, R = Me, X = Y = CN.

Table 1. ^{1}H NMR parameters of chain (**3**) and ring (**4**) tautomers in $CDCl_3$.



3 4

	3				**4**						Remarks
	H6	H3–H5	H10	H12	H6	H3–H5	H9	H10	H12	H14	
a X=Y=CO_2Me R=H	Not observed				7.89 1 H, d J=8.1 Hz	7.7–7.5 3 H, m	3.83 1 H, d J=7.6 Hz	6.04 1 H, d J=7.4 Hz	3.78 3 H, s	3.72 3 H, s	
b X=CO_2Me Y=CN, R=H	8.22 1 H, dd	7.7–7.5 3 H, m	9.04 1 H, s	3.96 3 H, s	8.0 1 H, dd	7.9–7.5 3 H, m	4.20 1 H, d J=5.8 Hz	6.00 1 H, d J=5.8 Hz	3.96 3 H, s		Diastereomer I ≈50%
					8.0 1 H, dd	7.9–7.5 3 H, m	4.18 1 H, d J=3.4 Hz	6.04 1 H, d J=3.4 Hz	3.91 3 H, s		Diastereomer II ≈50%
c X=CO_2Me Y=CN, R=Me	Not observed				7.87 1 H, d J=7.4 Hz	7.8–7.5 3 H, m	4.15 1 H, s	1.88 3 H, s	3.63 3 H, s		Diastereomer I ≈50%
					7.87 1 H, d J=7.4 Hz	7.8–7.5 3 H, m	4.10 1 H, s	1.88 3 H, s	3.70 3 H, s		Diastereomer II ≈50%
d X=Y=CN R=H	8.28 1 H, dd	8.0–7.6 3 H, m	8.72 1 H, s		8.0 1 H, dd	7.9–7.6 3 H, m	4.42 1 H, d J=4.9 Hz	5.84 1 H, d J=4.8 Hz			
e X=Y=CN R=Me	8.22 1 H, dd	7.9–7.5 2 H, m H3: 7.19 (1 H,dd)	2.56 3 H, s		7.96 1 H, dd	7.9–7.5 3 H, m	4.18 1 H, s	1.96 3 H, s			

observation is that C8, lying in the pivotal bond (C2–C8), has a different chemical shift in the two isomers. A possible reason for this may be that the trimethyl silyl ester group also is forced out of the plane of the benzene ring by the introduction of the methyl group. Also, C7 has different resonance positions in the isomers, and coupled with the largest relative chemical shift difference observed for C14 (the methyl group introduced in **6**), one might conclude that both ring substituents are forced out of the plane, the two pivotal bonds being C2–C8 and C1–C7, and that the different resonance positions reflect complicated conformational behavior with two non-equivalent energy minima.

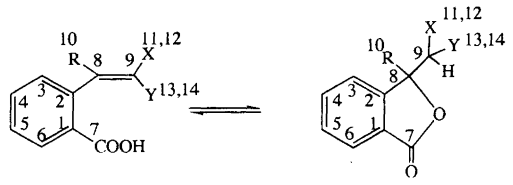
To explore the scope of this type of ring–chain tautomerism it was of some interest to replace the link between the two reacting groups, i.e., the benzene ring, by a heterocyclic aromatic ring and by an aliphatic double bond. Thus **7a**, **7b**, **8** and **9** were prepared by Knoevenagel condensation of the parent carbonyl compounds with malononitrile.

Ring–chain tautomerism

Solid-state spectra, both IR and ^{13}C NMR, show that when X and Y both are cyano groups, all compounds except **9**, exist in the open dimeric acid form, a situation which also was confirmed by crystal structure analysis for compounds **3e** and **7b**.[7] The solid state IR spectrum of **9** shows that only the ring form exists. On the other hand, when X and/or Y are ester groups, the compounds exist only in the ring form **4**. There seem to be no obvious reasons for these substituent effects; the stability enhancement caused by carboxylic acid dimerization (ca. 80–85 kJ mol^{-1}) should not be very much influenced by the change of substituents at the double bond; most likely what we are faced with here are crystal packing effects.

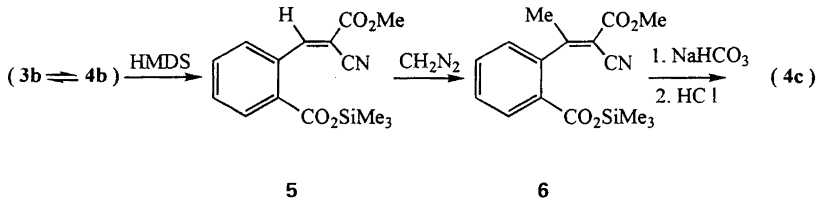
In solution, however, ring–chain tautomerism is observed (using ^{1}H and ^{13}C NMR spectroscopy) for some of the synthezised compounds and not for others, depending of the connecting link between the interacting groups and of the substituents on the double bond. For the aliphatic compound **9**, as in the solid state, only the ring form is observed and for the thiophene compounds **7a**, **7b** and **8** only the open chain form is observed in solution. The reason for the latter observation is most likely large ring strain in the lactone ring caused by the larger angles at C2 and C3 in the thiophene ring as compared with the corresponding benzene analogs discussed below.[7]

Table 2. ^{13}C NMR parameters of chain (**3**) and ring (**4**) tautomers in $CDCl_3$.



3 **4**

Compd.	C1	C2	C3–C6	C7	C8	C9	C10	C11–C13	C12–C14	Remarks
3a X=Y=CO_2Me R=H										Not observed
4a X=Y=CO_2Me R=H	146.4	126.1	134.2, 129.9 125.8, 123.0	165.9	112.2	55.7		165.9, 165.9	53.2, 53.0	
3b X=CO_2Me Y=CN, R=H	134.0	128.5	133.7, 131.9 131.4, 129.7	169.1	157.2	106.3		162.2, 114.6	53.4	
4b X=CO_2Me Y=CN, R=H	144.5	126.1	134.9, 130.8 126.4, 122.8	168.3	76.1	42.8		163.1, 112.2	54.3	Diastereomer I (≈50%)
	144.5	125.9	134.9, 130.8 126.3, 121.9	168.3	76.0	42.4		163.1, 111.9	54.3	Diastereomer II (≈50%)
3c X=CO_2Me Y=CN, R=Me										Not observed
4c X=CO_2Me Y=CN, R=Me	148.9	125.4	134.7, 130.4 125.9, 121.9	167.8	83.4	46.7	24.7	162.6, 113.4	53.8	Diastereomer I (≈50%)
	148.7	125.2	134.7, 130.4 125.8, 121.7	167.7	83.4	46.4	24.1	162.4, 113.2	53.7	Diastereomer II (≈50%)
3d X=Y=CN R=H	133.0	128.0	134.4, 132.7 129.6, 122.7	170.5	162.2	86.8		112.9, 111.6		
4d X=Y=CN R=H	142.7	125.7	135.6, 132.5 131.8, 126.9	167.4	28.8	74.9		109.1, 108.7		
3e X=Y=CN R=Me	139.3	125.7	134.4, 132.4 126.7, 121.6	169.4	180.5	86.4	25.7	111.9, 111.7		
4e X=Y=CN R=Me	146.8	125.1	135.7, 131.6 130.6, 127.2	166.7	34.3	82.6	23.3	109.7, 109.4		

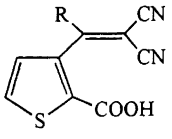


5 **6**

Scheme 5. Synthetic route from (**3b**⇌**4b**) to **4c**.

In the benzoic acids series (**3**⇌**4**) most of the compounds studied exhibit observable isomers, and NMR parameters are listed in Tables 1 and 2.

Before discussing the behavior of the individual compounds some introductory remarks must be made. Firstly, the rate of tautomerization is slow compared with the NMR timescale, so that spectra of each tautomer can easily be recorded. Secondly, the NMR method is



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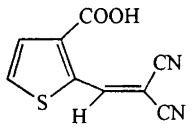
7a, R=H
7b, R=Me



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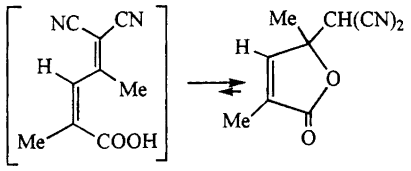


9

intrinsically insensitive so that the failure to observe any of the tautomers does not exclude the existence of ring–chain tautomerism in such cases; proof of such behavior will be demonstrated below.

If one estimates the limit of NMR observation to be $\approx 1\%$, then the numerical value of the free energy difference (ΔG°) must be smaller than 10–11 kJ mol^{-1} at room temperature in order to observe both tautomers.

As seen from Tables 1 and 2, and consistent with the solid state results, the presence of ester groups reduces the relative thermodynamic stability of the chain form. Also, the substituents on the other side of the double bond exert some influence on the tautomeric equilibrium, as compound **3b**, in contrast with **3c**, is stable enough to be observed by NMR spectroscopy, although with $K_e \approx 28$, corresponding to $\Delta G^\circ \approx -8.3$ kJ mol^{-1}.

An interesting demonstration of the point raised above regarding the intermediacy of a tautomer not observable by NMR is given below. A sample of **4c** containing more than 85% of diastereomer I (Table 1) was dissolved in $CDCl_3$ and the solution was monitored by ^{1}H NMR spectroscopy. The resonance signals due to diastereomer II increased with no concomitant signals from tautomer **3c** appearing at all. The solution was left overnight after which it contained approximately equal amounts of both diastereomers. Diastereomer I of **4c** was shown to have the (*RS*,*SR*) configuration using X-ray crystallography.[5]

4c (*RS*, *SR*) $\rightleftharpoons$ [**3c**] $\rightleftharpoons$ **4c** [(*RR*, *SS*) + (*RS*, *SR*)]

Isomerization of diastereoisomers **4c**. ^{1}H NMR spectroscopy was then applied to study the equilibrium (**3e** $\rightleftharpoons$ **4e**) as function of temperature in different solvents. This compound was chosen because the chemical shifts for the methyl groups of the two tautomers were well separated ($\Delta\delta \approx 0.6$ ppm), and also for the absence of diastereoisomerism in the ring tautomer.

It was soon discovered that the purity of the solvents used was very important, especially the presence of acidic impurities, a common problem when applying chlorinated solvents. Therefore special care was taken to avoid such impurities. All solvents were also carefully dried.[8]

To ensure that equilibrium was reached, the solutions were left at ambient temperature for 24 h before measurements of K_e were made. As discussed below, the relaxation time (the time to reach equilibrium from either starting point of a reaction A $\rightleftharpoons$ B) never exceeded 2–4 h. From the Van't Hoff plots the thermodynamic parameters were obtained (Table 3).

Ring–chain tautomerism involving acids (AH $\rightleftharpoons$ BH) is thought to involve several equilibria [eqn. (1)],[1] where three individual equilibrium constants (K_{e_1}, K_{e_2}, K_{e_3}) may be involved in solvents with sufficient ionizing power. Qualitatively, it appears from Table 3 that increasing solvent polarity seems to stabilize the chain form; a similar trend is found for the system 2-formylbenzoic acid $\rightleftharpoons$ 3-hydroxyphthalide.[9] A possible reason may be that increased polarity may stabilize the more polar carboxylate ion A^- compared with B^-, thereby reducing K_{e_2} in eqn. (1). Attempts to find a linear free energy correlation with any of the solvent parameters suggested[8] were in vain.

$$AH \rightleftharpoons A^- + H^+ \rightleftharpoons B^- + H^+ \rightleftharpoons BH \qquad (1)$$

In this investigation only solvents with low ionizing power were used, thus the question may be raised: Do these solvents have the ability effectively to solvate the ions A^- and/or B^-? In other words, are these ions real intermediates in the tautomerization process in such solvents, or are the conversions from AH into BH and backwards concerted processes?

Rate studies as function of reaction temperature might give some answers to such questions. In the 2-acylbenzoic series (Scheme 1) a general decrease in K_e with increasing temperature is observed, i.e., increased relative stability of the chain form.[10] This trend is also observed for all solvents in this work, with one exception, viz. in deuteriochloroform.

The rate of tautomerization for (**3e** $\rightleftharpoons$ **4e**) was then studied as function of temperature in deuteriochloroform solution. The kinetic expression used for a reaction A $\rightleftharpoons$ B is given in eqn. (2), where $[B]_e$ is the equilibrium concentration, [B] the concentration at time t, and k_f and k_r the rate of the forward and the reverse reaction, respectively. The activation parameters, using the Eyring equation,[12] are listed in Table 4.

$$\ln[([B]_e - [B])/[B]_e] = -(k_f + k_r)t \qquad (2)$$

The relaxation time (defined as the reciprocal of the sum of the forward and reverse rate constant)[13] calculated for the reaction in chloroform (≈ 1500 s at 300 K), justifies the selected time (>24 h) used to obtain equilibrium in the equilibration studies above (Table 3).

A possible reaction scheme for the ring–chain tautomerism for (**3e** $\rightleftharpoons$ **4e**, R = Me) in chloroform is outlined in Scheme 6. In principle two extremes exist: (1) a concerted transformation (**3** $\rightleftharpoons$ **4**) or (2) all species (**3** $\rightleftharpoons$ 3^- + H^+ $\rightleftharpoons$ 4^- + H^+ $\rightleftharpoons$ **4**) are involved in the tauto-

Table 3. Thermodynamic parameters for the tautomeric equilibrium (**3e**⇌**4e**) in different solvents extrapolated to 300 K.

Solvent	K_e	$\Delta G°$ [a]	$\Delta H°$ [a]	$\Delta S°$ [a]	$-T\Delta S°$ [a]	r [b]	Temp. range (T/°C) [c]
C_6D_6	5.0	−4.0	−8.4	−14.7	+4.4	0.988	5.0–53.5
$(CDCl_2)_2$	2.3	−2.1	−8.6	−21.8	+6.5	0.990	80.5–125.0
CD_2Cl_2	2.9	−2.7	−0.4	+7.5	−2.3	0.991	−21.5–28.0
$CDCl_3$	1.5	−0.9	+2.7	+12.1	−3.6	0.993	−44.0–44.0
CD_3CN	1.45	−0.9	−3.4	−8.4	+2.4	0.995	−35.0–70.0
$(CD_3)_2CO$	0.35	+2.6	−1.6	−14.2	+4.3	0.951	−76.5–−44.0

[a] Units: kJ mol^{-1} for $\Delta G°$, $\Delta H°$ and $T\Delta S°$; J mol^{-1} K^{-1} for $\Delta S°$. [b] Correlation coefficient from least squares calculation (Van't Hoff plot). [c] Accuracy ±0.5 °C.

Table 4. Activation parameters for the reaction (**3e**⇌**4e**) in $CDCl_3$ at 300 K.[a]

K_e [b]	10^4k_f	10^4k_r	$\Delta G_f^‡$	$\Delta G_r^‡$	$\Delta H_f^‡$	$\Delta H_r^‡$	$\Delta S_f^‡$	$\Delta S_r^‡$
1.5	2.7	3.9	94.0	93.1	56.5	60.0	−124	−110

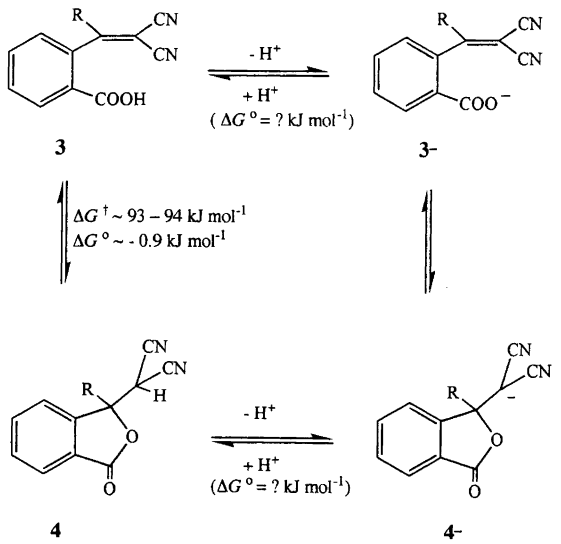
[a] Extrapolated to 300 K from kinetic measurements at temperatures in the range 9.8–43.0 °C (±0.5). Units: kJ mol^{-1} for $\Delta G^‡$, $\Delta H^‡$; J mol^{-1} for $\Delta S^‡$ and s^{-1} for k. [b] From Table 3.

merization process. The answer will depend upon the free energy differences in the two dissociation steps. If any of these is larger than the observed barrier, 93–94 kJ mol^{-1}, then that step should be ruled out. This energy difference corresponds to a pK_a value of 16.4, which is well above the values for both model compounds, benzoic acid and malononitrile, based on the quoted pK_a values in water. From the tabulated values of pK_a of malononitrile in two organic solvents (DMSO and *N*-methylpyrrolidinone; both protophilic dipolar aprotic solvents[14]),[15] there seem to be small differences from those observed in water (11–12), probably due to the intrinsic stabilization of the negative charge by the cyano groups; thus $\Delta G°$ for this dissociation step is about 70 kJ mol^{-1} in these solvents. Unfortunately, no pK_a values are recorded for chloroform or other protophobic[14] dipolar aprotic solvents.

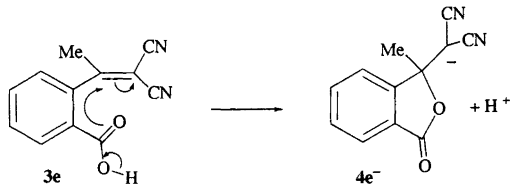
However, for benzoic acid large changes in the dissociation constant are observed in solvents with weak proton acceptor capacities (protophobic dipolar aprotic solvents).[15] Unfortunately, we have not succeeded in finding a recorded dissociation constant for benzoic acid in chloroform. The following pK_a values for benzoic acid have, however, been observed for other protophobic dipolar aprotic solvents: acetone 18.2, acetonitrile 20.7, isobutyl methyl ketone 22.4, propylene carbonate 19.7 and sulfolane 26.3.[15] This indicates that in chloroform $\Delta G°$ for benzoic acid may also be substantially higher than 90 kJ mol^{-1}. Provided that benzoic acid is a reasonably good model compound, **3**$^-$ has too high an energy to be involved in the tautomerization process in this particular solvent.

A very short intramolecular distance in **3e** is observed between the carbonyl oxygen and the alkene carbon atom next to the phenyl ring [(2.685(3) and 2.733(3) Å, respectively, in the two monomers of the dimer],[7] well within the van der Waals distance and most likely caused by an electrostatic attraction between the electronegative oxygen and the rather electron-deficient alkene carbon atom. This observation, coupled with the assumed high pK_a value of benzoic acid in chloroform, might indicate a more concerted tautomerisation process than that shown in Scheme 6 (Scheme 7).

Since pK_a values for malononitrile are not available for protophobic dipolar solvents, and especially for chloroform, one cannot exclude the possibility that the tautomerization process is even more concerted, going



Scheme 6. Route of tautomerization.



Scheme 7. Ionization of **3e** to form **4e**$^-$.

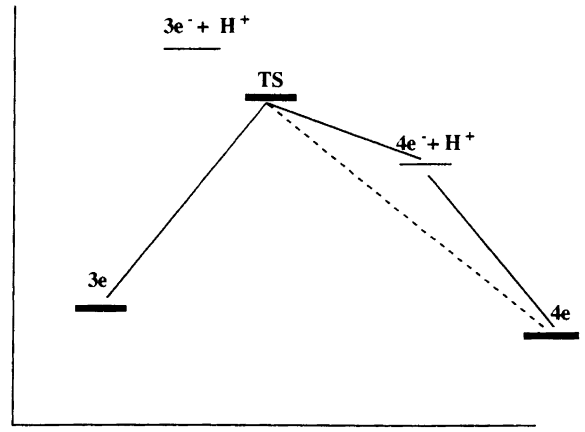


Fig. 1. Proposed route of tautomerization in chloroform.

directly from **3e** to **4e**. Both possibilities are included in the reaction diagram sketched out in Fig. 1.

Since all solvents used in this investigation could be classified as protophobic dipolar aprotic, it may very well be that the tautomerization process in these solvents may follow the same reaction pattern as in chloroform.

In protophilic dipolar aprotic solvents, however, the recorded pK_a values for benzoic acid are well below 16.4,[15] thus one would assume that in these solvents $\mathbf{3}^-$ could be an intermediate in the tautomerization process.

Experimental

General. Melting points are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer using an attenuated total reflectance (ATR) ZnSe-plate for solid samples (unless otherwise noted), high-resolution NMR spectra (^1H and ^{13}C) on Varian Gemini 200 and Bruker Spectrospin Avanche DMX 300 and DRX 500 spectrometers using $SiMe_4$ as an internal standard, solid state ^{13}C NMR spectra on a Bruker Spectrospin Avance DMX 200 spectrometer, ultraviolet spectra on a Shimadzu UV-260 spectrophotometer, and mass spectra on a Fison Instrument VG ProSpec Q. NMR peak assignments were made using 2D spectroscopy or other suitable pulse programs.

All solvents used were purified according to literature recommendations.[8]

3-(Dimethoxycarbonylmethyl)phthalide (**4a**). Amberlite IRA 93 (Fluka,[16] (15 g) was dried azeotropically using benzene (150 ml). After cooling, 2-formylbenzoic acid (30 g, 0.2 mol, Fluka) and dimethyl malonate (39.6 g, 0.3 mol) were added. During reflux for 48 h, water (3.5 ml, ≈0.2 mol) was collected (Dean–Stark separator). The mixture was filtered, after which the filtrate was evaporated, and the residue crystallized from 2-propanol (150 ml) to give 37 g (70%) **4a**, m.p. 73–75 °C. Anal. Found: C 59.63; H 4.75. Calc. for $C_{13}H_{12}O_6$: C 59.09; H 4.57. IR (KBr): ν_{max} 1761 [s, C=O (lactone)], 1747 [s, C=O (unconj. ester)] cm^{-1}. UV [$CHCl_3$ (log ε)]: λ 240 (3.44), 274 (3.20), 281 (3.20) nm. NMR data, see Tables 1 and 2.

2-(2-Cyano-2-methoxycarbonylethenyl)benzoic acid (**3b⇌4b**). 2-Formylbenzoic acid (15.0 g, 0.1 mol) and methyl cyanoacetate (9.9 g, 0.1 mol) were dissolved in methanol (20 ml) and cooled to 0 °C. Sodium hydroxide (4.0 g, 0.1 mol) in methanol (50 ml) was added and after a few minutes the precipitated sodium salt was filtered off and washed with diethyl ether, 90% yield. After acidification of an aqueous solution of this salt, (**3b⇌4b**) was obtained in 85% yield, shown by solution ^1H NMR to consist of small amounts of **3b** and the two diastereomeric forms of **4b** (the latter in approx. 50:50 ratio). When a chloroform solution of this mixture was slowly evaporated, a pure white compound was obtained, m.p. 142–143 °C ($CHCl_3$). Crystal structure determination showed that only one of the diastereoisomers (*RS,SR*) was present, with both enantiomers present in the centrosymmetric unit cell.[5] Anal. $C_{12}H_9NO_4$: C, H, N. IR [KBr (**4b**)]: ν_{max} 2240 (w, CN), 1750 [s, CO (γ-lactone)] cm^{-1}. UV [MeOH (log ε)]: λ 228 (4.21), 282sh, (3.70) nm. NMR, see Tables 1 and 2.

2-(2,2-Dicyanoethenyl)benzoic acid (**3d⇌4d**). 2-Formylbenzoic acid (30 g, 0.2 mol) and malononitrile (19.8 g, 0.3 mol) were dissolved in 2-butanol (200 ml). A solution of 0.6 M sodium 2-butoxide in 2-butanol (400 ml) was added with almost immediate precipitation, and after being stirred for 3 h the solution was filtered, and the precipitate dried and carefully washed with diethyl ether. Upon acidification of a concentrated aqueous solution of this salt, 29 g (73%) of (**3d⇌4d**) were obtained. M.p. 128–130 °C ($CHCl_3$). Anal. $C_{11}H_6N_2O_2$: C, H, N. IR [KBr (**3d**)]: ν_{max} 3500–2500 (OH), 2240 and 2235 (m, CN), 1711 (s, C=O), 1589 (m, C=C) cm^{-1}; [$CHCl_3$ (**3d⇌4d**)]: ν_{max} 3500–2500 (OH), 2421 (m, CN), 1796 [s, C=O (γ-lactone)], 1701 [s, C=O (carboxylic acid)], 1590 (m, C=C) cm^{-1}. UV [EtOH (log ε)]: λ_{max} 291 (4.08) nm. NMR data, Tables 1 and 2.

2-(2,2-Dicyano-1-methylethenyl)benzoic acid (**3e⇌4e**) was prepared from 2-acetylbenzoic acid (Fluka) and malononitrile [analogously to (**3d⇌4d**)] in 89% yield. M.p. 155–156 °C ($CHCl_3$). Crystal structure determined.[7] Anal. $C_{12}H_8N_2O_2$: C, H, N. IR [KBr (**3e**)]: ν_{max} 3500–2500 (OH), 2236 (m, CN), 1692 [s, C=O (carboxylic acid)], 1600 (m, C=C) cm^{-1}. UV [MeOH, (log ε)]: λ 225 (4.17), 283sh (3.74) nm. NMR data, Tables 1 and 2.

3-[(Cyanomethoxycarbonyl)methyl]-3-methylphthalide (**4c**).* To (**3b⇌4b**) (2.0 g, 8.7 mmol) was added hexamethyldisilazane (HMDS, Fluka, 15 ml). When NH_3 evolution had finished (≈5 h) the reaction mixture was evaporated (at 0.4 mmHg) to give 2.6 g (≈8.7 mmol) of

* See footnote on p. 491.

crude product which desilylated on attempted purification by chromatography on a silica column. NMR spectroscopy, however, showed that the product [*trimethylsilyl 2-(2-cyano-2-methoxycarbonylethenyl)-benzoate* (**5**)] was very pure: ^{1}H NMR ($CDCl_3$): δ 8.98 (1 H, s), 8.10 (1 H, dd), 7.76 (1 H, dd), 7.7–7.5 (2 H, m), 3.89 (3 H, s), 0.36 (9 H, s). ^{13}C NMR ($CDCl_3$): δ 164.4 (CO_2Me), 161.1 (CO_2SiMe_3), 156.9 (C8), 133.1 (C1 or C2), 130.5 (C2 or C1), 132.2–131.2–130.5–128.7 (C3–C6), 114.0 (CN), 105.3 (C9), 53.4 (OCH_3). The crude product (2.4 g, 8.0 mmol) was dissolved in diethyl ether and the calculated amounts of ethereal diazomethane added at 5 °C; after being stirred for 15 min the reaction solution was allowed to warm to room temperature. Slow evolution of gas indicated a decomposition of the initially formed Δ^1-pyrazoline.[6] When the gas evolution had finished, the diethyl ether was evaporated to give 2.5 g (≈8.0 mmol) product which was shown by NMR spectroscopy to be a clean mixture of two isomers in almost equal proportions; most likely the two atropisomers of *trimethylsilyl 2-(2-cyano-2-methoxycarbonyl-1-methylethenyl) benzoate* (**6**). ^{1}H NMR ($CDCl_3$): δ 8.1–8.0 (1 H, m), 7.7–7.3 (2 H, m), 7.2–6.9 (1 H, m), 3.79 (3 H, s), 3.54 (3 H, s), 2.58 (3 H, s), 2.48 (3 H, s), 0.30 (9 H, s). ^{13}C NMR ($CDCl_3$): δ 175.5–173.4 (C8), 164.5–164.3 (CO_2Me), 161.3–160.2 (CO_2SiMe_3), 142.2–140.8 (C1 or C2), 128.5–128.4 (C2 or C1), 132.4–131.9–131.4–130.7–28.6–127.8–126.5–125.1 (C3–C6, both isomers), 114.91–114.85 (CN), 104.11–104.06 (C9), 52.7–52.5 (OCH_3), 27.9–24.5 (C14). The isomeric mixture (2.5 g) was dissolved in diethyl ether (30 ml) and stirred overnight with saturated sodium bicarbonate solution (50 ml). The aqueous phase was washed with additional diethyl ether (2 × 50 ml), acidified and extracted with diethyl ether (3 × 50 ml). After drying ($MgSO_4$), evaporation gave 1.8 g (**4c**) [7.3 mmol, 84% total yield from (**3b**⇌**4b**)]. ^{1}H NMR (see Table 1) indicates a mixture of two diastereomers (≈50:50%). M.p. 109–111 °C (MeOH). IR [KBr (**4c**)]: ν_{max} 2255 (w, CN), 1772 [s, C=O (γ-lactone)], 1745 [s, C=O (unconj. ester)] cm^{-1}. UV [MeOH (log ε)]: λ 228 (4.29), 280 (shoulder, 3.59) nm. NMR, Tables 1 and 2.

3-(2,2-Dicyanoethenyl) thiophene-2-carboxylic acid (**7a**). 3-Formyl-2-thiophenecarboxylic acid[17] (4.0 g, 26 mmol) and malononitrile (2.0 g, 31 mmol) were dissolved in diethyl ether (20 ml). 0.5 M sodium ethoxide solution (60 ml) was added and the solution was left overnight with stirring at room temperature. After evaporation of the reaction solution, dilute sodium hydroxide solution was added and after extraction with diethyl ether, the solution was acidified and extraction with diethyl ether gave the crude product in 90% yield. Yellow needles, m.p. 171–172 °C (20% MeOH). Anal. $C_9H_4N_2O_2S$: C, H, N, S. IR: ν_{max} 3400–2700 (m, br), 2235 (w), 2205 (w), 1686 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.86 (1 H, s), 8.13 (1 H, d, J=5.4 Hz), 7.78 (1 H, d, J=5.2 Hz); (acetone-d_6): δ 8.94 (1 H, s), 8.03 (2 H, s). ^{13}C NMR (acetone-d_6): δ 160.7 (COOH), 151.2 (C_t=), 137.5, 136.2 (thiophene C2, C3), 132.3 (thiophene C5), 126.8 (thiophene C4), 113.6, 112.6 (2 × CN), 84.3 (C_q=). MS [EI, 70 eV, *m/z* (% rel. int)]: 204 (61, M^+), 187 (19, $M-OH$), 177 (49, $M-HCN$), 160 (100, $M-CO_2$). UV [MeOH (log ε)]: λ 238 (3.94), 322 (4.30) nm.

3-(2,2-Dicyano-1-methylethenyl) thiophene-2-carboxylic acid (**7b**). 3-Acetyl-2-thiophenecarboxylic acid[18] (2.0 g, 12 mmol), malononitrile (0.76 g, 12 mmol) and β-alanine (2.0 g)[19] were suspended in benzene (50 ml). Propanol (10 ml) and acetic acid (5 ml) were added and the suspension was refluxed until no further water was collected in a Dean–Stark collector (≈4 h). Diethyl ether (150 ml) was added and the suspension filtered. After evaporation, the remaining acetic acid was removed azeotropically with toluene. Crude yields: 92%. A diethyl ether solution was filtered through a short column (SiO_2). M.p. 140–142 °C (benzene). Crystal structure determined.[7] IR: ν_{max} 3400–2800 (m), 2236 (m), 1688 (s) cm^{-1}. ^{1}H NMR (acetone-d_6): δ 7.99 (1 H, d, J=5.1 Hz), 7.30 (1 H, d, J=5.1 Hz), 2.62 (3 H, s). ^{13}C NMR (acetone-d_6): δ 175.3 (COOH), 162.1 (C_t=), 143.0 (thiophene C2), 133.9 (thiophene C3), 131.6 (thiophene C5), 129.0 (thiophene C4), 112.72, 112.70 (2 × CN), 88.2 (C_q=), 24.9 (CH_3). MS [EI, 70 eV: *m/z* (% rel. int.)]: 218 (8, $[M]^{+\cdot}$), 200 (100, $[M-H_2O]^+$), 174 (22, $[M-CO_2]^+$). UV [MeOH (log ε)]: λ 237 (4.23), 277 (4.00) nm.

2-(2,2-Dicyanoethenyl) thiophene-3-carboxylic acid (**8**) was synthezised from 2-formyl-3-thiophenecarboxylic acid[20] and malononitrile (analogously to **7b**) in almost quantitative yield. Yellow crystals, m.p. 200–202 °C (50% MeOH). Anal. $C_9H_4N_2O_2S$: C, H, N, S. IR: ν_{max} 3400–2600 (br), 2231 (m), 1708 (s) cm^{-1}. ^{1}H NMR (acetone-d_6): δ 9.18 (1 H, d, ^5J=0.8 Hz), 8.18 (1 H, H5, dd, ^5J=0.8 and ^3J=5.1 Hz), 7.73 (1 H, H4), d, ^3J=5.1 Hz). ^{13}C NMR (acetone-d_6): δ 162.8 (COOH), 150.5 (C_t=), 138.8, 138.4 (thiophene C2–C3), 134.9 (thiophene C5), 131.5 (thiophene C4), 114.3, 113.4 (2 × CN), 81.4 (C_q=). MS [EI, 70 eV: *m/z* (rel. int.)]: 204 (100, $[M]^{+\cdot}$), 187 (27, $[M-OH]^+$), 177 (80, $[M-HCN]^{+\cdot}$), 160 (21, $[M-CO_2]^+$). UV [MeOH (log ε)]: λ 205 (4.27), 357 (4.53) nm.

3,5-Dimethyl-5-dicyanomethyl-2-(5 H)-furanone (**9**) was prepared from (*Z*)-2-methyl-4-oxo-2-pentenoic acid[21] and malononitrile [analogously to (**3d**⇌**4d**)] in 73% yield. White crystals, m.p. 94–95 °C ($CHCl_3$). Anal. $C_9H_8N_2O_2$: C, H, N. IR: ν_{max} 2274 (w), 2260 (m), [1774 (s), and 1765 (s) cm^{-1} (γ-lactone)]. ^{1}H NMR (acetone-d_6): δ 7.4–7.3 (1 H, q, J=1.5 Hz), 5.12 (1 H, s), 1.94 (3 H, d, J=1.6 Hz), 1.75 (3 H, s). ^{13}C NMR (acetone-d_6): δ 169.9 [C=O (lactone)], 146.9 (C_t=), 132.2 (C_q=), 110.7, 110.5 (2 CN), 33.3 [$C(CN)_2$], 21.9, 10.7 (2 CH_3). MS [EI, 70 eV: *m/z* (rel. int.)]: 176 (1.5, $[M]^{+\cdot}$), 111

(100, $[M-C_3HN_2]^+$ 43 (80, $[C_3H_7]^+$) UV [MeOH (log ε)]: λ 205.1 (4.00), 308.1 (4.03) nm.

References

1. Valters, R. E. and Flitsch, W. *Ring-Chain Tautomerism*, Plenum Press, New York 1985.
2. Whelton, B. D. and Huitric, A. C. *J. Org. Chem. 35* (1970) 3143.
3. Baer, H. H. and Urbas, L. In: Feuer, H. Ed., *The Chemistry of the Nitro and Nitroso Groups*, Interscience, New York 1970, Vol. 2, Chapter 3, p. 175; cf. Baer, H. H. and Kienzle, F. *Can. J. Chem. 43* (1965) 190.
4. Teitei, T. *Agric. Biol. Chem. 45* (1981) 1669; *Aust. J. Chem. 35* (1982) 1231.
5. Rømming, C. *Personal communication.*
6. Kolsaker, P., Ellingsen, P. O. and Wøien, G. *Acta Chem. Scand., Ser. B 32* (1978) 683; cf. Popp. F. D. and Catala, A. *J. Org. Chem. 26* (1961) 2738.
7. Rømming, C., Kolsaker, P., Wiberg, A. and Skjetne, T. *Acta Chem. Scand. 50* (1996) 40.
8. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd edn., VCH, Weinheim 1988, pp. 414–416 and refs. therein.
9. Sterk, H. *Monatsh. Chem. 99* (1968) 1764.
10. Bowden, K. and Taylor, G. R. *J. Chem. Soc. B* (1971), 1390 and refs. cited therein.
11. Wilkinson, F. *Chemical Kinetics and Reaction Mechanisms*, Van Nostrand Reinhold, New York 1980, p. 50.
12. Wynne-Jones, W. F. K. and Eyring, H. *J. Chem. Phys. 3* (1935) 492.
13. Ref. 11, p. 52.
14. Ref. 8, p. 63.
15. Izutsu, K. *Acid–Base Dissociation Constants in Dipolar Aprotic Solvents*, IUPAC Chemical Data Series No. 35, Blackwell, Oxford, UK 1990.
16. Astle, M. J. and Zaslowsky, J. A. *Ind. Eng. Chem. 44* (1952) 2867.
17. Gronowitz, S., Gestblom, B. and Mathiasson, B. *Ark. Kemi 20* (1963) 407.
18. Robba, M., Roques, B. and Bonhomme, M. *Bull. Soc. Chim. Fr.* (1967) 2495.
19. El-Maghraby, M. A., Sadek, K. U., Selim, M. A. and Elnaghi, M. H. *Bull. Chem. Soc. Jpn. 61* (1988) 1375.
20. Gronowitz, S., Biezais, A. and Mathiasson, B. *Ark. Kemi 21* (1965) 265.
21. Scheffold, R. and Dubs, P. *Helv. Chim. Acta 50* (1967) 798.

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