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ANION FORMATION VERSUS NITRILE ⇆ KETENIMINE TAUTOMERISM IN ALKYLIDENE MALONONITRILES AND CYANOACETATES

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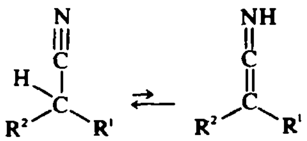
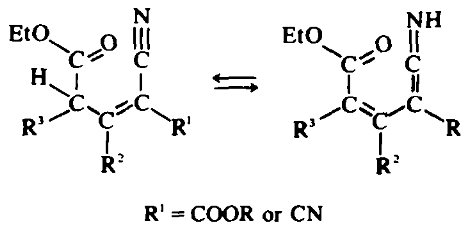
Abstract—The long wavelength UV absorption band present in the spectra of some alkylidene malononitriles and cyanoacetates is shown to be a consequence of anion formation and not of nitrile ⇆ ketenimine tautomerism as was claimed recently.

Cyano compounds which contain one or more H atoms on the α-C atom are in principle capable of tautomeric equilibrium between the nitrile form and the prototropic ketenimine form. However, the majority of nitriles appear to favour the cyano form strongly in this equilibrium.[1]



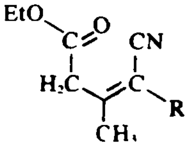
Consequently, only a very small number of cyano compounds with special structural features has been reported to contain the ketenimine tautomer in detectable amounts, e.g. tricyanomethane.[2]

In a recent publication[3]† Kasturi *et al.* conclude from UV spectroscopic data that the condensation products of β-keto-esters with malononitrile or ethyl cyanoacetate under certain circumstances also contain the ketenimine species. According to the authors, the presence of such a tautomeric form in these alkylidene malononitriles and cyanoacetates (which normally should show UV absorption only at *ca.* 240 nm) could be inferred from the existence of a long wavelength UV absorption band around 350 nm, indicative of extended conjugation. Noteworthy, this absorption band was only observed in polar, protic media such as ethanol and not in hexane or even acetonitrile. Furthermore, λ_{max} was unaffected by the addition of alkali, but ε was tremendously increased. This intensity of absorption in alkaline solution was ascribed by the authors to the increased concentration of the ketenimine tautomer.[4] Finally, it was stated that the chemical transformations of the alkylidene malononitriles in the presence of alcohol or water, e.g. the formation of pyridine derivatives, support the idea of nitrile ⇆ ketenimine tautomerism; therefore the authors assigned to the ketenimine tautomer an essential role in the mechanism postulated for the formation of heterocyclic compounds and their precursors.

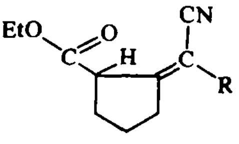


R^1 = COOR or CN
R^2 = alkyl
R^3 = alkyl

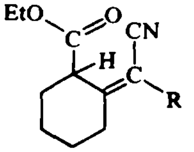
In the course of our own work on the Knoevenagel condensation of β-keto-esters with malonic acid derivatives[5] we have observed similar phenomena in the UV spectra of the reaction products, including **1**, **2**, **3**, **4**, **5** and **6**.



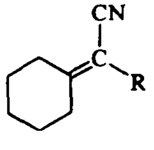
1: R = CN
2: R = COOEt



3: R = CN
4: R = COOEt



5: R = CN
6: R = COOEt



7: R = CN
8: R = COOEt

However, we have ascribed the presence of a long wavelength UV absorption band in the spectra of these products to partial dissociation to the corresponding *anions*. In our view, this assignment is supported convincingly by the following observations:

(1) The pH at half neutrality of **1** to **6** (which is roughly a measure for the pK_a of these compounds) was determined in 80% aqueous ethanol by potentiometric titration with 0·1 N aq. NaOH (Table 1).

From these data it followed that **1** and **3** must be ionized appreciably in neutral solution, but similar solutions of **4**, **5** and especially **6** contain the respective anions in hardly detectable amounts, whereas **2** has an intermediate position. This trend is supported by the ε-values at *ca.* 355 nm (95% ethanol solution) reported by Kasturi for **1** to **5** and is also in accordance with our own measurements in 80% ethanol solutions (Table 1).‡

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†We thank Prof. Kasturi for communicating his results to us prior to publication.

‡Not much significance can be assigned to the absolute magnitude of ε of neutral solutions unless the pH and the concentration are accurately known.

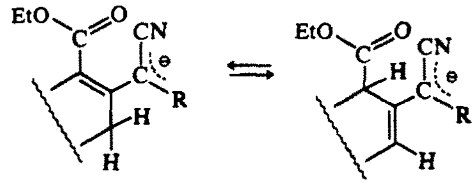
Table 1. Physical data of some alkylidene malononitriles and cyanoacetates

compound	pH at half neutrality	UV		UV according to Kasturi[3]		IR		
		80% aqueous EtOH	80% EtOH + 20% 1N NaOH	95% EtOH	95% EtOH-NaOH (0.1 M)	$CHCl_3$	96% EtOH	96% EtOH + Et_3N
1	6.2	λ 235 nm ε 10,500 λ 346 nm ε 10,000	λ 232 nm ε 7,500 λ 346 nm ε 36,300	λ 232 nm ε 13,255 λ 355 nm ε 34,800	λ 229 nm ε 13,940 λ 355 nm ε 41,530	CN 2235 (m) C=O 1740 (s)	CN 2240 (m) 2190 (vw) 2160 (vw) 2140 (vw) C=O 1740 (s)	CN - 2190 (vs) 2160 (vs) 2140 (vs) C=O -
2	8.6	λ 234 nm ε 10,800 λ 349 nm ε 200	λ 247 nm ε 11,500 λ 349 nm ε 34,200	λ 236 nm ε 14,910 λ 355 nm ε 7,205	λ 246 nm ε 15,275 λ 355 nm ε 38,970	CN 2235 (m) C=O 1735 (s)	CN 2240 (m) C=O 1740 (s)	CN - 2180 (s) C=O 1740 (m)
3	6.7	λ 243 nm ε 9,300 λ 353 nm ε 2,800	λ 235 nm ε 7,300 λ 353 nm ε 22,800	λ 228 nm ε 13,700 λ 356 nm ε 19,584	λ 224 nm ε 24,700 λ 356 nm ε 35,430	CN 2235 (m) C=O 1730 (s)	CN 2240 (m) 2180 (vw) 2145 (vw) C=O 1740 (s)	CN - 2180 (vs) 2145 (vs) C=O 1740 (vw)
4	10.7	λ 237 nm ε 12,100 λ 357 nm -	λ 248 nm ε 9,600 λ 357 nm ε 12,500	λ 238 nm ε 11,800 λ 356 nm ε 270	λ 248 nm ε 9,400 λ 356 nm ε 12,950	CN 2225 (m) C=O 1720 (s)	CN 2240 (m) C=O 1730 (s)	CN 2240 (m) 2170 (s) C=O 1730 (s)
5	10.8	λ 242 nm ε 13,400 λ 358 nm -	λ 233 nm ε 14,000 λ 358 nm ε 10,100	λ 240 nm ε 13,200 λ 356 nm ε 65	λ 238 nm ε 15,635 λ 356 nm ε 12,780	CN 2235 (m) C=O 1740 (s)	CN 2240 (m) C=O 1740 (s)	CN 2240 (m) 2185 (m) 2140 (m) C=O 1740 (s)
6	> 12	λ 238 nm ε 12,000 λ 355 nm -	λ 253 nm ε. 13,000 λ 385 nm ε 4,500	not measured	not measured	CN 2225 (m) C=O 1725 (s)	CN 2250 (m) C=O 1740 (s)	CN 2250 (m) C=O 1740 (s)

Further proof that ionisation phenomena are responsible for the appearance of the 350 nm band could be deduced from the fact, that Beer's law was not obeyed (ε increased with dilution) and that no absorption band was observed around 350 nm in aprotic apolar media such as hexane. In the latter case only a band at *ca* 240 nm was present in the UV spectra of **1** to **6** with approximately the same shape and intensity as was found with cyclohexylidenemalononitrile **7** and ethyl cyclohexylidenecyanoacetate **8**.

Addition of a drop of hydrochloric acid to a 10^{-4} M solution of **1**, **2** or **3** in ethanol (80% or 95%) caused complete disappearance of the 350 nm band because of suppression of the ionisation, whereas in alkaline solution (80% EtOH/20% 1 N NaOH or 0·1 N NaOH in EtOH) the ionisation is more or less complete, causing maximal appearance of the long wavelength UV band (with possible exception of **6**, the pH at half neutrality of which could not be determined by titration in protic solution).

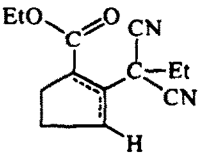
(2) In principle, proton abstraction from alkylidene malononitriles or cyanoacetates in protic solution will lead to an equilibrium mixture of the anions **A** and **B**.[5b]



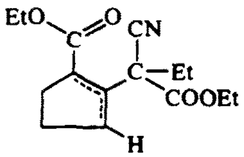
A R = CN or COOEt **B**

The intensity of the absorption at 350 nm can be connected directly with the concentration of anion **A** (with extended conjugation), whereas the UV absorption of anion **B** with unconjugated ester group does not differ considerably from the absorption of the unionized molecule (λ_{max} *ca.* 240 nm) as was inferred from the UV spectra of **7** and **8** in neutral and basic solution† (only qualitatively determined because of the rapid decomposition of these compounds by base).

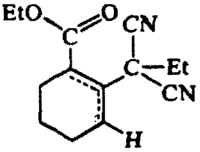
The approximate position of this equilibrium mixture of anions (which presumably is governed mainly by steric factors) could be judged not only from the ε values of basic solutions of the respective compounds at *ca.* 350 nm and 240 nm (Table 1), but also from the results of *alkylation experiments.*‡



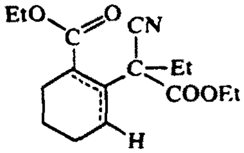
9a + 9b



10a + 10b



11a + 11b



12a + 12b

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†Ethyl cyanoacetate itself has a strong absorption at λ_{max} 245 nm (ε 11·400) in basic solution.[6]

‡It seems reasonable to assume that the alkylation rates of the anions **A** and **B** of a given compound will not be very different. No double bond isomerisation was observed in the alkylation products themselves under similar conditions.

Treatment of the sodium salts of **3**, **4**, **5** and **6** with EtI in boiling ethanol yielded alkylation products resulting from attack on the central C atom of the malononitrile or cyanoacetate moiety[7] of both types of anions, however in greatly differing proportions as judged from NMR data (peak height of the vinylic hydrogen of the alkylation products derived from anion **B**—Experimental). In agreement with its high extinction at long wavelength, an ethanolic solution of the sodium salt of **3** gave almost exclusively alkylation product **9a** with conjugated ester group, derived from anion **A**, whereas alkylation of **4** and **5**, respectively, furnished approximately equal amounts of **10a** and **10b**, and of **11a** and **11b**, respectively. **6** yielded an alkylation product mainly derived from anion **B**, in accordance with its relatively low extinction at *ca.* 350 nm in strongly basic solution. Compounds **1** and **2** could not be alkylated in a similar way because of dimerization and other side reactions under the conditions applied.[5b]

These results explain the differences in intensity of the absorption at 350 nm observed by Kasturi and by us (Table 1); they are caused by different positions of the equilibrium between the anions **A** and **B**, which in its turn is correlated with the pK_a of the corresponding acids: with increasing pK_a anion **B** is favoured.

(3) The IR spectra of **1** to **6** measured in $CHCl_3$ solution have no absorption in the region 2500–1800 cm^{-1} other than a medium strong CN band at *ca.* 2230 cm^{-1} (Table 1). In 96% ethanol solution however, **1** and **3** show in addition very weak bands between 2200 and 2100 cm^{-1} which grow considerably in intensity if Et_3N is added. At the same time the CN absorption at 2240 cm^{-1} and the ester CO band at 1740 cm^{-1} disappear almost completely, strongly suggesting the presence of anion **A**, barely visible in "neutral" solution but very pronounced in basic solution. As was to be expected in view of the acidity of **2**, **4**, **5** and **6**, the IR spectra of these compounds in 96% ethanol showed no special features. However, except for **6** (which is too weak an acid), addition of Et_3N also brought about the appearance of strong bands between 2200 and 2100 cm^{-1}, indicative of anion formation in cyano compounds.[8]* *No absorption bands were found between 2100 and 1900 cm^{-1}, which would be expected*[8,9] *if any ketenimine had been present.*

From the evidence presented it is clear that the presence and the behaviour of the long wavelength band in the UV spectra of the described alkylidene malononitriles and cyanoacetates can be fully explained on the basis of the inherent acidity of these compounds, some of which are ionized noticeably in 96% ethanol. Moreover, the alleged existence of nitrile ⇆ ketenimine tautomerism is contradicted by the absence of ketenimine absorptions in the IR spectra of neutral and basic ethanolic solutions of **1** to **6**.† Therefore, there is no basis present to invoke to any reasonable extent the participation of these ketenimine species in chemical transformations, such as cyclizations leading to pyridine derivatives.[3,5c]

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 237 spectrophotometer, UV spectra with a Perkin-Elmer 137 spectrophotometer and NMR spectra with a Varian A-60 spectrometer (chemical shifts relative to tetramethylsilane as an internal standard, $\delta = 0$ ppm). Potentiometric titrations with 0·1 N NaOH of *ca.* 8×10^{-3} M solns of **1** to **6** in 80% aq. EtOH were performed with a Metrohm Potentiograph E336.

Knoevenagel condensation products **1**, **2**, **3**, **4**, **5**, **6**, **7** and **8** were synthesized by the Cope-variant[14] of the Knoevenagel condensation[12] according to reported procedures (**1**,[3,5b] **2**[3,13]‡ **3**,[3,5b] **4**,[4,5b] **5**,[3,5] **6**,[5b,c,14] **7**[5b,c,15] and **8**[5b,16]).

General procedure for the alkylation of Knoevenagel condensation products in ethanol. To a stirred and cooled soln of 1 mmole NaOEt in 5 ml dry EtOH (N_2 atm) was added rapidly a soln of 1 mmole Knoevenagel reaction product in 1 ml dry EtOH. After 5 min at room temp. 0·5 ml EtI was added and the resulting mixture refluxed until neutrality was reached. The crude mixture was concentrated *in vacuo* and taken up in ether and water. The ether extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*, leaving the product as a yellow oil, which was purified by distillation.

Ethyl 2-(1,1-*dicyanopropyl*)-1-*cyclopentene*-1-*carboxylate* (**9a**) *and ethyl* 2-(1,1-*dicyanopropyl*)-2-*cyclopentene*-1-*carboxylate* (**9b**), yield 85%; b.p. 107–108°/0·1 mm; IR ($CHCl_3$): 2245 (CN, very weak), 1710 cm^{-1} (ester CO); NMR ($CDCl_3$): δ 1·32 and 1·33 (2 × t, 2 × 3H, $\underline{CH}_3CH_2$), 1·85–3·05 (m, 8H, cyclopentane ring protons and CH_3–$\underline{CH}_2$–C), 4·30 (q, 2H, CH_3–$\underline{CH}_2$–O); 6·4 ppm (m, less than 0·1 H, vinylic proton of **9b**). (Found: C, 67·18; H, 6·82; N, 12·32. Calc. for $C_{13}H_{16}N_2O_2$: C, 67·22; H, 6·94; N, 12·06%).

Ethyl 2 - (1 - *cyano* - 1 - *ethoxycarbonylpropyl*) - 1 - *cyclopentene* - 1 - *carboxylate* (**10a**) *and ethyl* 2 - (1 - *cyano* - 1 - *ethoxycarbonylpropyl*) - 2 - *cyclopentene* - 1 - *carboxylate* (**10b**), yield 81%; b.p. 115–116°/0·05 mm (lit.[7b] b.p. 112–115°/0·05 mm); IR ($CHCl_3$): 2245 (CN, very weak), 1740–1710 cm^{-1} (ester CO, very strong); NMR ($CDCl_3$): δ 0·9–1·55 (overlapping triplets, 9H, $\underline{CH}_3$–CH_2), 3·65 (m, *ca.* 1/2H, C=C–$\underline{CH}$–COOR of **10b**), 4·0–4·6 (overlapping quartets, 4H, CH_3–$\underline{CH}_2$–O), 6·40 ppm (m, *ca.* 1/2H, vinylic proton of **10b**). (Found: C, 64·21; H, 7·57; N, 5·13. Calc. for $C_{15}H_{21}NO_4$: C, 64·49; H, 7·58; N, 5·02%).

Ethyl 2 - (1,1 - *dicyanopropyl*) - 1 - *cyclohexene* - 1 - *carboxylate* (**11a**) *and ethyl* 2 - (1,1 - *dicyanopropyl*) - 2 - *cyclohexene* - 1 - *carboxylate* (**11b**), yield 87%; b.p. 120–125°/0·05 mm; IR ($CHCl_3$): 2250 (CN, very weak), 1730 cm^{-1} (ester CO); NMR ($CDCl_3$): δ 1·15–1·50 (overlapping triplets, 6H, $\underline{CH}_3CH_2$), 3·28 (broad s, 1/2H, C=C–$\underline{CH}$–COOR of **11b**), 4·0–4·55 (overlapping quartets, 2H, $CH_3\underline{CH}_2O$), 6·37 ppm (broad t, 1/2H, vinylic proton of **11b**). (Found: C, 68·39; H, 7·47; N, 11·15. Calc. for $C_{14}H_{18}N_2O_2$: C, 68·27; H, 7·37; N, 11·38%).

Ethyl 2 - (1 - *cyano* - 1 - *ethoxycarbonylpropyl*) - 1 - *cyclohexene* - 1 - *carboxylate* (**12a**) *and ethyl* 2 - (1 - *cyano* - 1 - *ethoxycarbonylpropyl*) - 2 - *cyclohexene* - 1 - *carboxylate* (**12b**), yield 91%; b.p. 124–125°/0·02 mm; IR ($CHCl_3$): 2245 (CN, very weak), 1725 cm^{-1} (ester CO); NMR ($CDCl_3$): δ 0·9–1·5 (overlapping triplets, 9H, $\underline{CH}_3CH_2$), 3·35 (broad s, 0·8H, C=C–$\underline{CH}$–COOR of **12b**), 3·95–4·5 (overlapping quartets, 4H, $CH_3\underline{CH}_2O$), 6·33 ppm (broad t, 0·8H, vinylic proton of **12b**). (Found: C, 65·17; H, 7·95; N, 4·68. Calc. for $C_{16}H_{23}NO_4$: C, 65·50; H, 7·90; N, 4·78%).

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*The ethanolic solutions also displayed a tremendous increase in ϵ at λ_{max} 350 nm after addition of Et_3N.

†As early as 1965 Almange[10] has disproved the existence of nitrile ⇆ ketenimine tautomerism in 1,2-dicyano esters and 1,1,1-tricyano compounds as claimed by Kasturi *et al.*[3,11]

‡Distillation of this compound must be conducted at 10^{-3} mm Hg pressure or lower to prevent polymerisation.

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