Ring-chain tautomerism. Part 8.[1] Substituted 2-(2-oxopropyl) and 2-(2-oxo-2-phenylethyl)benzoic and 2-(2-acetyl and 2-benzoylphenyl)acetic acids

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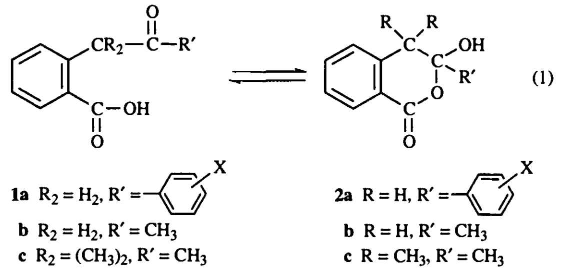
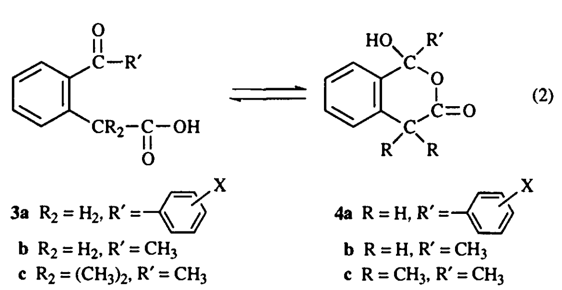
The observed pK_a values for 2-[2-(substituted phenyl)-2-oxoethyl]benzoic, 2-[2-(substituted benzoyl)phenyl]acetic, 2-(2-oxopropyl) and 2-(1,1-dimethyl-2-oxopropyl)benzoic, 2-(2-acetylphenyl)acetic and 2-(2-acetylphenyl)-2,2-dimethylacetic acids in 80% (*m*/*m*) 2-methoxyethanol–water have been measured. The occurrence of ring–chain tautomerism has been examined in these acids by IR and NMR spectroscopic methods. The substituted benzoyl acids are predominantly in the chain (normal) form and the Hammett reaction constants have been used to study the transmission of polar effects in these systems. The equilibrium constants for ring–chain tautomerism for the acetyl acids have been determined directly by IR and NMR spectroscopy and indirectly from their observed pK_a values. The results for ring-chain tautomerism in acyl carboxylic acids employing a comprehensive series of linking groups are discussed in terms of stereochemistry and steric 'bulk' interactions.

Introduction

Carboxylic acids with proximate acyl groups have the potential to engage in ring–chain tautomerism.[2] Our previous quantitative studies[1,3–5] of this behaviour have been concerned with structures involving rigid linking systems. In order to gain further understanding of the effects of both ring size and conformational freedom on such tautomerism, we have studied 1,2-$CR_2C_6H_4$ [R_2 = H_2 or $(CH_3)_2$] as the connecting link. These systems have one conformationally mobile link. These structures are shown in the equilibria between **1** and **2** and between **3** and **4** as shown in eqns. (1) and (2). Furthermore, the influence of *gem*-dialkyl effects[6] on such equilibria have been assessed. Certain of these systems have been previously studied in a qualitative manner for solid forms by IR spectroscopy.[7] The equilibrium constants, K_e, for the tautomeric equilibrium are given by eqn. (3). The observed pK_a





$$K_e = a_{ring}/a_{chain} \qquad (3)$$

Table 1 Carbonyl stretching frequencies of the benzoyl acids **1a**/**2a** and **3a**/**4a** and their corresponding chain (normal) methyl esters **5a** and **7a** in $CHCl_3$

	ν_{max}/cm^{-1}			
Substituent	**1a**/**2a**	**5a**	**3a**/**4a**	**7a**
H	1717, 1691	1720, 1685	1734, 1657	1735, 1660
4-CH_3	1716, 1688	1720, 1683	1732, 1655	1735, 1657
4-OCH_3	1717, 1685	1719, 1678	1732, 1650	1733, 1653
4-Cl	1717, 1692	1722, 1687	1735, 1657	1737, 1661
3-CF_3	1718, 1695	1721, 1691	1736, 1662	1737, 1666

can be related to the true pK_a^T by the relation (4).[8] If a reliable

$$pK_a^T = pK_a - \log(K_e + 1) \qquad (4)$$

estimate of pK_a' can be made, K_e can be found by measuring the observed pK_a. Direct quantitative studies of such tautomeric equilibria have been made using, in particular, IR and NMR spectroscopic methods.[2]

In this study, we have investigated ring–chain tautomerism in 2-[2-(substituted phenyl)-2-oxoethyl]benzoic (**1a**/**2a**) 2-[2-(substituted benzoyl)phenyl]acetic acids (**3a**/**4a**), 2-(2-oxopropyl) and 2-(1,1-dimethyl-2-oxopropyl)benzoic (**1b**/**2b** and **1c**/**2c**), 2-(2-acetylphenyl)acetic and 2-(2-acetylphenyl)-2,2-dimethylacetic acids (**3b**/**4b** and **3c**/**4c**) using IR and NMR spectroscopy, as well as their ionization in 80% (*m*/*m*) 2-methoxyethanol (MCS)–water. These results are discussed in terms of polar, steric and stereochemical effects.

Results

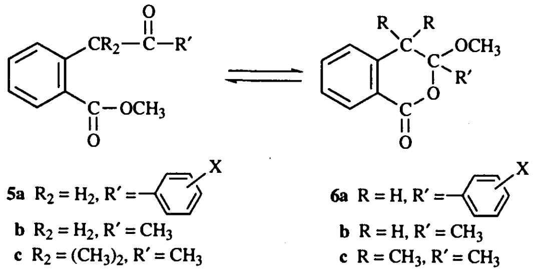
IR Measurements

The carbonyl stretching vibrations of the benzoic, **1a**/**2a**, and phenylacetic acids, **3a**/**4a**, and their chain (normal) methyl esters, **5a** and **7a**, are shown in Table 1. The spectra of all the acids corresponded closely to those of the chain esters. The ring tautomers, **6a** and **8a**, would be expected to give a signal at *ca.* 1731 and 1750 cm^{-1}, respectively (*cf.* refs. 9,10). The latter signals are absent in the spectra of the acids and could have been observed in the presence of the other tautomer. Furthermore,

Table 2 Carbonyl stretching frequencies of substituted benzoic and phenylacetic acids and their corresponding chain (normal) and ring (pseudo) methyl esters in $CHCl_3$

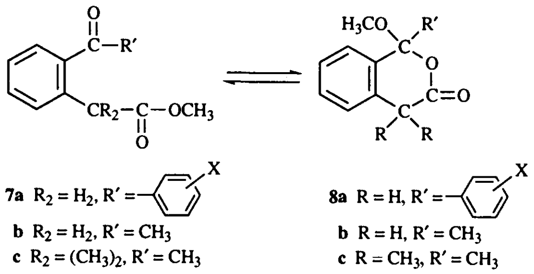
	ν_{max}/cm^{-1}		
1b/2b	1724, 1719	**5b**	1721[a]
1c/2c	1726[a]	**5c**	1723[a]
3b/4b	1733, 1687	**7b**	1742, 1728, 1687
3c/4c	1737, 1692	**7c**	1742, 1726, 1691
		8c	1730

[a] Broad signals.



5a $R_2 = H_2$, R' =
b $R_2 = H_2$, $R' = CH_3$
c $R_2 = (CH_3)_2$, $R' = CH_3$

6a R = H, R' =
b R = H, $R' = CH_3$
c $R = CH_3$, $R' = CH_3$



7a $R_2 = H_2$, R' =
b $R_2 = H_2$, $R' = CH_3$
c $R_2 = (CH_3)_2$, $R' = CH_3$

8a R = H, R' =
b R = H, $R' = CH_3$
c $R = CH_3$, $R' = CH_3$

Table 3 Equilibrium constants (K_e) for ring-chain tautomerism of the substituted benzoic and phenylacetic acids by ^1H NMR method in $CDCl_3$ at 20 °C[a]

δ						
Ring ester		Chain ester		Acid		
CH_3		CH_3		Averaged CH_3		K_e
6b	[1.60][b]	**5b**	2.27	**1b/2b**	2.15	0.2(±0.1)
6c	1.60	**5c**	2.06	**1c/2c**	1.68	5(±2)
8b	[1.83][b]	**7b**	2.60	**3b/4b**	2.53	c
8c	[1.83][b]	**7c**	2.57	**3c/4c**	2.22	0.9(±0.3)

[a] The chemical shifts were reproducible to ±0.02 ppm. [b] Estimated from other ring esters with similar structure.[9,24] [c] Value cannot be calculated with any certainty.

Table 4 Ionization of the benzoyl acids **1a/2a** and **3a/4a** in 80% (*m*/*m*) 2-methoxyethanol-water at 25 °C[a]

	pK_a	
Substituent	**1a/2a**	**3a/4a**
H	6.91	6.89
$4-CH_3$	6.97	6.97
$4-OCH_3$	6.95	6.95
4-Cl	6.80	6.83
$3-CF_3$	6.81	6.82

[a] The pK_a values were reproducible to ± 0.02 unit.

Table 5 Ionization of substituted benzoic and phenylacetic acids in 80% (*m*/*m*) 2-methoxyethanol-water at 25 °C[a]

	Observed pK_a	Estimated pK_a^T	K_e
1b/2b	7.01	6.89	0.3(±0.2)
1c/2c	9.20	7.01	150(±30)
3b/4b	6.77	6.87	b
3c/4c	7.80	7.47	2.1(±0.4)

[a] The observed pK_a values were reproducible to ±0.02 unit. Those estimated are considered to be ± 0.05 unit. [b] See footnote c, Table 3.

the relative intensities of the twin bands observed for the acid and the corresponding chain methyl esters are closely comparable. In a most favourable case, 2% of the ring tautomer could have been detected and K_e would then be equal to 0.02. Thus, this can be considered a lower limiting value for this type of measurement.

The carbonyl stretching vibrations of the remaining substituted benzoic, **1b/2b** and **1c/2c**, and phenylacetic acids, **3b/4b** and **3c/4c**, and their chain (normal) and ring (pseudo) methyl esters, **5b**, **5c**, **7b**, **7c** and **8c**, are shown in Table 2. The ring methyl esters, **6b**, **6c** and **8b**, could not be prepared; but reliable estimates of their carbonyl stretching vibration frequencies can be made from that of **8c** and of other six-membered ring methyl esters[9,11] and lactones,[10] as 1748, 1748 and 1730 cm^{-1}, respectively. The closeness of the frequencies of the ester, lactone and ketone carbonyl stretching vibrations made any quantitative interpretation impossible for the two benzoic acids. The intensities of the aryl methyl ketone vibrations of the two phenylacetic acids and methyl esters at *ca.* 1690 cm^{-1} could be used alone to make an estimate of K_e for **7b/8b** and **7c/8c**, which were *ca.* 0.04 and 1.0, respectively. The latter results agree with those qualitative results for the solid acids using IR measurements.[7] However, these results are not as reliable as those using NMR and pK_a values described below.

NMR Measurements

In the ^1H NMR spectra of the benzoyl acids, **1a/2a** and **3a/4a**, and their chain methyl esters, **5a** and **7a**, the methylene signals are at δ *ca.* 4.70, 4.72 and 3.85, 3.90, respectively. This clearly indicated that the acids were predominantly present as the chain tautomer, but precluded any quantitative evaluation of K_e. The same measurements for the remaining substituted benzoic and phenylacetic acids and their chain and ring methyl esters are shown in Table 3. Values of K_e were calculated in the manner previously described.[3] The ^{13}C NMR spectra of the benzoyl acids **1a/2a** and **3a/4a** were, in regard to the carbonyl carbon signals, almost identical to those of the corresponding chain methyl esters. However, the spectra of the acetyl acids **1b/2b**, **1c/2c**, **3b/4b** and **3c/4c** gave evidence of both chain ring tautomers with signals in $CDCl_3$ at δ *ca.* 173 or 178 (carboxylic acid carbonyl), δ 207 or 198 (keto carbonyl) and δ 164 (lactone carbonyl) and 110 (lactol carbon). However, the nature of the ^{13}C NMR spectra made any quantitative conclusions impossible.

pK_a Measurements

The apparent pK_a values of the acids in 80% (*m*/*m*) 2-methoxyethanol (MCS)-water at 25 (±0.1) °C are shown in Tables 4 and 5.

Discussion

Ionisation

The IR and NMR spectral evidence indicates that the benzoyl acids **1a/2a** and **3a/4a** are predominantly in the chain (normal) form. The pK_a values of the parent acids of these two series can be compared with the literature[12] values, measured under the same conditions, for 2-methylbenzoic and phenylacetic acid which are 6.87 and 6.73, respectively. Thus, both benzoyl acids show a small increase in pK_a. A small decrease in pK_a might have been expected for the substitution of an electron-withdrawing benzoyl group into the two acids. However,

Table 6 Hammett reaction constants, ρ, for the ionization of the 2-(2-substituted phenyl-2-oxoethyl)benzoic and 2-(2-substituted benzoylphenyl)acetic acids[a]

Acid system	ρ	$\log K_o$	r	s	n
2-(2-Oxo-2-phenylethyl) benzoic	0.225	−6.90	0.950	0.04	5
2-(2-Benzoylphenyl) acetic	0.256	−6.90	0.932	0.06	5

[a] r is the correlation coefficient, s the standard deviation, and n the number of substituents.

conformational influences on the benzoyl group could result in a configuration giving a 'reversal' of the normal dipolar substituent effect to give a small increase in the pK_a values, as has been observed in other systems.[1,3]

The effect of substitution on the reactivity in these benzoyl systems can be assessed using the Hammett eqn. (5). The correlations are shown in Table 6 and are only moderately satisfactory.

$$\log (K/K_0) = \rho\sigma \qquad (5)$$

The transmission ratios, ρ/ρ_0 are *ca.* 0.13 and 0.15 for the 2-(2-oxo-2-phenylethyl)benzoic and 2-(2-benzoylphenyl)-acetic acids, respectively, where ρ_0 is the reaction constant for the reference system, benzoic acids, under identical conditions, which is 1.69.[13] The transmission ratios, on the basis of a simple 'inductive' transmission, would be expected to be equal and can be calculated[14] to be about 0.1$_5$, as is observed. However, a ρ/ρ_0 value found for the ionisation of substituted 2-phenylacetylbenzoic acid under identical conditions was found to be *ca.* 0.3$_5$. The latter system has the same links, which are now reversed. Such differences in ρ/ρ_0 values appear to arise from the transmission being *via* an electrostatic field effect. The different systems take up different conformations, affecting the 'through-space' transmissional capacities.

The observed pK_a values of the remaining benzoic and phenylacetic acids, shown in Table 5, are likely to be affected by ring-chain tautomerism as indicated by IR and NMR spectral studies. It is possible to estimate reliable values of pK_a^T for these four acids, shown in Table 5, from those for the parent benzoyl acids, shown in Table 4, and from the effects of *gem*-dimethyl substitution on *ortho*-toluic and phenylacetic acids found in published studies.[12] Use of eqn. (4) enables the calculation of the K_e values as shown in Table 5.

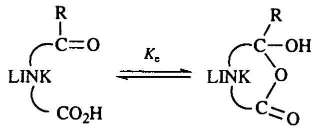
Ring-chain tautomerism

All the evidence indicates that the benzoyl acids **1a**/**2a** and **3a**/**4a** exist predominantly as chain (normal) tautomers, as does 2-(2-acetylphenyl)acetic acid, **3b**/**4b**. The values of K_e for 2-(2-oxopropyl)benzoic, **1b**/**2b** and 2-(2-acetylphenyl)-2,2-dimethylacetic acid, **3c**/**4c**, are about 0.2$_5$ and 1.0, respectively, in both solvent systems. The K_e values for 2-(1,1-dimethyl-2-oxopropyl)benzoic acid, **1c**/**2c**, are much larger; but the values found by the NMR method for $CDCl_3$ and the ionization studies for 80% aqueous MCS do not agree closely with each other.

The increased tendency to ring formation for acetyl rather than benzoyl systems is consistent with earlier studies[3,4a,5] and arises from the resonance interactions present in chain tautomers of the latter system. The increased tendency to ring formation for the keto-1,2-$CR_2C_6H_4$-carboxylic acids, rather than the keto-1,2-$C_6H_4CR_2$-carboxylic acids, appears to arise from the greater decrease in steric 'bulk' interactions in forming the ring from the chain tautomer in the former system. The tetrahedral carbon formed on cyclization in the former system is proximate or α to the rigid aryl ring and interacts with it strongly. However, the same carbon in the latter system is β to the ring and in a position which is more tolerant to steric interactions because of the greater conformational flexibility.

In the present study, the *gem*-dialkyl effect is observed as an effect on equilibria; whereas, the effect is often found in cyclization rate effects.[6] It seems best accommodated by an effect arising from bulk steric interactions by the *gem*-dimethyl groups preferentially destabilising the conformers (rotamers) of the chain tautomers, as compared to the less congested ring tautomers.

An extensive series of links of the type shown in eqn. (6) below has now been quantitatively investigated for ring-chain tautomerism in keto-carboxylic acid systems.[3–5,8,15] The order of increasing tendency to form ring tautomers for the links (keto-link-carboxylic acid) is: CH_2CH_2 ≪ 1,2-$CH_2C_6H_4$ < $CH_2C(CH_3)_2$ < 1,2-$C_6H_4C(CH_3)_2$ < *cis*-CH=CH < *cis*-CH=C(CH_3) < 1,2-C_6H_4 < *cis*-C(CH_3)=CH < *cis*-C(CH_3)=C-(CH_3) < CH(CH_3)C(CH_3)$_2$ < 1,8-$C_{10}H_6$ < 1,2-C(CH_3)$_2C_6H_4$ < 4,5-$C_{14}H_8$ < *cis*-CPh=CPh. This order is determined by the relief of steric strain and compression on forming the ring tautomer.[16] For rigid systems, this will depend mainly on the proximity of the acyl and carboxylic acid groups. For rigid links and systems having some conformational freedom, the greater the unfavourable steric interactions present the more relief obtained by forming the cyclic tautomer. Ring-size, in itself, does not seem to be a determining factor.



(6)

Experimental

Materials

The Friedel–Crafts acylation of benzene, toluene and anisole by homophthalic anhydride and aluminium chloride was employed to prepare both relevant 2-[2-(substituted phenyl)-2-oxoethyl]benzoic and 2-[2-(substituted benzoyl)phenyl]acetic acids, as described by Renson and Christiaens[7] and by Legrand and Lozac'h.[17] The condensation of the sodium salt of homophthalic anhydride with 4-chloro- or 3-trifluoromethyl-benzoylchloride provided 2-[2-(4-chloro and 3-trifluoromethylphenyl)-2-oxoethyl]benzoic acids, as described by Cousse *et al.*[18] The method of Renson and Christiaens,[7] involving the oxidation of 1-(substituted phenyl)indenes, was used in the synthesis of 2-[2-(4-chloro- and 3-trifluoromethyl-benzoyl)phenyl]acetic acids.[7,19] The remaining 2-(2-oxopropyl)benzoic and 2-acetylbenzoic acids were prepared by lit. methods.[7,20–22] The purity of the acids was monitored by IR and ^1H and ^{13}C NMR spectroscopy. The mps of the acids, after repeated recrystallization and drying under reduced pressure (P_2O_5), were in agreement with lit. values,[7,17–22] except for the previously unreported compound following: 2-[2-(3-trifluoromethylbenzoyl)phenyl]acetic acid was recrystallized from benzene as colourless crystals, mp 152–153 °C. (Found: C, 62.2; H, 3.5; F, 18.3. $C_{16}H_{11}F_3O_3$ requires C, 62.3; H, 3.6; F, 18.5%).

The preparation and purity of the chain(normal) methyl esters of the acids has been reported.[23] The ring(pseudo) methyl ester of 2-(1,1-dimethyl-2-oxopropyl)benzoic acid (3-methoxy-3,4,4-trimethyl-1-isochromanone), **6c**, was prepared *via* the methanolysis of the acid chloride as described by Renson and Christiaens.[7] This method failed to give the ring methyl esters of the other acids, as also found by Renson and Christiaens.[7] Ring methyl esters of 2-acetylbenzoic and 8-acetyl-1-naphthoic acids were prepared as previously described.[9,24]

The solvents were purified as described previously.[1,4]

IR Measurements

The carbonyl stretching vibrations of the acids and their chain (normal) and ring (pseudo) methyl esters were determined as previously described[3,4] for solutions (0.02 mol dm^{-3}) in

$CHCl_3$ at 35 (±1) °C. A Perkin-Elmer model 1600 FTIR spectrometer was used in these studies and the wavenumber measurements were reproducible to ±1 cm^{-1}.

NMR Measurements

The spectra of the compounds were measured using a JEOL EX270 spectrometer operating at 270 MHz. The ^1H NMR spectral chemical shifts were measured in ppm relative to $SiMe_4$ and the ^{13}C NMR spectral chemical shifts in ppm relative to $SiMe_4$.

pK_a Measurements

The apparent pK_a values of the acids in 80% (*m*/*m*) 2-methoxyethanol (MCS)–water at 25 (±0.1) °C were measured as described previously.[13,25] All the determinations are the results of at least two separate determinations.

Acknowledgements

We thank the SERC and Rhône-Poulenc for the award of a CASE studentship (to J. M. B.) and Dr M. Caton for his advice and interest.

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Paper 6/01525E
Received 4*th March* 1996
Accepted 18*th April* 1996