Ring–chain tautomerism. Part 9.[1] 2-Acylbenzamides, 8-acyl-1-naphthamides and 5-acyl-4-phenanthramides

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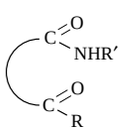
Ring–chain tautomerism in *N*-methyl- and *N*-(substituted phenyl)-2-formylbenzamides, 2-benzoylbenzamides, 8-formyl-1-naphthamides, 8-benzoyl-1-naphthamides and 5-formyl-4-phenanthramides has been investigated by IR and ^{1}H NMR spectroscopy and the measurement of their pK_a values in 30% (v/v) dimethyl sulfoxide–water. The tautomeric pair synthesised, *i.e.* hydroxylactam–acylamide or aminolactone–iminocarboxylic acid, appears to be a function of the method of preparation and/or the basicity of amine used. The cyclic tautomer, *i.e.* hydroxylactam or aminolactone, is predominant in all cases studied. However, equilibrium constants have been estimated from the pK_a values for aminolactone–iminocarboxylic acid tautomerisation in which the effect of the links follow similar trends as found for the corresponding hydroxylactone–acylcarboxylic acid tautomeric systems.

Introduction

Ring–chain tautomerism has been shown to occur in a number of keto- and formyl-amides.[2] These could exist as chain or open (normal) tautomers, *i.e.* acylamide **1** and iminocarboxylic acid **2** and as ring or cyclic (pseudo) tautomers, *i.e.* hydroxylactam **3** and aminolactone **4**. These are two pairs of tautomers, *i.e.* **1/3** and **2/4**, and these can be interconverted within the pair by



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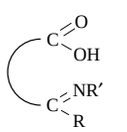

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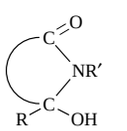

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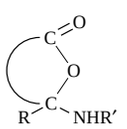


4

a simple prototropic shift. The two tautomeric equilibrium constants, $K_e^{3,1}$ and $K_e^{4,2}$, are given by eqns. (1) and (2), *i.e.*

$$K_e^{3,1} = a_3/a_1 \quad (1)$$

$$K_e^{4,2} = a_4/a_2 \quad (2)$$

ring/chain, in which *a* represents the activity of the species noted. The pairs can only be interconverted by powerful catalysis (strong acid/base or nucleophilic/electrophilic, thermal or photochemical) under very much more vigorous[2,3] conditions than those required for the simple prototropic shift.

In particular, studies have been made of 2-acylbenzamides and 8-acyl-1-naphthamides.[4–9] Despite some confusion in earlier studies, there is excellent evidence, particularly from IR spectra, for the occurrence of both tautomeric pairs, with the predominance of the cyclic tautomers **3** and **4** in the *N*-methyl and phenyl systems.[2,4–9] The formation of the particular tautomeric pair appears usually to be a function of the synthetic method used.

In this study, we have investigated ring–chain tautomerism in *N*-methyl- and *N*-(substituted phenyl)-2-formylbenzamides, 2-benzoylbenzamides, 8-formyl-1-naphthamides, 8-benzoyl-1-naphthamides and 5-formyl-4-phenanthramides using several techniques, in particular IR spectroscopy and pK_a values. The results are related to the structure of the systems under study, as well as that of ring–chain tautomerism in related keto- and formyl-carboxylic acids.

Results and discussion

IR spectroscopy

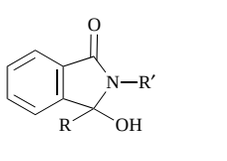
There are two important regions in the IR spectra of tautomeric amides, *i.e.* the carbonyl (CO) and nitrogen–hydrogen (NH) or oxygen–hydrogen (OH) stretching frequencies, for structural diagnostic purposes. The results for the tautomeric amides under study are shown in Table 1. These measurements were made at low concentrations to minimise any effects of dimerisation, which is known to occur for certain hydroxylactams **3**.[10] The compounds **5/6a**, **5/6b**, **7/8a**–**7/8c** and **11/12a**–**11/12c** in $CHCl_3$ have a broad band at *ca.* 3330 cm^{-1} which indicates an OH stretching frequency; whereas the compounds **9/10a**–**9/10d**, **13/14a**–**13/14c** and **17/18a**–**17/18c** in $CHCl_3$ have a sharp band at *ca.* 3430 cm^{-1} which indicates an NH stretching frequency.[5,7,8]

The CO stretching frequencies of compounds **5/6a**, **5/6b** and **7/8a**–**7/8d** are at *ca.* 1700 cm^{-1} in $CHCl_3$ and *ca.* 1690 and 1720 cm^{-1} in CCl_4 and are associated with a five-membered hydroxylactam ring **3**.[5,7] The twin bands observed in CCl_4 probably arise from either a dimer[10] or Fermi resonance, as previously observed for five-membered lactone rings.[11] However, the CO band at *ca.* 1690 cm^{-1} has been associated with the acylamide **1**; but it was considered more likely to arise from intermolecularly hydrogen-bonded dimers of the hydroxylactams **3**.[2,3,10] For compounds **9/10a**–**9/10d**, the major CO stretching band at *ca.* 1763 cm^{-1} in $CHCl_3$ and 1779 cm^{-1} in CCl_4 is associated with a five-membered aminolactone ring **4**.[5,7] A very weak CO band at *ca.* 1704 cm^{-1} in $CHCl_3$ and *ca.* 1740 cm^{-1} in CCl_4 is probably associated with the iminocarboxylic acid **2**.[5,7] The CO stretching frequencies of compounds **11/12a**–**11/12e** are at *ca.* 1646

Table 1 IR spectra and ionisation constants of 2-acylbenzamides, 8-acyl-1-naphthamides and 5-acyl-4-phenanthramides

Compound	IR [a] ν_{CO}/cm^{-1} in CCl_4	IR [a] ν_{CO}/cm^{-1} in $CHCl_3$	IR [a] ν_{XH}/cm^{-1} in $CHCl_3$	pK_a in 30% (v/v) DMSO–water at 30.0 °C [b]	λ/nm [c]
5/6a	1693.2, 1721.6	1692.0	3337.6	11.77 (11.62) [d]	285
5/6b	1688.0, 1713.2	1692.0	3324.8	11.53	290
7/8a	1691.2, 1720.4	1708.0	3337.6	12.14 [e]	310
7/8b	1691.2, 1720.8	1702.4	3342.4	12.46 [e]	310
7/8c	1692.8, 1723.2	1710.0	3334.4	11.75 [e]	310
7/8d	1694.4, 1724.4	1711.6	(i)	12.01 [e]	310
9/10a	1777.2 (1739) [f]	1760.8 (1701) [f]	3408.0 (s)	5.81	315
9/10b	1777.2 (1738) [f]	1760.0 (1700) [f]	3410.4 (s)	5.99	315
9/10c	1780.8 (1740) [f]	1762.4 (1707) [f]	3413.2 (s)	5.83	315
9/10d	1782.4 (1743) [f]	1768.4 (1707) [f]	3412.0 (s)	5.78	300
11/12a	1666.0	1648.8	3340.4	13.29	340
11/12b	1664.0	1646.5	3341.2	12.94	340
11/12c	1664.0	1646.7	3342.0	12.93	340
11/12d	1659.6	1644.0	(i)	12.91	340
11/12e	1659.0	1643.0	(i)	13.23	340
13/14a	1731.2	1715.2	3426.8 (s)	8.60	350
13/14b	1731.2	1715.2	3428.0 (s)	8.60	350
13/14c	1737.2	1718.0	3426.4 (s)	8.99	350
13/14d	1740.0	1721.6	(i)	9.34	350
13/14e	1726.9	1711.6	(i)	8.40	270
13/14f	1727.4	1711.6	(i)	8.36	270
13/14g	1727.6	1711.6	(i)	8.41	270
13/14h	1731.3	1716.4	(i)	8.27	270
15/16a	(i)	1629.2	(i)	13.09	315
17/18a	1714.0	1699.2	3440.0 (s)	7.58	330
17/18b	1713.6	1699.2	3440.0 (s)	7.62	330
17/18c	1715.6	1699.6	3439.6 (s)	7.75	330
17/18d	1724.0	1701.6	(i)	7.73	330

[a] The wavenumber measurements were reproducible to ±0.2 cm^{-1}. The symbol (i) indicates compound was too insoluble for accurate measurement and (s) indicates sharp band. [b] The pK_a values were considered to be reproducible to ±0.04 unit. [c] Wavelength used in the determination of the pK_a values. [d] In water at 30.0 °C. [e] The slope of log ([HA]/[A]) *versus* pH was *ca.* 0.25 (see Discussion). [f] Weak absorption.



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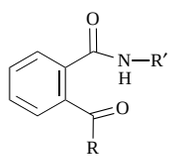
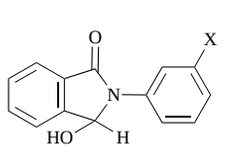


6

5/6a R = H, R′ = CH_3
5/6b R = Ph, R′ = CH_3



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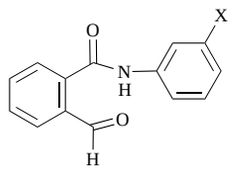
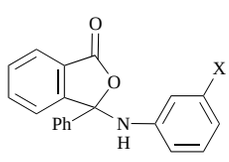


8

7/8a X = H
7/8b X = CH_3
7/8c X = Cl
7/8d X = CF_3



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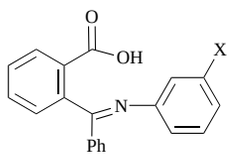


10

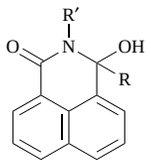
9/10a X = H
9/10b X = CH_3
9/10c X = Cl
9/10d X = NO_2

cm^{-1} in $CHCl_3$ and *ca.* 1661 cm^{-1} in CCl_4 and are associated with a six-membered hydroxylactam ring **3**.[8] In contrast, for compounds **13/14a**–**13/14h**, the CO stretching frequencies of *ca.* 1715 cm^{-1} in $CHCl_3$ and *ca.* 1732 cm^{-1} in CCl_4 are associated with a six-membered aminolactone ring **4**.[8] The same pattern occurs for compound **15/16a**, with a CO stretching frequency of *ca.* 1629 cm^{-1} in $CHCl_3$ associated with a seven-membered hydroxylactam ring **3**, and compounds **17/18a**–**17/18d**, with a CO stretching frequency of *ca.* 1700 cm^{-1} in $CHCl_3$ and *ca.* 1717 cm^{-1} in CCl_4 associated with a seven-membered aminolactone ring **4**.

The decrease in the CO stretching frequencies with increasing ring size in both the aminolactones **4** and hydroxylactams **3**, as well as the increase in CCl_4 compared with that in $CHCl_3$, parallel those previously found for comparable alkoxy and aryloxylactones.[12]

NMR Spectroscopy

^{1}H NMR spectra can be used for the investigation of the structure of the formylamides and the *N*-methylamides. For solution in dimethyl sulfoxide (DMSO), the compounds **5/6a**, **7/8a**–**7/8d**, **11/12a**–**11/12c**, **15/16a** have two signals (d, 1H, *J* 9 Hz) at *ca.* 6.5 and 6.1 ppm, which are consistent with α- or quat. H and OH, respectively, of the hydroxylactam **3**.[5] Similarly, the compounds **13/14a**–**13/14d** and **17/18a**–**17/18d** have two signals (d, 1H, *J* 7 Hz) at *ca.* 6.7 and 4.9 ppm, which are consistent with α- or quat. H and NH, respectively, of the aminolactone **4**. The *N*-methylamides gave signals (s, 3H) at *ca.* 3.1 (**5/6a**, **11/12a**, **15/16a**) or 2.6 ppm (**5/6b**, **11/12d**), which agree with the cyclic lactam N–CH_3 structure **3** for these compounds. Treatment of the above compounds with excess NaOD–D_2O removed coupling between the α- or quat. H and OH/NH. However, the chemical shift of the α- or quat. H for compounds **13/14a**–



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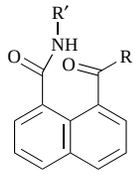
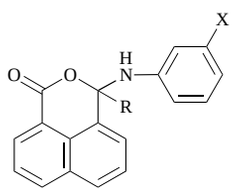


12

11/12a R = H, R′ = CH_3
11/12b R = H, R′ = $(CH_2)_2CH_3$
11/12c R = H, R′ = $(CH_2)_3CH_3$
11/12d R = Ph, R′ = CH_3
11/12e R = Ph, R′ = CH_2CH_3



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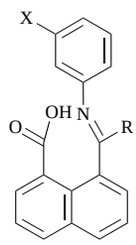
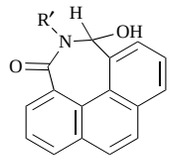


14

13/14a R = H, X = H
13/14b R = H, X = CH_3
13/14c R = H, X= Cl
13/14d R = H, X = NO_2
13/14e R = Ph, X = H
13/14f R = Ph, X = CH_3
13/14g R = Ph, X = Cl
13/14h R = Ph, X = NO_2



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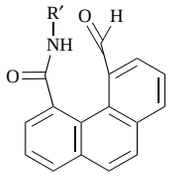
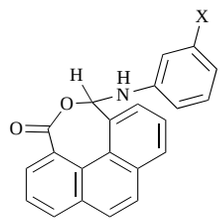


16

15/16a R′ = CH_3



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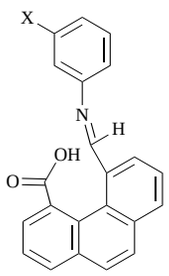

18

17/18a X = H
17/18b X = CH_3
17/18c X = Cl
17/18d X = NO_2

13/14d and **17/18a**–**17/18d** changed to *ca*. 9.3 ppm which corresponds to the formyl hydrogen of the anion of **2**. The chemical shift of the α- or quat. H and/or N–CH_3 for compounds **5/6a**, **7/8a**–**7/8d**, **11/12a**–**11/12c** and **15/16a** decreased by *ca.* 0.2 ppm.

^{13}C NMR spectra for all the compounds indicate one carbonyl C (sharp at 162–170 ppm) and one quat. C (sharp at 80–99 ppm), together with the required number of other signals consistent with the ring tautomers **3** or **4**. Tautomer **1** would have required two carbonyl carbon signals and tautomer **2** one carbonyl and one imino carbon signal.

pK_a Values

The pK_a values of the compounds in 30% (v/v) DMSO–water are shown in Table 1. The observed pK_a for compounds occurring as a tautomeric pair can be related to the true pK_a^T of the more acidic tautomer by eqn. (3),[13] as long as the tautomer

$$pK_a^T = pK_a - \log(K_e + 1) \quad (3)$$

interconversion is rapid. The interconversion between **1** and **3** and between **2** and **4** for compounds closely related to those in the present study has been shown to be relatively rapid either in the presence or absence of acid–base catalysis.[2] However, interconversion between **1/3** and **2/4** cannot be achieved for such systems under the conditions employed in this study.[2]

If a reliable estimate of pK_a^T can be made, K_e can be found by measuring the observed pK_a. For the pair of tautomers **2/4**, the pK_a values of carboxylic acids **2** are much greater than those of amines **4** in both water and DMSO.[14] Estimates of the true pK_a^T values of the (phenylimino)methylcarboxylic acids in 30% aqueous DMSO can be made from the values of 2-substituted benzoic acids in the same medium[15] and of 8-substituted 1-naphthoic acids and 4-phenanthroic acid in aqueous alcohols.[16] The *para*-σ value of the CH=NPh group is 0.42.[17] Thus, the estimated pK_a^T values of 2-[(phenylimino)methyl]benzoic, 8-[(phenylimino)methyl]-1-naphthoic and 5-[(phenylimino)-methyl]-4-phenanthroic acids in 30% aqueous DMSO at 30 °C are 3.4 (±0.1), 3.5 (±0.1) and 3.3 (±0.2), respectively. Combination of the latter with the observed values of pK_a for the compounds gives K_e values equal to 2.5 (±0.6) × 10^2, 1.3 (±0.3) × 10^5, 8 (±2) × 10^4 and 2 (±0.9) × 10^4 for the K_e[4,2] for the 3-phenyl-3-phenylaminoisobenzofuran-1(3*H*)-one **9/10a**, 3-phenylaminonaphtho[1,8-*cd*]pyran-1(3*H*)-one **13/14a**, 3-phenyl-3-phenylaminonaphtho[1,8-*cd*]pyran-1(3*H*)-one **13/14e** and 6-phenylaminophenanthro[4,5-*cde*]oxepin-4(6*H*)-one **17/18a**. The order of increasing tendency to form the ring tautomer is: 1,2-C_6H_4 ≪ 4,5-$C_{14}H_8$ < 1,8-$C_{10}H_6$. This is a similar order of tendency for links displayed by the keto–carboxylic tautomeric system.[1] This order is determined, mainly, by the relative relief of steric strain and compression on forming the ring tautomer.[1]

For the pair of tautomers **1/3**, the pK_a values of alcohols and amides are more comparable in both water and DMSO than the pair discussed above; but that of 1-phenyl-1-benzamidomethanol can be predicted to be less than that of a benzamide. Thus, the pK_a value of PhCH(NRCOPh)OH can be estimated to be *ca*. 12.3 in water[18] and of PhCONHPh is 14.58 in aqueous DMSO.[19] The pK_a values of compounds **5/6a**, **5/6b**, **7/8a**–**7/8d**, **11/12a**–**11/12e** and **15/16a** appear to correspond to that of the hydroxylactam **3**. The pK_a values of compounds **5/6**, **7/8**, **11/12** and **15/16** all correspond to the expected value for a hydroxylactam **3** and appear to be relatively unaffected by any tautomeric equilibria. The pK_a of **5/6a** in water (11.62) and in 30% aqueous DMSO (11.77) are similar as expected. The increase in pK_a observed for **7/8a**, **11/12a** and **15/16a**, compared to that of **5/6a** probably results from increased steric 'bulk' inhibition of solvation of the alkoxide.

The slope of log ([HA]/[A^-]) *versus* pH was generally *ca*. 1.0 as expected. However, for compounds **7/8a**–**7/8d** the slope was *ca*. 0.25. The latter probably results from partial dimerisation of **7/8**,[10] with the dimer being a stronger acid due to hydrogen-bonded stabilization of the mono-anion of the dimer.

In principle, the Hammett equation (4)[20] can be applied to

$$\log(K/K_o) = \rho\sigma \quad (4)$$

the five 3-substituted phenyl series of compounds **7/8**, **9/10**, **13/14a**–**13/14d**, **13/14e**–**13/14h** and **17/18**. It was found that only series **13/14a**–**13/14d** gives a satisfactory correlation, with ρ equal to 0.98 (±0.06) for four substituents and a correlation coefficient of 0.997. The ρ value for this series (observed log K_a) will be that equal to ρ for ionisation (log K_a^T) minus ρ for the

Table 2 Physical properties of previously unreported compounds

Compound	Mp/°C	Appearance	Elemental analysis Found (%) (Required) C	H	N	Other
5/6b ($C_{15}H_{13}NO_2$)	185–186	Colourless needles from ethyl acetate	75.0 (75.3)	5.6 (5.5)	5.7 (5.9)	
7/8b ($C_{15}H_{13}NO_2$)	132–134	Colourless needles from ethyl acetate	75.4 (75.3)	5.5 (5.5)	5.7 (5.9)	
7/8c ($C_{14}H_{10}ClNO_2$)	165–166	Colourless needles from ethyl acetate	64.8 (64.8)	3.9 (3.9)	5.2 (5.4)	13.5 (Cl) (13.7) (Cl)
7/8d ($C_{15}H_{10}F_3NO_2$)	200–202	Colourless needles from ethyl acetate	61.2 (61.4)	3.5 (3.4)	4.7 (4.8)	19.2 (F) (19.4) (F)
9/10b ($C_{21}H_{17}NO_2$)	188–190	Colourless needles from ethyl acetate	79.7 (80.0)	5.4 (5.4)	4.2 (4.4)	
9/10c ($C_{20}H_{14}ClNO_2$)	180–182	Colourless needles from ethyl acetate	71.3 (71.5)	4.2 (4.2)	4.1 (4.2)	10.5 (Cl) (10.6) (Cl)
9/10d ($C_{20}H_{14}N_2O_4$)	193–195	Pale yellow needles from ethyl acetate	69.1 (69.4)	4.3 (4.1)	7.9 (8.1)	
11/12b ($C_{15}H_{15}NO_2$)	112–114	Colourless needles from toluene	74.5 (74.7)	6.3 (6.3)	5.7 (5.8)	
11/12c ($C_{16}H_{17}NO_2$)	126–128	Colourless needles from toluene	75.0 (75.3)	6.7 (6.7)	5.4 (5.5)	
11/12e ($C_{20}H_{17}NO_2$)	185–186	Colourless needles from toluene	78.9 (79.2)	5.6 (5.7)	4.5 (4.6)	
13/14a ($C_{18}H_{13}NO_2$)	183–185	Colourless needles from toluene	78.6 (78.5)	4.8 (4.8)	5.0 (5.1)	
13/14b ($C_{19}H_{15}NO_2$)	181–183	Colourless needles from toluene	78.9 (78.9)	5.2 (5.2)	4.8 (4.8)	
13/14c ($C_{18}H_{12}ClNO_2$)	190–191	Colourless needles from toluene	69.8 (69.8)	3.9 (3.9)	4.4 (4.5)	11.3 (Cl) (11.5) (Cl)
13/14d ($C_{18}H_{12}N_2O_4$)	230–232	Pale yellow needles from toluene	67.3 (67.5)	3.9 (3.8)	8.6 (8.8)	
13/14f ($C_{25}H_{19}NO_2$)	190–192	Colourless needles from toluene	82.0 (82.2)	5.3 (5.2)	3.7 (3.8)	
13/14g ($C_{24}H_{16}ClNO_2$)	193–195	Colourless needles from toluene	74.4 (74.7)	4.2 (4.2)	3.8 (3.6)	9.0 (Cl) (9.2) (Cl)
13/14h ($C_{24}H_{16}N_2O_4$)	199–200	Yellow needles from toluene	72.6 (72.7)	4.0 (4.1)	6.9 (7.1)	
15/16a ($C_{17}H_{13}NO_2$)	226–228	Colourless needles from toluene	77.5 (77.6)	5.0 (5.0)	5.2 (5.3)	
17/18a ($C_{22}H_{15}NO_2$)	198–200	Colourless needles from toluene	81.4 (81.2)	4.6 (4.7)	4.1 (4.3)	
17/18b ($C_{23}H_{17}NO_2$)	185–186	Colourless needles from toluene	81.1 (81.4)	5.0 (5.1)	4.0 (4.1)	
17/18c ($C_{22}H_{14}ClNO_2$)	196–197	Colourless needles from toluene	73.1 (73.4)	3.9 (3.9)	3.8 (3.9)	9.8 (Cl) (9.9) (Cl)
17/18d ($C_{22}H_{14}N_2O_4$)	244–246	Yellow needles from toluene	71.1 (71.4)	3.8 (3.8)	7.6 (7.6)	

tautomeric equilibria (log K_e) as $K_e \gg 1$.[21] Correlations of the observed log K_a can be expected to be poor due to the combination of the inexact nature of the two correlations. However, the successful correlation for the series **13/14a**–**13/14d**, resulting in a ρ value of 0.98, does agree with the dominant role of the tautomeric equilibria over that of ionisation shown in comparable systems.[2]

Structure–synthesis relations

The reduction of the *N*-substituted imides, which are already in a cyclic or ring form, gives the hydroxylactams **3**. Reaction of the acylcarboxylic acid chlorides, which are predominantly ring tautomers,[2] with anilines results in formation of the aminolactones **4**; whereas reaction with alkylamines results in hydroxylactams **3**.[7] Furthermore, the ring or cyclic (pseudo) methyl ester of the acylcarboxylic acid reacts with alkylamines to give **3**. Strongly basic and nucleophilic alkylamines attack the quat. carbon, presumably *via* an S_N2-type process; whereas weakly basic and nucleophilic anilines attack the carbonyl carbon, presumably *via* a $B_{AC}2$-type process. This appears to be an example of selectivity based on the HSAB principle.[22] Thus the relatively hard base, the alkylamine, attacks the relatively hard Lewis acid centre, the carbonyl group, of the ambident electrophilic substrate; whereas the relatively weak base, the aniline, attacks the relatively weak Lewis acid centre of the substrate.[23]

Structure–tautomeric equilibria relations

All the link systems studied here, *i.e.* 1,2-benzene, 1,8-naphthalene and 4,5-phenanthrene, give predominantly the tautomeric ring systems, *i.e.* **3** or **4**. While there is evidence for the occurrence of the chain tautomer **1** as a minor component in equilibria with **3**, there is no evidence for the occurrence of **2** in equilibria with **4**.

Experimental

Materials

2-Methyl- or 2-(substituted phenyl)-2,3-dihydro-3-hydroxyisoindol-1-ones were prepared by the reduction of *N*-methyl or substituted phenylphthalimides using magnesium/aqueous ammonium chloride.[24] 2-Benzoylbenzoic acid was converted to the acid chloride using thionyl chloride, which was reacted with methylamine or substituted anilines to give the 2,3-dihydro-3-hydroxy-2-methyl-3-phenylisoindol-1-one, **5/6b** and 3-phenyl-3-(substituted phenylamino)-isobenzofuran-1-one, **9/10**.[6] The same method using either 8-formyl or 8-benzoyl-1-naphthoic and 5-formyl-4-phenanthroic acids was used to prepare the 2,3-dihydro-3-hydroxy-2-alkylbenz[*de*]isoquinolin-1-ones **11/12a**–**11/12c**, 3-phenyl-3-(substituted phenylamino)- and 3-(substituted phenylamino)-naphtho[1,8-]pyran-1(3*H*)-ones **13/14**, 6-hydroxy-5-methyl-5,6-dihydro-phenanthro[4,5-*cde*]azepin-4-

one **15/16a** and 6-(substituted phenylamino)phenanthro[4,5-*cde*]oxepin-4(6*H*)-ones **17/18**. The synthesis of 2,3-dihydro-3-hydroxy-2-alkyl-3-phenylbenz[*de*]isoquinolin-1-ones, **11/12d** and **11/12e**, was achieved by the reaction of the ring or cyclic (pseudo) methyl 8-benzoyl-1-naphthoate with the alkylamine.[25] The compounds were purified when required using column chromatography (silica), eluting with dichloromethane–ethyl acetate. The mps of the compounds, after repeated recrystallisation and drying under reduced pressure (P_2O_5) were either in good agreement with the reported[6,8,24,25] values or are reported in Table 2. The structures and purity of the compounds were monitored by ^{1}H and ^{13}C NMR and IR spectroscopy, as well as mass spectrometry. Solvents were purified by standard procedures or were of spectral purity (Uvasol, Merck).[26]

IR Measurements

The IR spectra were recorded on a Zeiss Specord M-80 spectrometer at room temperature using NaCl cells with pathlengths of 0.1 and 1.0 mm and the concentration of the solutions were normally chosen to reach maximal absorptions of 75–80%, but were at lower concentrations where there was evidence of dimerisation.[10] Peak positions were determined with an accuracy of ±0.2 cm^{-1} for carbonyl and ±0.4 cm^{-1} for other stretching frequencies against polystyrene standard spectra.

NMR Measurements

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

pK_a Measurements

The pH measurements were made at 30.0 (±0.1) °C using a Russell combination pH electrode and an AGB-75 pH meter. The pH electrode was standardised using borate and potassium hydrogen phthalate solutions. The pK_a values were measured in 30% (v/v) DMSO–aqueous buffer solutions using the method of Albert and Serjeant.[27] Buffers used were citrate, phosphate and glycine with HCl or NaOH. The ionisation was studied spectrophotometrically by use of a Perkin-Elmer lambda 5 or 16 UV–VIS spectrophotometer and the cell temperature was controlled to 30.0 (±0.05) °C by means of a Haake DC3 circulator. When required, a 30% (v/v) aqueous DMSO solution containing 2.8 mol dm^{-3} NaOH was used to ensure complete ionisation. The substrate concentrations were *ca*. 5×10^{-5} mol dm^{-3}. The pK_a values and the wavelengths used are shown in Table 1. Good isosbestic points were observed.

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References

1 Part 8. K. Bowden and J. M. Byrne, *J. Chem. Soc.*, *Perkin Trans. 2*, 1996, 1921.
2 R. E. Valters and W. Flitsch, *Ring–Chain Tautomerism*, Plenum Press, New York, 1985.
3 R. E. Valters, *Russ. Chem. Rev.*, 1973, **42**, 464; 1974, **43**, 665.
4 W. Graf, E. Girod, E. Schmid and W. G. Stoll, *Helv. Chim. Acta*, 1959, **42**, 1085.
5 W. Flitsch, *Chem. Ber.*, 1970, **103**, 3205.
6 M. V. Bhatt, K. M. Kamath and M. Ravindranathan, *J. Chem. Soc.* (*C*), 1971, 1772; M. V. Bhatt and M. Ravindranathan, *J. Chem. Soc.*, *Perkin Trans. 2*, 1973, 1160.
7 R. E. Valter and V. P. Tsiekure, *Chem. Heterocycl. Compd.*, 1972, 458; R. E. Valter and V. R. Zin'kovskaya, *Chem. Heterocycl. Compd.*, 1973, 1041; R. E. Valter and V. P. Tsiekure, *Chem. Heterocycl. Compd.*, 1975, 1258.
8 R. E. Valter and V. R. Zin'kovskaya, *Chem. Heterocycl. Compd.*, 1973, 1127; V. R. Zin'kovskaya and R. E. Valter, *Latv. PSR Zinat. Akad. Vestis*, *Khim. Ser.*, 1974, 207. (*Chem. Abs.*, 1974, **81**, 91 325w).
9 M. Ahmed and J. M. Vernon, *J. Chem. Soc.*, *Perkin Trans. 1*, 1975, 2048.
10 S. P. Valtere, Z. E. Zarina, G. A. Karlivans and R. E. Valter, *Latv. PSR Zinat. Akad. Vestis*, *Khim. Ser.*, 1978, 575. (*Chem. Abs.*, 1979, **90**, 54 316j).
11 A. Perjessy, O. Hritzova, Z. Sustekova, P. Hrnciar and K. Bowden, *Monatsh. Chem.*, 1997, **128**, 235.
12 K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 1390, 1395; K. Bowden and A. M. Last, *J. Chem. Soc.*, *Perkin Trans. 2*, 1973, 1144; F. Anvia, K. Bowden, F. A. El-Kaissi and V. Saez, *J. Chem. Soc.*, *Perkin Trans. 2*, 1990, 1809.
13 C. Pascual, D. Wegmann, U. Graf, R. Scheffold, P. F. Sommer and W. Simon, *Helv. Chim. Acta*, 1964, **47**, 213.
14 F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.
15 M. Hojo, M. Utaka and Z. Yoshida, *Tetrahedron*, 1971, **27**, 2713.
16 K. Bowden and D. C. Parkin, *Can. J. Chem.*, 1969, **47**, 185; K. Bowden and A. M. Last, *J. Chem. Soc.*, *Perkin Trans. 2*, 1973, 1144.
17 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
18 G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 75.
19 K. Bowden and K. Bromley, *J. Chem. Res.*, 1990, (*S*) 344; (*M*) 2682.
20 C. D. Johnson, *The Hammett Equation*, Cambridge University Press, Cambridge, 1973.
21 K. Bowden and F. P. Malik, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 635.
22 T.-L. Ho, *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York, 1977.
23 Y. Kubota and T. Tatsuno, *Chem. Pharm. Bull.*, 1971, **19**, 1226.
24 A. Dunet and A. Willemart, *Bull. Soc. Chim. Fr.*, 1948, 1045.
25 A. Warshawsky and D. Ben-Ishai, *Tetrahedron Lett.*, 1968, 541; *J. Heterocycl. Chem.*, 1969, **6**, 681.
26 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon, Oxford, 3rd edn., 1988.
27 A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases*, Methuen, London, 1962.

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