SHORT PAPER

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Chromone studies. Part 10.[1] Substituent effects on the basicity of 2-(*N,N*-dimethylamino)chromones†

Perry T. Kaye[a]*, Aloysius T. Nchinda[a], Liezel V. Sabbagh[a] and Cedric W. McCleland[b]

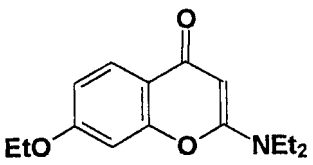
[a]*Department of Chemistry, Rhodes University, Grahamstown, 6140, South Africa*
[b]*Department of Chemistry, University of Port Elizabeth, PO Box 1600, Port Elizabeth, 6000, South Africa*

The pK_a values for a series of 12, substituted 2-(*N,N*-dimethylamino)chromones have been determined by potentiometric titration and found to lie within a narrow range (1.92–2.52), protonation of the carbonyl oxygen being supported by ^{13}C NMR data and semi-empirical and *ab initio* calculations.

Biologically active chromones include sodium cromoglycate, a chromone-2-carboxylic acid derivative used in the treatment of bronchial asthma,[2] and various 2-aminochromones (such as the 2-diethylamino derivative **1**) which exhibit antiplatelet activity.[3] In previous studies we have examined the influence of substituents on, *inter alia*, the acidity of chromone-2-carboxylic acids[4] and the C(2)–N rotational barriers in *N,N*-disubstituted 2-amino-chromones.[1] In this communication, we discuss the influence of remote substituents on the basicity of 2-(*N,N*-dimethylamino) analogues.

The substituted 2-(*N,N*-dimethylamino)chromones **2–13** were prepared, as described previously,[1] following established routes.[5, 6] Their pK_a values in ethanol–water (1:1) were determined by potentiometric titration[7] and the results are detailed in Table 1. In chromone itself (pK_a 1.77),[8] protonation is favoured at the carbonyl oxygen, delocalisation of the ether oxygen lone pair stabilising the conjugate acid (Fig. 1a). The increased basicity of the title compounds (pK_a 1.92–2.52) may be attributed to the additional delocalisation of the nitrogen lone pair (Fig. 1b). Evidence for protonation at the carbonyl oxygen is provided by ^{13}C NMR data for solutions of the methoxy derivatives **9** and **11** in CD_3OD–D_2O (1:1) to which conc.HCl had been added in aliquots corresponding to 0.25, 0.50, 0.75 and 1.0 equivalents. In both cases, the most significant chemical shift changes (Δδ up to 7–8ppm upfield) were exhibited by the carbonyl carbon C(4). Moreover, AM1 semi-empirical MO calculations show that protonation of the oxygen atom is favoured over nitrogen by *ca* 27 kcal mol^{-1}.

From an examination of the tabulated data it is apparent that the measured pK_a values lie within a relatively narrow range, indicating that the remote substituents have *relatively* little effect. Their influence is, nevertheless, discernible. The trend observed for the 7-substituted derivatives [pK_a : **9** (R^3=OMe) > **2** (R^3= H) > **4** (R^3=F) ≃ **6** (R^3= Cl) ≃ **7** (R^3= Br)] reflects the general expectation that basicity should be increased by electron-releasing substituents and decreased by electron-withdrawing substituents. A similar pattern is exhibited by the 8-substituted derivatives [pK_a: **10** (R^4=OMe) > **2** (R^4= H) > **5** (R^4=F) > **6** (R^4= NO_2)], although the pK_a value for the 8-fluoro analogue **5** is lower than might have been expected (*vide infra*). The data for the 6-substituted derivatives, however, appear anomalous; the 6-methoxy compound **11** is *less* basic than the parent system **2** and, in spite of the presence of the strongly electron-withdrawing nitro group, the 6-nitro derivative **12** is comparable in basicity to the 7-halogeno analogues **4, 6 and 7**.



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Explanations for the anomalous data were sought in semi-empirical and *ab initio* calculations. Optimised AM1 semi-empirical geometries of the protonated 2-(*N,N*-dimethylamino)-chromones were used to calculate their heats of formation and the charges on the carbonyl oxygen, consideration being given to the possibility of syn or anti orientations of the proton. The oxygen charges were also calculated at the *ab initio* level (3–21G single point calculations on the AM1 geometries), except for the case where R^3=Br. Stabilisation energies, which reflect the influence of the substituents (R^1–R^4) on the relative stability of the protonated species, were calculated from an isodesmic equation [equation (1)] in which the AM1 heats of formation were used (Table 1). Plots of these stabilisation energies against the AM1 charges give reasonably linear correlations (r^2 = 0.97), as do plots of the charges against pK_a provided the data points for compounds **5, 8,** and **12** are omitted.[a] It thus appears that with the exception of these three compounds, the observed pK_a data are, in fact, essentially consistent with theoretical expectations.

The apparently anomalous behaviour of the 6-nitro derivative **12** may reflect substrate-specific intramolecular field effects or solvent-mediated hydrogen-bonding stabilisation of the conjugate acid, as illustrated in Fig. 2. In the case of the 8-nitro analogue **13**, such stabilisation is not possible and the

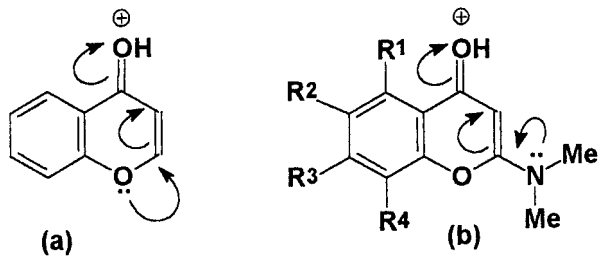
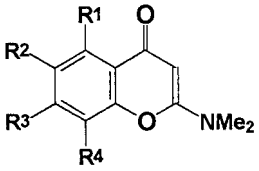


Fig. 1 Lone-pair delocalisation stabilising the conjugate acids of: (a) chromone and (b) the 2(*N,N*-dimethylamino)chromones **2–13**.

* To receive any correspondence.
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

[a]With successive inclusion of data for compounds **5**, **8** and **12**, the correlation coefficient decreases correspondingly (r^2 = 0.97 → 0.84 → 0.74 → 0.52). The 3–21G data exhibit a similar pattern.

Table 1 Data for 2-(N,N-dimethylamino)chromones **2–13**



Compd	R^1	R^2	R^3	R^4	pK_a [a]	S.E.[b] / kcal mol^{-1}	Calculated charge on carbonyl oxygen AM1	3–21G	Heat of formation /kcal mol^{-1} Neutral chromone	Protonated chromone[c]
2	H	H	H	H	2.47	0	–0.324	–0.640	–11.47	127.30
3	H	F	H	H	2.20	3.19	–0.317	–0.633	–55.47	86.49
4	H	H	F	H	2.25	2.69	–0.322	–0.638	–56.16	85.30
5	H	H	H	F	1.98	2.79	–0.304	–0.634	–54.07	87.49
6	H	H	Cl	H	2.22	2.16	–0.321	–0.636	–17.87	123.06
7	H	H	Br	H	2.26	2.67	–0.319	–[d]	–5.64	135.79
8	MeO	H	H	H	2.52	–6.80	–0.300	–0.614	–45.13	86.84
9	H	H	MeO	H	2.52	–1.88	–0.327	–0.644	–49.77	87.11
10	H	H	H	MeO	2.50	–1.83	–0.325	–0.639	–46.19	90.75
11	H	MeO	H	H	2.39	–0.30	–0.326	–0.643	–48.87	89.59
12	H	NO_2	H	H	2.27	9.55	–0.306	–0.626	–6.66	141.65
13	H	H	H	NO_2	1.92	7.32	–0.318	–0.635	–5.26	140.83

[a]At 25°C in H_2O-EtOH (1:1); estimated error ± 0.06. [b]Stabilisation energy (AM1) relative to **2**; see equation 1.
[c]Anti conformer, with the exception of compound **8**. [d]The substituent, Br, is not included in the basis set used.

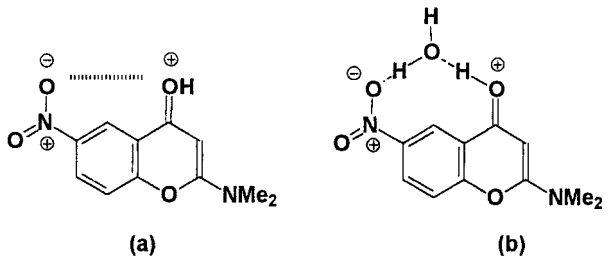


Fig. 2 Possible stabilisation of the protonated 6-nitro derivative **12** by: (a) an intramolecular field effect; and (b) solvent-mediated hydrogen bonding.

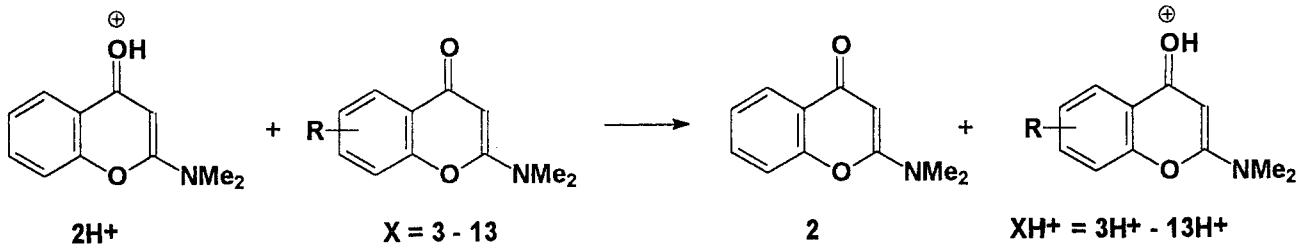
low pK_a value (1.92) clearly reflects the electron-withdrawing character of the 8-nitro substituent. While the three methoxy derivatives **8**, **9** and **10** exhibit similar basicities (pK_a *ca* 2.5), the 5-methoxy analogue **8** has a significantly more negative stabilisation energy (–6.80 kcal mol^{-1}), which accounts for its poor correlation and which probably arises from two factors, *viz*: (i) relative destabilisation of the free base **8**, and (ii) intramolecular hydrogen-bonding stabilisation of the conjugate acid. Hydrogen-bonding effects may also explain the low pK_a value (1.98) measured for the 8-fluoro analogue **5**, in that the juxtaposition of the fluorine and pyran oxygen atoms may permit chelation of a water molecule. Such intra-molecular hydrogen-bonding would not only inhibit lone-pair delocalisation by both atoms into the chromone nucleus, but also expose the electron-withdrawing inductive effect of the fluorine substituent.

Experimental

Materials: The 2-(*N*,*N*-dimethylamino)chromones **2–13,** which were prepared following literature methods[1,5, 6] and which gave satisfactory spectroscopic analyses, were purified, where necessary, by flash chromatography and recrystallisation. Compounds **3**, **5**, **8**, **10** and **13** are new and gave satisfactory elemental (high-resolution MS) analyses. Aqueous-ethanolic solutions of the 2-(*N*,*N*-dimethylamino) chromones were prepared by dissolution of the appropriate quantity in distilled absolute EtOH (10 ml) and dilution with H_2O (boiled prior to use; 9mL) to afford, at half-neutralisation point, aliquots (20ml) having a concentration of 0.01 mol dm^{-3}.

Method: The stirred 2-(*N*,*N*-dimethylamino)chromone solutions were titrated against hydrochloric acid (0.1063 mol.dm^{-3}) at 25 ± 0.1 °C (stirring was stopped when taking pH readings). The titrant was added in 0.20 ml portions, the pH being measured after each addition using Beckmann ϕ50 and Mettler Toledo MP225 pH meters and calibrated at pH 4.008 (using a potassium hydrogen phthalate buffer) and at pH 1.679 (using a potassium tetroxalate buffer). All titrations were replicated, and the pK_a values of the 2-(*N*,*N*-dimethylamino) chromones **2-13** determined following the method described by Albert and Serjeant.[7]

Computational details: Computations were effected using HyperChem (release 4.5)[9] and MOPAC (version 6.0)[10] packages on personal computers (Pentium 90MHz/16MB RAM and 133MHz/32MB RAM). Structures were assembled in HyperChem and partially refined using its MM+ molecular mechanics facility before being exported to MOPAC. Geometries were then optimised without constraint through implementation of the AM1 Hamiltonian and using the eigenvector-following routine (keyword EF). Use of the keyword PRECISE ensured that all geometry optimisations achieved energy gradient norms of at least 0.01kcal mol^{-1} Å^{-1}. Single-point HF/3-21G *ab initio* calculations on selected structures were carried out in HyperChem to an SCF convergence limit of 1x10^{-5} kcal mol^{-1}. Convergences were accelerated through application of the DIIS procedure.



Stabilisation energy = [ΔHf (**2**) + ΔHf (**XH$^+$**)] – [ΔHf (**2H$^+$**) + ΔHf (**X**)] (1)

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