

Electrophilic Aromatic Reactivities via Ring–Chain Tautomerism of Tetrahydro-1,3-Oxazines and 1,3-Oxazolidines

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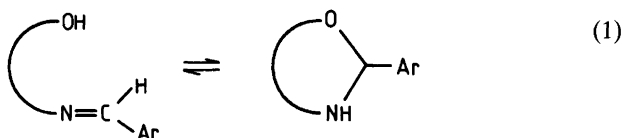
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Brown's electrophilic σ^+ -constants have been estimated for 2-, 3- and 4-pyridyl substituents with the aid of the ring-chain tautomeric equilibria of several sets of 2-aryl substituted 1,3-oxazolidines and 1,3-oxazines at ambient temperature. The σ^+ -values so obtained were best comparable to those determined earlier by solvolytic methods except that for 2-pyridyl which was approximately double. This deviation is due to extra stabilization of the ring from (by ca. 2–3 kJ mol⁻¹) caused by intramolecular hydrogen bonding as indicated by FT-IR measurements.

To determine Brown's¹ electrophilic substituent constants (σ^+) for different heteroaromatic systems is of current interest.² The earlier determinations³ are based on kinetic measurements carried out with different methods such as bromination, hydrogen exchange, nitration, pyrolysis, and solvolysis.

The ring-chain tautomerism of 1,3-O,N-heterocycles [eqn. (1)] is a well known process. McDonagh and Smith⁴



published the first quantitative data, measured by ¹H NMR spectroscopy, and found a linear correlation between log *K* and Hammett σ values. Later Paukstelis⁵ found a better correlation between log *K* with Hammett–Brown σ^+ values. Recently, in comparative studies of differently substituted 2-aryltetrahydro-1,3-oxazine⁶ and 1,3-oxazolidine^{7–9} systems it has been found that the ring-chain tautomeric process can be described by eqn. (2) where

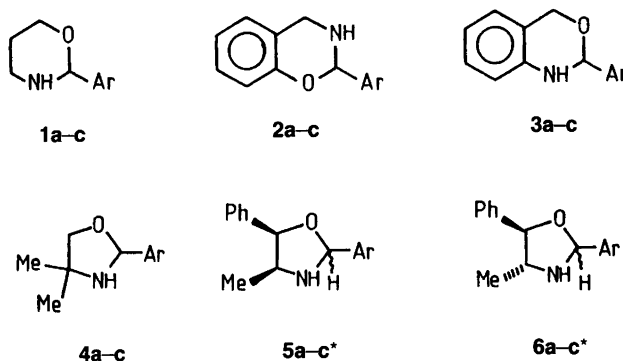
$$\log K_x = \rho\sigma^+ + c \quad (2)$$

$K_x = [\text{ring}]/[\text{chain}]$ and ρ is a constant characteristic for the ring system. The constant ρ depends only weakly, but c ($= \log K_H$) very strongly on the nature of the solvent used.

In CDCl₃ solution at ambient temperature ρ is, on

average, 0.76(4) for 1,3-oxazines⁶ and 0.57(3) for 1,3-oxazolidines.⁸ Therefore eqn. (2) offers a good means of evaluating σ^+ values. In order to estimate the σ^+ values for 2-, 3- and 4-pyridyl substituents a number of 1,3-oxazines (1–3) and 1,3-oxazolidines (4–6) was prepared from 3-aminopropanol, 2-hydroxybenzylamine, 2-aminobenzyl alcohol, 2-amino-2-methylpropanol, (\pm)-norephedrine and L-(–)-norpseudoephedrine and from the 2-, 3- and 4-pyridinecarbaldehydes. All condensations took place quantitatively at ambient temperature within 2 h.

Compounds 1–6 exist as mixtures of ring-chain tautomers [eqn. (1)], although only the ring forms are shown. The ring-chain tautomeric ratios were based on the integrals of the corresponding lines in the ¹H NMR spectra at 400 MHz. Earlier⁶ mainly the 2-H (ring form, ca. 5.5 ppm) and the corresponding CH=N (open-chain form, ca. 8.3 ppm) lines were used for integration, but in the present study the pyridyl protons often overlap the 8.3 ppm region, and other well separated lines, sometimes from the aromatic, some-



a, Ar = 2-pyridyl; b, 3-pyridyl; c, 4-pyridyl.

* Both C-2 epimers are present in the solvent in a ca. 1:1 ratio.

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Table 1. Ring-chain ratios and calculated σ^+ values for compounds (1–6)a–c.

Compound	Ring form (%)	log <i>K</i>	Calculated σ^+ values
1a	89	0.908	1.43
2a	71	0.389	1.28
3a^a			
4a	92	1.061	1.29
5a	76 ^b	0.501	1.59
6a	95 ^b	1.279	1.77
			Average 1.5±0.2
1b	62.5	0.222	0.50
2b	36	−0.250	0.50
3b^a			
4b	79	0.575	0.41
5b	44 ^b	−0.105	0.47
6b	81.5 ^b	0.644	0.57
			Average 0.49±0.05
1c	86	0.788	1.27
2c	71	0.389	1.28
3c^a			
4c	91	1.005	1.19
5c	70 ^b	0.368	1.35
6c	92 ^b	1.061	1.36
			Average 1.29±0.06

^aDue to the overlapping lines the ring-chain ratio could not be reliably determined. ^bThe combined amount of the C-2 epimers.

times from the aliphatic region were integrated. Due to the interference caused by the pyridyl protons the percentage contributions of ring form shown in Table 1 could be evaluated only to within ±0.5%.

For the calculation of the σ^+ values for the pyridyl substituents eqn. (2) and the actual ρ and c values (1, 0.74 and −0.15; 2, 0.82 and −0.66; 3, 0.78 and 1.11; 4, 0.55 and 0.35; 5, 0.54 and −0.36; 6, 0.53 and 0.34, respectively) taken from literature^{6,8,9} were used (Table 1).

Table 2 lists the σ^+ values found in literature for the 2-, 3-, and 4-pyridyl substituents. The σ^+ values given by our approach for 3- and 4-pyridyl groups are practically equal to the solvolytic values, which can often be determined most reliably.

Table 2. Hammett–Brown σ^+ constants for pyridyl substituents.

Method	Lit.	2-Py	3-Py	4-Py
Pyrolysis	10	0.80	0.30	0.87
Rate of deuteration	11	—	—	0.67
Nitration	12	—	0.60–0.71	—
Solvolysis	13	0.72–0.73	0.45–0.57	1.13–1.20
Solvolysis	14	0.75	0.54	1.16
Pyrolysis	15	0.76–0.89	0.28–0.30	0.85–0.87
Ring-chain tautomerism	This work	1.5±0.2	0.49±0.05	1.29±0.06

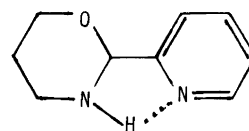


Fig. 1.

For the 2-pyridyl substituent our σ^+ value was, on average, twice as big as the earlier ones. This is, however, easy to explain. Obviously the ring form of these derivatives is subject to extra stabilization (by ca. 2–3 kJ mol^{−1}) due to an intramolecular hydrogen bond (see Fig. 1). The somewhat higher scattering of the σ^+ values of the 2-pyridyl derivatives (1a–6a) than that of the 3- and 4-pyridyl series can result from some variation in the strengths of the intramolecular hydrogen bonds and/or in the role of intermolecular hydrogen bonds via the hydroxylic groups of the open-chain forms. Intramolecular hydrogen bonding in the open-chain forms would require formation of an unfavourable nine-membered ring. In order to verify the above conclusion the concentration-dependent (0.1–0.004 mol dm^{−3}) FT-IR spectra of 1a and 6a were studied in CDCl₃ solution. In both cases a strong absorption corresponding to the intramolecular hydrogen bond in the ring form (see the formula) was found at 3320 and 3277 cm^{−1}, respectively. According to the FT-IR spectra, the open-chain form of compound 1a exhibited much stronger intermolecular hydrogen bonds than that of compound 6a (in both cases the amount of this type of bonding decreased with decreasing concentration) thus counterbalancing the stabilizing effect of the intramolecular hydrogen bond in the ring form. Therefore the ring form of 6a is somewhat more stabilized in relation to its open-chain form than is the case for 1a. This situation is in turn reflected in the substantially larger σ^+ value of 6a.

Thus the present results prove that ring-chain tautomerism is a simple and quick method of determining, e.g. the Hammett–Brown σ^+ constants. On the other hand, it can also be concluded that the distinct ρ values for 1,3-oxazines and 1,3-oxazolidines, even if they are constant at a given temperature within each series of compounds, reflect their different physical behaviour.

Experimental

All reactants were commercial products except 2-hydroxybenzylamine which was prepared according to a literature¹⁶ method.

¹H NMR spectra were recorded at ambient temperature on a JEOL GX-400 FT NMR spectrometer in CDCl₃ (3–5 mg per 2 cm³), at 298(2) K with Me₄Si as an internal standard. The number of data points was 32 K and that of scans usually 40 (sometimes 80).⁶ The determination of ring–chain tautomeric ratios was generally based on the integrals of methylene and methine protons. If these protons were not well separated, other well-separated signals were used.

The IR spectra of **1a** and **6a** were recorded on a Mattson Galaxy 6020 FT-IR spectrophotometer in 0.1, 0.05, 0.025 and 0.004 mol dm⁻³ CDCl₃ solutions. A variable path-length cell with KBr windows was used to ensure that the same number of absorbing molecules was present in each measurement.

General procedure for the reaction of amino alcohols with pyridinecarbaldehydes. The amino alcohol (1 mmol) was dissolved in 10 cm³ of absolute ethanol, and 1 mmol of the pyridinecarbaldehyde was added. After the mixture had been allowed to stand for 2 h at room temperature, the solvent was evaporated off. Most of the products were oily – they were dried under vacuum for 24 h. The crystalline products were recrystallized once; **2b**, m.p. 124–126 °C, EtOAc; **2c**, 161–163 °C, EtOH; **3b**, 97–99 °C, hexane; **3c**, 94–95 °C, hexane; **6c**, 126–130 °C, hexane/acetone. According to their ¹H NMR spectra the purity of all products was more than 97%. All compounds gave satisfactory micro-analyses: C, H, N.

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