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The Hammett-Brown electrophilic substituent constants  $\sigma^+$  for five heteroaryl-substituted phenyl groups were estimated *via* the ring-chain tautomeric equilibria of three sets of oxazolidines and 1,3-oxazines in deuteriochloroform solution. For oxazolidines derived from norephedrine and norpseudoeephedrine, the  $\sigma^+$  values were also determined *via* the gas-phase ring-chain equilibria, by means of mass spectrometry. The results show that the heteroaromatic substituents studied have a slight electron-withdrawing character, with  $\sigma^+$  in the range -0.03 to 0.59. The gas-phase  $\sigma^+$  values are significantly higher than the solution values.

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### Introduction.

The ring-chain tautomerism of tetrahydro-1,3-oxazines and oxazolidines, which involves the reversible addition of a hydroxy group to a C=N bond, is a well-established process; it was recently reviewed [2,3]. The effects of substituents on the tautomerism of 2-aryl-substituted tetrahydro-1,3-oxazines and oxazolidines have been studied in detail [4,5]. In all series, the ring-chain tautomeric equilibria measured in deuteriochloroform at room temperature can be described by the equation

$$\log K_X = \rho \cdot \sigma^+ + c \quad (1)$$

where  $K_X = [\text{ring}(s)]/[\text{chain}(s)]$ ,  $\sigma^+$  is the Hammett-Brown substituent constant and  $c = \log K_{X=H}$ . The measured data show that  $\rho$  is characteristic of the ring systems, whereas the intercept values  $c$  are characteristic of the substituents [4,5].

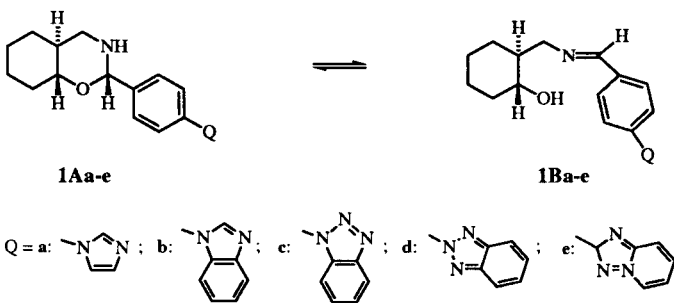
Table 1

Characteristic  $^1\text{H}$  NMR Chemical Shifts, Ring-chain Ratios and Calculated  $\sigma^+$  Values for Compounds 1a-e, 2a-e, 3a-e and 4a-e

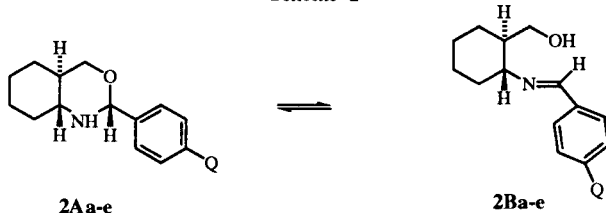
| Compound | Chemical shifts ( $\delta$ , ppm) |           | Ring form [a]<br>(%) | log K  | Calculated $\sigma^+$ |
|----------|-----------------------------------|-----------|----------------------|--------|-----------------------|
|          | O-CH-N (s)                        | -CH=N (s) |                      |        |                       |
| 1a       | 5.25                              | 8.24      | 81                   | 0.630  | 0.18                  |
| 1b       | 5.30                              | 8.28      | 85                   | 0.753  | 0.35                  |
| 1c       | 5.33                              | 8.31      | 84                   | 0.720  | 0.30                  |
| 1d       | 5.30                              | 8.28      | 80                   | 0.602  | 0.14                  |
| 1e       | 5.29                              | [b]       | 75                   | 0.477  | -0.03                 |
| 2a       | 5.25                              | [b]       | >98                  |        | [c]                   |
| 2b       | 5.30                              | [b]       | >98                  |        | [c]                   |
| 2c       | 5.32                              | [b]       | >98                  |        | [c]                   |
| 2d       | 5.28                              | [b]       | >98                  |        | [c]                   |
| 2e       | 5.28                              | [b]       | >98                  |        | [c]                   |
| 3a       | 5.66, 6.13                        | 8.27      | 37                   | -0.231 | 0.24                  |
| 3b       | 5.72, 6.19                        | 8.34      | 41                   | -0.158 | 0.37                  |
| 3c       | 5.72, 6.18                        | 8.32      | 38                   | -0.213 | 0.27                  |
| 3d       | 5.73, 6.17                        | 8.34      | 37                   | -0.231 | 0.24                  |
| 3e       | 5.71, 6.15                        | [b]       | 30                   | -0.368 | -0.01                 |
| 4a       | 5.85, 5.93                        | 8.34      | 73                   | 0.432  | 0.17                  |
| 4b       | 5.89, 5.98                        | 8.39      | 76                   | 0.501  | 0.30                  |
| 4c       | 5.92, 6.00                        | 8.40      | 77                   | 0.525  | 0.35                  |
| 4d       | 5.89, 5.98                        | [b]       | 74                   | 0.454  | 0.22                  |
| 4e       | 5.87, 5.96                        | [b]       | 69                   | 0.347  | 0.01                  |

[a] For 3 and 4, the sum of the two ring forms is given. [b] Overlaps with the aromatic lines. [c] See the text.

Scheme 1



Scheme 2



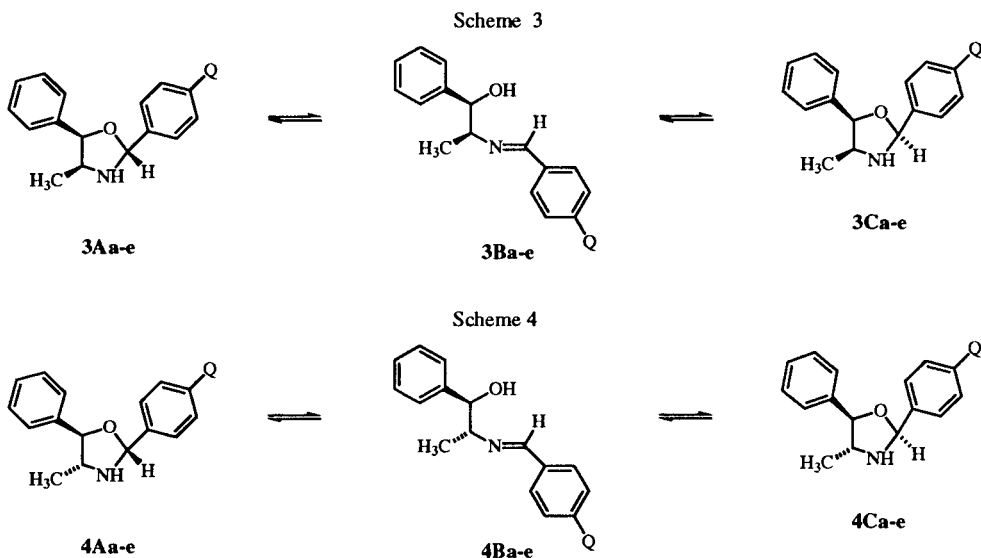


Table 2

$\sigma^+$  Values Determined Mass Spectrometrically in the Gas Phase at 14 eV, Based on  $K = [\text{ring}]/[\text{chain}] = [\text{B}]/[\text{A}] = [\text{M}-106]^{++} / [\text{M}-107]^+$

| Compound | [A]  | [B]  | log K | $\sigma^+$ |
|----------|------|------|-------|------------|
| 3a       | 40.7 | 91.5 | 0.352 | 0.37±0.05  |
| 4a       | 29.0 | 93.9 | 0.510 | 0.39±0.12  |
| 3b       | 31.1 | 92.1 | 0.471 | 0.58±0.12  |
| 4b       | 22.6 | 94.3 | 0.620 | 0.59±0.09  |
| 3c       | 31.8 | 92.3 | 0.465 | 0.56±0.11  |
| 4c       | 24.8 | 94.0 | 0.579 | 0.52±0.14  |
| 3d       | 40.0 | 90.2 | 0.353 | 0.36±0.05  |
| 4d       | 28.3 | 93.1 | 0.517 | 0.40±0.09  |
| 3e       | 45.5 | 89.0 | 0.291 | 0.26±0.02  |
| 4e       | 31.9 | 92.3 | 0.461 | 0.30±0.07  |

For characterization of the steric and electronic contributions of the substituents, a constant has been introduced, defined as the intercept difference for the basic system and the compound in question. A positive constant indicates stabilization of the ring form, while a negative value means a destabilizing effect of the substituents [4,5].

By means of ring-chain tautomerism, numerous reactions of tetrahydro-1,3-oxazines and oxazolidines, such as ring opening with nucleophiles, C-2 epimerization, transimination, *etc.*, can be rationalized [6].

For prediction of the behavior of substituents, the determination of electrophilic substituent constants is of cur-

Table 3

Effect of Probe Temperature on  $\sigma^+$  Values Determined Mass Spectrometrically in the Gas Phase at 14 eV for Compound 4d

| T (K) | [A]  | [B]  | log K | $\sigma^+$ |
|-------|------|------|-------|------------|
| 393   | 15.8 | 96.2 | 0.784 | 0.88       |
| 403   | 12.6 | 96.9 | 0.886 | 1.06       |
| 423   | 33.6 | 91.1 | 0.437 | 0.25       |
| 433   | 30.5 | 92.6 | 0.482 | 0.33       |
| 443   | 32.9 | 92.0 | 0.446 | 0.27       |

Table 4

Averages of Calculated  $\sigma^+$  Values Determined in Solution and in the Gas Phase

| Substituent | $\sigma^+$ solution | $\sigma^+$ gas phase | $\Delta$ [a] |
|-------------|---------------------|----------------------|--------------|
| a           | 0.20                | 0.38                 | 0.18         |
| b           | 0.34                | 0.59                 | 0.25         |
| c           | 0.31                | 0.54                 | 0.23         |
| d           | 0.20                | 0.38                 | 0.18         |
| e           | -0.01               | 0.28                 | 0.29         |

[a]  $\Delta = \sigma^+$  gas phase -  $\sigma^+$  solution.

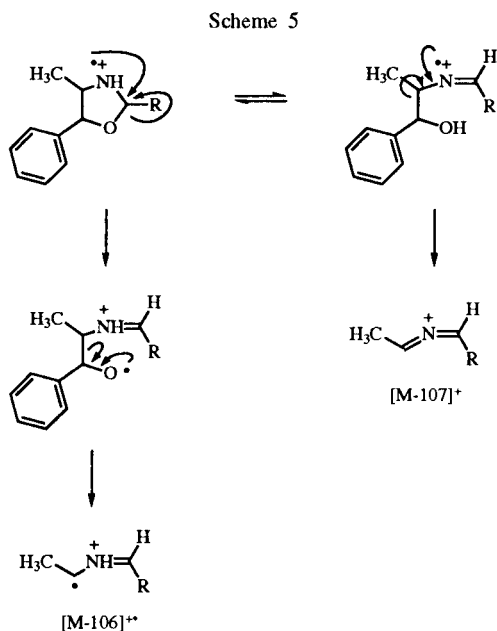


Table 5  
Analytical Data on Compounds **1a-e**, **2a-e**, **3a-e** and **4a-e**

| Compound  | Mp (°C)<br>Solvent | Molecular Formula<br>MW                          | Analysis Calcd. %/Found % |      |       |
|-----------|--------------------|--|---------------------------|------|-------|
|           |                    |  | C                         | H    | N     |
| <b>1a</b> | 99-101             | C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O | 72.06                     | 7.47 | 14.83 |
|           | Et <sub>2</sub> O  | 283.38   | 71.96                     | 7.60 | 14.65 |
| <b>1b</b> | 120-122            | C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> O | 75.65                     | 6.95 | 12.60 |
|           | MeOH               | 333.44   | 75.78                     | 6.99 | 12.59 |
| <b>1c</b> | 141-142            | C <sub>20</sub> H <sub>22</sub> N <sub>4</sub> O | 71.83                     | 6.63 | 16.75 |
|           | MeOH               | 334.43   | 71.89                     | 6.66 | 17.02 |
| <b>1d</b> | 176-179            | C <sub>20</sub> H <sub>22</sub> N <sub>4</sub> O | 71.83                     | 6.63 | 16.75 |
|           | MeOH               | 334.43   | 71.77                     | 6.86 | 16.60 |
| <b>1e</b> | 168-172            | C <sub>20</sub> H <sub>22</sub> N <sub>4</sub> O | 71.83                     | 6.63 | 16.75 |
|           | MeOH               | 334.43   | 71.70                     | 6.89 | 16.48 |
| <b>2a</b> | 97-99              | C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O | 72.06                     | 7.47 | 14.83 |
|           | Hexane             | 283.38   | 72.30                     | 7.32 | 14.72 |
| <b>2b</b> | 114-117            | C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> O | 75.65                     | 6.95 | 12.60 |
|           | Hexane             | 333.44   | 75.50                     | 7.12 | 12.48 |
| <b>2c</b> | 113-115            | C <sub>20</sub> H <sub>22</sub> N <sub>4</sub> O | 71.83                     | 6.63 | 16.75 |
|           | MeOH               | 334.43   | 71.65                     | 6.89 | 16.44 |
| <b>2d</b> | 154-155            | C <sub>20</sub> H <sub>22</sub> N <sub>4</sub> O | 71.83                     | 6.63 | 16.75 |
|           | MeOH               | 334.43   | 71.70                     | 6.90 | 16.49 |
| <b>2e</b> | 161-163            | C <sub>20</sub> H <sub>22</sub> N <sub>4</sub> O | 71.83                     | 6.63 | 16.75 |
|           | MeOH               | 334.43   | 71.72                     | 6.68 | 16.81 |
| <b>3a</b> | 117-120            | C <sub>19</sub> H <sub>19</sub> N <sub>3</sub> O | 74.73                     | 6.27 | 13.76 |
|           | Et <sub>2</sub> O  | 305.38   | 74.64                     | 6.50 | 13.72 |
| <b>3b</b> | 108-109            | C <sub>23</sub> H <sub>21</sub> N <sub>3</sub> O | 77.72                     | 5.96 | 11.82 |
|           | Hexane             | 355.45   | 77.84                     | 6.23 | 11.59 |
| <b>3c</b> | [a]                | C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O | 74.14                     | 5.66 | 15.72 |
|           |                    | 356.43   |                           |      |       |
| <b>3d</b> | 125-126            | C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O | 74.14                     | 5.66 | 15.72 |
|           | MeOH               | 356.43   | 73.89                     | 5.87 | 16.75 |
| <b>3e</b> | 148-149            | C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O | 74.14                     | 5.66 | 15.72 |
|           | MeOH               | 356.43   | 73.93                     | 5.76 | 15.77 |
| <b>4a</b> | 160-161            | C <sub>19</sub> H <sub>19</sub> N <sub>3</sub> O | 74.73                     | 6.27 | 13.76 |
|           | Et <sub>2</sub> O  | 305.38   | 74.61                     | 6.41 | 13.79 |
| <b>4b</b> | 129-133            | C <sub>23</sub> H <sub>21</sub> N <sub>3</sub> O | 77.72                     | 5.96 | 11.82 |
|           | Hexane             | 355.45   | 77.81                     | 6.04 | 11.69 |
| <b>4c</b> | 150-151            | C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O | 74.14                     | 5.66 | 15.72 |
|           | Hexane             | 356.43   | 73.96                     | 5.81 | 15.48 |
| <b>4d</b> | 169-170            | C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O | 74.14                     | 5.66 | 15.72 |
|           | MeOH               | 356.43   | 74.34                     | 5.80 | 15.66 |
| <b>4e</b> | 161-162            | C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O | 74.14                     | 5.66 | 15.72 |
|           | MeOH               | 356.43   | 74.01                     | 5.71 | 17.45 |

[a] The nmr spectrum indicated that the purity of **3c** was more than 96%.

rent interest from a chemical aspect [7-10]. The establishment of optimal substituents is also of pharmacological importance in drug research [11].

Our present aim was to estimate Hammett-Brown substituent constants  $\sigma^+$  for heteroaryl-substituted phenyl groups *via* ring-chain tautomerism. The method was recently successfully used to determine the  $\sigma^+$  data for 3- and 4-pyridyl substituents [12].

#### Results and Discussion.

For estimation of the  $\sigma^+$  values of five heteroaryl-substituted phenyl groups, series of tetrahydro-1,3-oxazines **1**, **2** and oxazolidines **3**, **4** were prepared by the reactions of the corresponding aldehydes with *trans*-2-amino-methylcyclohexanol, *trans*-2-hydroxymethylcyclohexyl-

amine, norephedrine or norpseudoephedrine. The condensations took place almost quantitatively within 3 hours at room temperature.

As Schemes 1-4 show, **1-4** exist as mixtures of ring-chain tautomers in deuteriochloroform solution [13]. The ring-chain ratios were determined from the integrals of the methylene (open forms) and methine (ring forms) protons. In some cases, other well-separated peaks were used to calculate the ring-chain ratios. For **1a-e** and **2a-e**, the tautomeric mixture contains two components (ring and chain), while for **3a-e** and **4a-e** the mixtures exist as three-component (ring<sup>1</sup>-open-ring<sup>2</sup>) equilibria. This difference can be explained in that the energy difference between the two epimeric forms is much higher for the six-membered system than for the five-membered oxazolidines.

In **2**, the ring form predominated, the open-chain form comprising less than 2-3%, and these data could therefore not be used in the calculations.

For calculation of the  $\sigma^+$  values of the different heteroaryl-substituted phenyl groups, eq (1) and the  $\rho$  and  $c$  values measured earlier [4,14] were utilized. The  $\rho$  and  $c$  values used were as follows: **1**,  $\rho = 0.73$ ,  $c = 0.50$ ; **3**,  $\rho = 0.54$ ,  $c = -0.36$ ; **4**,  $\rho = 0.53$ ,  $c = 0.34$ .

Table 1 lists the ring-chain ratios, the calculated  $\sigma^+$  values and also the average  $\sigma^+$  values for the five heteroaryl-substituted phenyl groups a-e. The results show that the heteroaromatic substituents studied have a slight electron-withdrawing character, with  $\sigma^+$  in the range 0.1 to 0.4.

#### Gas-phase Results.

Our earlier results [15,16] showed that eq (1) holds for the gas-phase tautomeric equilibria of oxazolidines derived from norephedrine and norpseudoephedrine. For comparison, the  $\sigma^+$  values were calculated by using the gas-phase equilibria of **3a-e** and **4a-e**.

The mass spectrometric behavior of **3a-e** and **4a-e** closely resembled that of other norephedrine and norpseudoephedrine derivatives. The molecular ion peaks were small or non-existent. Even under 70 eV electron impact, only two abundant fragment ions were present, e.g.  $[M-106]^+$  and  $[M-107]^+$ , reflecting the loss of  $C_7H_6O$  and  $C_7H_7O^+$  respectively, from the molecular ions. The formation of these fragment ions can be explained by radical site-initiated cleavage reactions (Scheme 5), which are typical reactions when a molecule contains a heteroatom, especially nitrogen.

As previously, the ratio of the abundances of the ions  $[M-106]^+$  and  $[M-107]^+$  (14 eV) was taken as a measure of the [ring]/[chain] equilibrium. For the calculation of  $\sigma^+$ , eq (1) was used, where the actual  $\rho$  and  $c$  values are as follows [15]: norephedrine derivatives **3**: 0.58 and 0.15 (14 eV), and norpseudoephedrine derivatives **4**: 0.55 and 0.30 (14 eV). The results obtained are presented in Table 2.

When mass spectrometry is used to study ring-chain tautomerism, the question always arises of whether or not a real gas-phase equilibrium has been achieved. In order to obtain insight into this problem, the ring-chain equilibrium for **4d** was studied as a function of probe temperature (Table 3). At low temperatures, the relative amount of the ring form was larger than that at higher temperatures, but above a certain temperature, the ratio [B]/[A] remained constant, showing that the solid-phase equilibrium has no effect on the equilibrium observed in the gas phase. The higher relative amount of the ring form at low temperatures is due to its higher volatility than that of the chain form.

Thus, the results presented in Table 4 show, that ring-chain tautomerism permits a simple and quick method for determination of the constants  $\sigma^+$ , both in solution and in the gas phase. The results reveal that the heteroaromatic substituents

studied have a slight electron-withdrawing character, except in **e**, where there is a bridgehead nitrogen. The gas-phase  $\sigma^+$  values are significantly higher than the solution values.

## EXPERIMENTAL

( $\pm$ )-Norephedrine and L(-)-norpseudoephedrine were commercial products. ( $\pm$ )-*trans*-2-Aminomethyl-1-cyclohexanol [17], ( $\pm$ )-*trans*-2-hydroxymethyl-1-cyclohexylamine [18] and heteroaryl-substituted benzaldehydes [19-24] were prepared according to literature procedures.

$^1H$  nmr spectra were recorded in deuteriochloroform solution, at ambient temperature on a Bruker DRX 400 MHz nmr spectrometer, with TMS as internal standard. The number of scans was usually 40. The spectra were run 24 hours after dissolution of the substance, to reach constant tautomeric rates [4,14]. The determination of the ring-chain tautomeric ratios was generally based on the integrals of the methylene and methine protons. If these signals were not well separated, other well-separated peaks were integrated.

Mass spectrometric measurements were made with a Jeol JMS D300 mass spectrometer equipped with a combined EI/CI ion source and connected to a personal computer equipped with Windows-based software: The Shrader System (Shrader Laboratories Inc., Detroit, USA). Samples were introduced through a direct inlet probe at 433 K. Typical source conditions were: temperature 443 K, electron energies 14 eV and 70 eV, accelerating voltage 3 kV and ionization current 300  $\mu A$ , if not stated otherwise.

#### General Procedure for Reaction of Amino Alcohols with Aldehydes.

The appropriate amino alcohol (0.5 mmole) was dissolved in 5 ml of absolute ethanol and 0.5 mmole of the aldehyde was added. The mixture was left to stand for 3 hours at room temperature, and the solvent was then evaporated off. The oily products were triturated with hexane or diethyl ether, giving crystalline products (Table 5). Compound **2b** remained oily, and was dried in a vacuum desiccator for 24 hours.

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