# Quaternization Reaction of Aromatic Heterocyclic Imines in Methanol − A Case of Strong Anti-Reactivity Selectivity Principle with Isoselective Temperature

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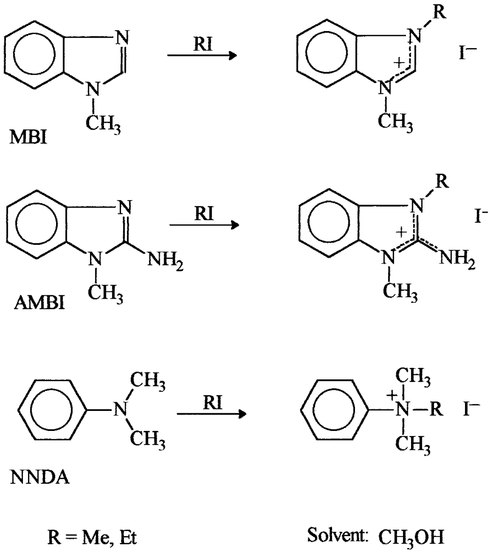
Accurate second-order rate constants were measured at 5 °C intervals in the temperature range 20–60 °C for the Menshutkin reaction of 1-methylbenzimidazole, 2-amino-1-methylbenzimidazole and *N*,*N*-dimethylaniline with iodomethane and iodoethane in methanol. In every case a good linearity in the Eyring plots was observed. Values for the activation enthalpy and entropy are reported. Analysis in terms of Exner's redefinition of the reactivity–selectivity principle (RSP) identified the present reaction series as a case of strong anti-RSP for selectivity towards the substrate. This case is shown to represent an isoselective relationship with the isoselective temperature lower than the experimental temperatures ($\beta_{is}$ = –52 °C). The isokinetic relationship does not hold in the reaction series with a fixed substrate. These findings suggest an early transition state in the Menshutkin reaction of polyfunctional aromatic imines.

## Introduction

The quaternization reactions of nitrogen bases are of great importance in organic chemistry and biochemistry, and have played an important role in the development of reaction mechanisms. In previous works, the solvation characteristics of Menshutkin reactions (MR) in several aliphatic alcohols were analysed in terms of temperature and pressure effects.[1,2,3] Other thermodynamic and kinetic data for *N*-quaternization reactions were reviewed and discussed by Abboud and co-workers.[4,5,6] However, there are relatively few reports regarding quaternization reactions of polyfunctional aromatic imines,[7] which are frequently the basic or nucleophilic centre in biochemical pathways. More specifically, benzimidazole has been noted for its similarity in structure and size with the nucleobase purine.[8]

The MR is the classical example of an $S_N2$ ionogenic reaction, whose mechanism is usually described as a concerted $A_ND_N$ reaction in which the nucleophile displaces the leaving group in a single step, with no intermediate being formed.[9]



Scheme 1

In this work, we report rate constants for MR of the imines 1-methylbenzimidazole (MBI) and 2-amino-1-methylbenzimidazole (AMBI), and of the amine *N*,*N*-dimethylaniline (NNDA), with iodomethane (MeI) or iodoethane (EtI) (Scheme 1), in methanol (MeOH), in the temperature range 20−60 °C at ambient pressure. Owing to hydrogen-bonding interactions, nucleophilic displacement reactions are slower in methanol than in dipolar aprotic solvents of similar ionising power.[7b,10] However, this solvent effect does not shadow marked structural effects on rates and activation parameters. In fact, it was found that quaternization rates for the imine bases MBI and AMBI are more sensitive to an increase in temperature than for the amino base NNDA. These results are analysed in terms of extrathermodynamic relationships,[11] namely the reactivity−selectivity principle (RSP),[12] the isoselective relationship (ISR)[13] and the isokinetic relationship (IKR).[14] Although these concepts are interlinked, they are different. As a consequence of either its verification or failure, each one of these relationships can

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Table 1. Rate constants and mean deviations at different temperatures for quaternization reactions of nitrogen bases with MeI or EtI, in methanol

| $T$ [K] | $k(\sigma k)$ [$10^{-6}$ dm$^3$ mol$^{-1}$ s$^{-1}$][a] Nitrogen base + MeI | | | $k(\sigma k)$ [$10^{-7}$ dm$^3$ mol$^{-1}$ s$^{-1}$][a] Nitrogen base + EtI | | |
|---|---|---|---|---|---|---|
| | MBI | AMBI | NNDA | MBI | AMBI | NNDA |
| 293 | 1.900 (0.006) | 8.04 (0.03) | 36.10 (0.08) | 2.155 (0.007) | 3.56 (0.02) | 16.84 (0.04) |
| 298 | 3.535 (0.009) | 14.37 (0.04) | 55.9 (0.2) | 4.06 (0.01) | 6.95 (0.02) | 27.45 (0.09) |
| 303 | 6.08 (0.01) | 26.1 (0.2) | 83.7 (0.1) | 7.41 (0.05) | 12.83 (0.04) | 44.0 (0.1) |
| 308 | 10.28 (0.02) | 44.6 (0.1) | 127.4 (0.2) | 14.40 (0.04) | 24.71 (0.07) | 69.5 (0.1) |
| 313 | 17.09 (0.03) | 72.2 (0.4) | 189.0 (0.3) | 25.9 (0.1) | 45.5 (0.3) | 108.1 (0.2) |
| 318 | 28.38 (0.05) | 129.2 (0.2) | 276.6 (0.7) | 47.15 (0.09) | 81.0 (0.3) | 166.0 (0.3) |
| 323 | 44.9 (0.1) | 223 (1) | 399.8 (0.8) | 89.2 (0.4) | 138.4 (0.4) | 251.0 (0.5) |
| 328 | 71.3 (0.2) | 350 (1) | 572 (1) | 143.5 (0.4) | 247.0 (0.9) | 374.5 (0.8) |
| 333 | 111.7 (0.2) | 568 (4) | 807 (3) | 240 (2) | 420 (1) | 553.1 (0.9) |

[a] Rate constants are in temperature-independent units.

bring valuable mechanistic information in terms of similarity analysis. The RSP embodies the broad expectation that faster reactions entail decreasing selectivity of a given reagent for different substrates. At a more advanced level, both ISR and IKR draw conclusions from the observation of statistically validated linear correlations between enthalpies and entropies of activation. The IKR examines a possible enthalpy−entropy compensation within a single reaction series, whereas the ISR directs attention to this type of compensation between reaction series. In the present work, an interesting case of strong *anti*-RSP is found for which the ISR holds with an isoselective temperature well below the experimental range. IKR was not observed. These findings are interpreted in terms of structural effects on the enthalpy and entropy of activation.

## Results and Discussion

### Rate Constants and Activation Parameters

Rate constants, $k$, for the reactions in Scheme 1 are presented in Table 1. Accurate second-order rate constants with a mean deviation of less than 0.75% (with most of them < 0.5%) were obtained from conductivity data as explained in the exp. section. These values are expressed in temperature-independent concentration units referred to 298 K.

In polyfunctional nitrogen bases, the quaternization site should be at the imine nitrogen (see Scheme 1). Experimental evidence for this was obtained by TLC and $^1$H NMR spectroscopy (see Experimental Section), in accordance with related reactions[15] and with predictions based on the resonance structures for the quaternary cations that might be formed from MBI and AMBI.

The kinetic data in Table 1 were fitted by a least-squares method to the Eyring Equation:

$$\ln(k/T) = a + b/T \tag{1}$$

From the regression coefficients $a$ and $b$ and their standard deviations, the Gibbs energy of activation, $\Delta^{\ddagger}G^0$, the enthalpy of activation, $\Delta^{\ddagger}H^0$, the entropy of activation, $\Delta^{\ddagger}S^0$, and the respective standard deviations were calculated. These quantities are presented in Table 2. Activation parameters are referred to standard states whose concentrations are expressed in temperature-independent units.[16] The small standard deviations reported in Table 2 are a consequence of using a highly reliable conductance technique for obtaining rate constants,[1,3] coupled with measurements at nine different temperatures spanning a wide range under accurate temperature control.

Table 2. Thermodynamic functions of activation and standard deviations in methanol at 40 °C

| Reaction | Thermodynamic function of activation[a] $\Delta^{\ddagger}G^0$ ($\sigma\Delta^{\ddagger}G°$) [kJ mol$^{-1}$] | $\Delta^{\ddagger}H^0$ ($\sigma\Delta^{\ddagger}H°$) [kJ mol$^{-1}$] | $-\Delta^{\ddagger}S^0$ ($\sigma\Delta^{\ddagger}S°$) [J K$^{-1}$ mol$^{-1}$] |
|---|---|---|---|
| MBI + MeI | 105.47 (0.03) | 79.5 (0.4) | 82.7 (1.2) |
| AMBI + MeI | 101.53 (0.02) | 84.0 (0.6) | 55.9 (1.9) |
| NNDA + MeI | 99.22 (0.02) | 60.6 (0.1) | 123.1 (0.4) |
| MBI + EtI | 110.30 (0.03) | 94.2 (0.7) | 51.2 (2.2) |
| AMBI + EtI | 108.92 (0.02) | 94.2 (0.3) | 46.8 (1.0) |
| NNDA + EtI | 106.67 (0.02) | 68.3 (0.1) | 122.3 (0.1) |

[a] Referred to standard states whose concentration is 1 mol dm$^{-3}$ at 25 °C.

The reaction between MBI and MeI was previously studied by Kondo et al.[7a] They reported values at 30 °C for the rate constant and activation parameters that are within the uncertainties of the corresponding values given in Tables 1 and 2. For the reactions of NNDA with MeI and EtI, there is a reasonable agreement between our values and those determined by Harris and Weale.[17]

A preliminary analysis of the values in Table 2 for activation parameters indicated some degree of complexity. A significant structural difference between amines and imines is that the hybridization of the nitrogen nucleophile in the former is sp$^3$ and in the latter is sp$^2$. Since the nucleophilicity of an sp$^3$ base is generally stronger than that of an sp$^2$ base,[18] then the observed $\Delta^{\ddagger}G^0$ values (Table 2) follow this trend. Furthermore, in the absence of strong specific solvation effects, the activation enthalpy should also be a good measure of the nucleophilicity, as it is in the gas phase.[6] Although this expectation is broadly confirmed by the $\Delta^{\ddagger}H^0$ values (Table 2) while comparing amino (sp$^3$) and imino (sp$^2$) nitrogen nucleophiles, it fails to distinguish between the two imines. The present results could only be satisfact-

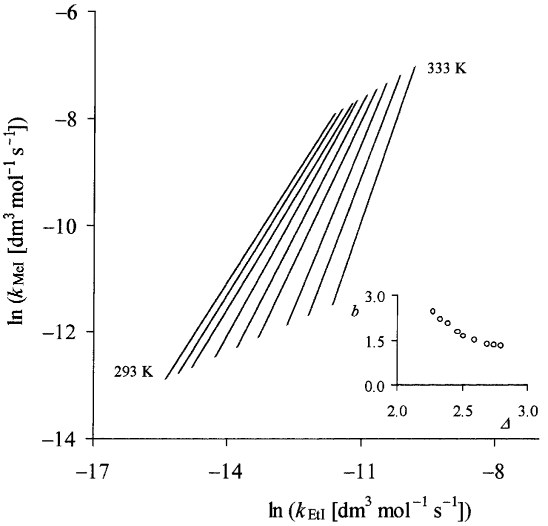

Figure 1. Reactivity−selectivity plot for the data in Table 1, showing a case of RSP(−); in the insert, slopes *b* from the RSP plot are marked as a function of the average selectivity Δ at each temperature

orily interpreted in terms of extra-thermodynamic relationships.

## Reactivity−Selectivity Principle

The selectivity of the different nucleophiles towards both substrates was analysed in terms of the RSP, using its modern formulation due to Exner.[12] Figure 1 shows a plot of fast reactivities ($\ln k_{MeI}$) against slow reactivities ($\ln k_{EtI}$). The slope *b* is always greater than unity, thus indicating that a reversal of RSP, denoted as RSP(−),[12] takes place. In other words, at each temperature the selectivity of the nucleophile increases with increasing nucleophilicity. Exner[12] also suggested that a possible linear correlation should be examined between slope *b* and the average selectivity Δ, which is measured by $\ln(k_{MeI}/k_{EtI})$. As shown in the insert to Figure 1, a fairly linear relationship corresponding to a strong RSP(−) in Exner's terminology is observed. In the present case, the straight lines in Figure 1 should intersect at one point situated on the side of high reactivity. Since we used the temperature to bring about different reaction conditions, this interesting example of a strong RSP(−) signals the presence of an isoselective relationship.

On the other hand, the quaternization of 3- and 4-substituted pyridines in 2-nitropropane as solvent was found to be a case of indifferent RSP.[19] However, we are led to speculate that this apparent failure of the RSP may be due to experimental conditions of temperature and solvent in which a cross-over RSP might be approached.

## Isoselective and Isokinetic Relationships

An ISR results from a particular temperature dependence of selectivities.[13] Using the data in Table 1 together with literature data for the nucleophile triethylamine,[1,20] a plot of nucleophile selectivity as a function of $T^{-1}$ was drawn (Figure 2). Interestingly, the present reactions behave well with respect to the temperature dependence of selectivities: the higher the temperature, the lower the selectivity. The data in Table 1 were fitted to the ISR Equation:[21]

$$\ln(k_{MeI}/k_{EtI})_{ij} = a + b_i(T_j^{-1} - \beta_{is}^{-1}) \quad (2)$$

where subscript *i* identifies the nucleophile (*i* = MBI, AMBI, NNDA) and *j* the reaction temperature, with *a*, $b_i$ and $\beta_{is}$ being adjustable parameters. Data for triethylamine were not included in this fit because the corresponding kinetic measurements were made in different laboratories using different techniques.[1,20] The mathematical problem of several regression lines constrained by one point of intersection[22] was readily solved (see exp. section), thus avoiding the approximate solution.[23] Figure 2 shows a family of straight lines intersecting at a common temperature. The latter point is designated as the isoselective temperature, $\beta_{is}$. The value $\beta_{is}$ = (221±12) K was obtained.

As shown by Exner and Giese,[21] the statistical validation of an ISR uses the same methods developed for validating an IKR.[14,22,23]

Here we followed a simple statistical analysis based on the *F*-test as recommended by Linert:[23]

$$F = (S_0/S_{00} - 1)f_2/f_1 \quad (3)$$

where $S_0$ and $S_{00}$ are the residual sum of squares for the constrained and unconstrained lines, respectively, $f_1$ is the number of straight lines minus one, and $f_2$ is the number of fitted points minus twice ($f_1$ + 1), i.e. the degrees of freedom in the constrained fit. From the calculated value *F* = 2.7391 the existence of an ISR cannot be rejected at a significance level higher than 90%. In other words, the present Menshutkin reactions appear to comply with the ISR. Furthermore, the alignment of the two points for the triethylamine (an aliphatic sp$^3$ nitrogen nucleophile) observed in Figure 2 allows us to suggest that the ISR may be of general validity in Menshutkin reactions.

According to Giese,[24] a low isoselective temperature, i.e. $\beta_{is}$ below the range of measurement, is to be expected for reactions with an early transition state, in which case violations of the RSP are frequent.[12,25] Hence, the present value of $\beta_{is}$ = −52 °C, together with a reversal of RSP, provide strong evidence for early transition states in the quaternization reaction of polyfunctional aromatic imines. This is in agreement with similar observations concerning Menshutkin reactions in general.[4,26] Also worthy of note in Figure 2 are the similar selectivity values that were found for NNDA and AMBI, despite striking structural differences in these nitrogen nucleophiles (Scheme 1). The latter differences are also evidenced by the dramatic variation in activation entropies when the nucleophile is changed from NNDA to AMBI (Table 2).

The verification of this ISR entails a proportionality between differences in activation enthalpies, $\Delta^{\ddagger}H^0_{EtI} - \Delta^{\ddagger}H^0_{MeI}$, and differences in activation entropies, $\Delta^{\ddagger}S^0_{EtI} - \Delta^{\ddagger}S^0_{MeI}$, $\beta_{is}$ being the corresponding proportionality constant.[24] In turn, an IKR expresses a linear relationship between enthalpies and entropies of activation within a given

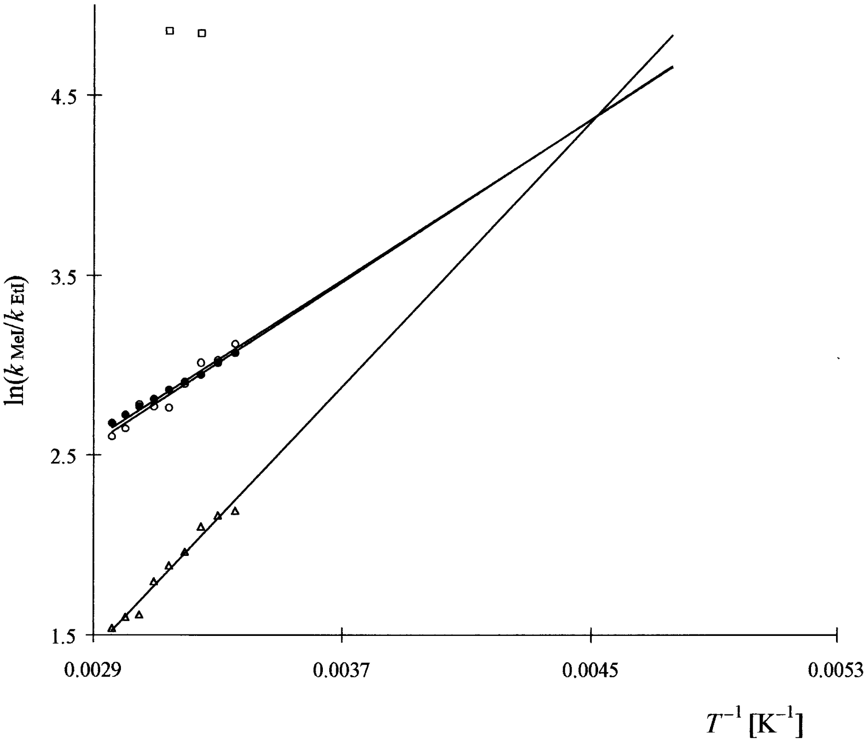

Figure 2. Isoselective plot for the data in Table 1; (●) NNDA, (○) AMBI, (Δ) MBI; the bundle of straight lines is drawn according to Equation (2), which gives an isoselective temperature $\beta_{is}$ = −52 °C; also shown are selectivity values for $Et_3N$ (□) as a nucleophile, calculated from literature data[1,20]

reaction series. Exner and Giese[21] have established the conditions for observing an ISR when each of two reaction series complies with the IKR. Thus Exner's plots for determining a possible IKR[11,14] for varying nucleophiles with each of the iodoalkanes were drawn. However, these plots showed zigzag lines that clearly indicated a failure of the IKR. Consequently, there is no enthalpy−entropy compensation arising from structural changes in the nucleophile, even though there is no doubt that these reactions share a common mechanism. Interestingly, contrary to a previous report[13] we have found two reaction series linked by an ISR, but for which the IKR does not hold. A coherent picture emerges in terms of similarity analysis. It appears that IKR fails because there is great structural variation in the nucleophiles, whereas the ISR holds because the substrates are very similar.

We observe that Exner's reformulation[12] of the RSP provides a useful starting point for similarity analysis in physical organic chemistry. Thus, while using the temperature to change the reaction conditions, a case of strong RSP(−) indicates that the ISR holds with an isoselective temperature lower than the experimental temperatures. Conversely, a case of strong RSP(+) should be associated with an ISR for which $\beta_{is}$ is higher than the experimental temperatures.

To conclude, we have found that the reactivity−selectivity principle[12] and the isoselectivity relationship[13,21,24] are powerful tools for the correlation analysis

Table 3. Melting points, $T_f$, and chemical shifts, δ, of $^1$H NMR spectra for quaternary salts recrystallized from methanol

| Salt | $T_f$ [°C] | δ, $^1$H NMR (60 MHz, [D$_6$]DMSO) |
|---|---|---|
| 1,3-Dimethylbenzimidazolium iodide | 201−202 | 4.13 (s, 6 H), 7.57−8.20 (m, 4 H), 9.77 (s, 1 H) |
| 1-Ethyl-3-methylbenzimidazolium iodide | 193−194 | 1.57 (t, 3 H, $J$ = 4 Hz), 4.31 (s, 3 H), 4.60 (q, 2 H, $J$ = 4 Hz), 7.60−8.33 (m, 4 H), 9.00 (s, 1 H) |
| 2-Amino-1,3-dimethylbenzimidazolium iodide | 259−261 | 1.13 (t, 3 H $J$ = 4 Hz), 2.93 (s, 12 H), 3.27 (2 H) |
| 2-Amino-1-ethyl-3-methylbenzimidazolium iodide | 237−238 | 1.30 (t, 3 H, $J$ = 4 Hz), 3.70 (s, 3 H), 4.33 (q, 3 H $J$ = 4 Hz), 7.27−8.80 (m, 4 H), 8.77 (s, 1 H) |
| *N*,*N*,*N*-trimethylanilinium iodide | 201−202 | 3.67 (s, 9 H), 7.50−8.13 (m, 5 H) |
| *N*-ethyl-*N*,*N*-dimethylanilinium iodide | 133−134 | 1.07 (t, 3 H, $J$ = 4 Hz), 3.67 (s, 6 H), 4.00 (q, 2 H, $J$ = 4 Hz), 7.60−8.23 (m, 5 H) |

of reactions sharing a common mechanism in spite of marked structural variations.

## Experimental Section

**Materials:** MeI ($\geq$99.5%) and EtI ($\geq$99.5%) were obtained from Fluka. NNDA (99%) and MBI (99%), were purchased from Aldrich and used as received. AMBI (95%) from Aldrich was recrystallized twice from ethanol/propan-2-ol and dried in a desiccator over phosphorus pentoxide. Solvents were purchased from Riedel de Haën ($\geq$99.9%) and their water content was kept lower than 0.02%.

The quaternary salts were prepared in acetonitrile from the corresponding alkyl iodide and nitrogen base. Repeated recrystallization from methanol afforded salts with the melting points shown in Table 3. Data from $^{1}$H NMR spectra, recorded on a JEOL PMX60SI instrument using $[D_6]$DMSO as solvent and TMS as internal standard, are also shown in Table 3.

**Apparatus:** A Wayne Kerr B905 bridge (accuracy ± 0.05%) and commercial conductivity cells (980-K19/120) were used to obtain the conductivity data from which rate constants and calibration curves were calculated. Cell constants ranged from 0.9 to 1.1 cm$^{-1}$. Kinetic experiments were carried out in a thermostated bath as described previously.[1,3] The temperature was kept constant to within ± 0.01 K.

**Kinetic Measurements:** All solutions were prepared by weight in methanol dried with oxygen-free nitrogen. Reacting solutions with equal initial concentrations in both reactants (between 0.01 and 0.05 mol dm$^{-3}$, depending on the reaction) were followed conductimetrically up to 15−20% conversion. In this way, the disturbing effects from methanolysis of iodoalkanes and reverse Menshutkin reactions could be avoided in the rate measurements of these slow reactions. For each kinetic run no less than 150 data points were recorded. Triplicate kinetic runs were made at each temperature. By using a calibration procedure described elsewhere,[1,3] conductivity data were converted into quaternary-salt concentrations. In this work, duplicate measurements for at least ten calibrating solutions in the concentration range 0.0001−0.0075 mol dm$^{-3}$ were made for each working temperature and reaction product. Rate constants were then calculated from the slope of linear plots describing the integrated second-order rate law for equal initial concentration in both reactants, which gave excellent correlation coefficients. TLC analyses of the reaction mixtures, at the beginning and at the end of the kinetic experiments, were run on silica gel plates.

**Computation:** Least-squares analyses were executed on a Pentium-inside PC-compatible computer. For the nonlinear fitting to Equation (2), the program MICROMATH® Scientist® for Windows™ (Microsoft Corporation) was used to minimise the sum of squared deviations between all the experimental selectivity data and the corresponding calculated values at the same temperature assuming a bundle of straight lines. The adjustable parameter $\beta_{is}$ in Equation (2) then defines a common point of intersection for the different straight lines.

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