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EQUILIBRIUM STUDIES: SUBSTITUENT EFFECTS ON METHOXYPYRIDINE-1-METHYLPYRIDONE EQUILIBRIA

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Abstract— The effects of 6-chloro, 5,6-benzo, 3,4-benzo, 4-methoxy-6-methyl, 6-methyl-4-one, 5,6-benzo-4-methoxy, and 5,6-benzo-4-one substitution on 2-methoxypyridine-1-methyl-2-pyridone equilibria have been determined by measurement of the heat evolved on equilibration of substituted isomer pairs at 130–150° or by determination of the equilibrium constant at 115, 125 and 140°. In all cases the 2-one isomer is more stable in the liquid phase. Estimates of differences in gas phase enthalpies and in chemical binding energies are made for these isomer pairs. The results provide a quantitative estimate of the stability difference between isomeric 1-methyl 2- and 4-pyridones and show that of the substituents investigated only 6-chloro substitution has a significant enthalpy effect. It is suggested that for substituted compounds in this series extrapolation of enthalpy differences from the parent system will be valid in most cases and that the 1-methyl-2-one isomer will usually be the more stable. Comparison of alkylomeric and protomeric equilibria is considered and it is suggested that, for a single equilibrium, reactions corrected for intermolecular and solvent effects and for kinetic and zero-point energy differences provided the least ambiguous test of approximate quantum mechanical methods. Syntheses of 2-methoxy-1,6-dimethyl-4-pyridone and 2-methoxy-1-methyl-4-quinolone which involve the use of a trimethylsilyl blocking group provide a procedure which should be adaptable to the production of the less available alkylomeric isomers of many isomer pairs.

EQUILIBRATION of alkyltropic isomers by the catalytic function of the common alkylated derivative[1,2] has been used in conjunction with calorimetric or equilibrium constant measurements to obtain quantitative information about the differences in stabilities of imidate-amide (**1**),[3] pyridine–pyridone (**1**),[3] and thiopyridine–thiopyridone (**2**)[4] isomer pairs; and the relationship of the general equilibration reaction to the many conversions of imidates to amides in which the intermediacy of a common alkylated derivative has been suggested or recognized[5] has been discussed.[3] For the isomer pairs 2-methoxypyridine (**3**)—1-methyl-2-pyridone (**4**) and 4-methoxypyridine (**5**)—1-methyl-4-pyridone (**6**), the pyridone isomers **4** and **6** are the more stable in the liquid phase by enthalpies of 12·1 ± 0·8 and 8·5 ± 0·3 kcal/mol, res-

$$CH_3—X—Y=Z \xrightleftharpoons{[CH_3—X\cdots Y\cdots Z—CH_3]^+} X=Y—Z—CH_3$$

1, X = O, Y = C, Z = NR
2, X = S, Y = C, Z = NR

pectively.[3] Estimates of heats of vaporization of the isomers suggest that in the vapor phase **4** is more stable than **3** by an enthalpy of 7·7 ± 2·0 kcal/mol, and that **5** and **6** are of comparable enthalpy.[3] The relevant values are presented as the first two entries in Table 1, along with an estimate of the differences in chemical binding energy for these isomer pairs.

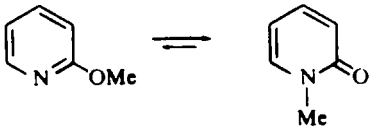
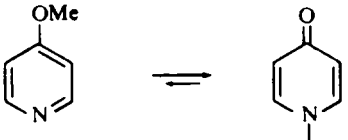
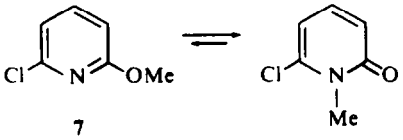
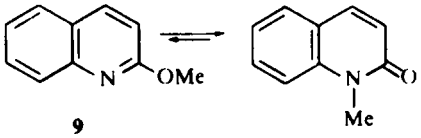
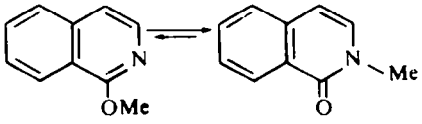
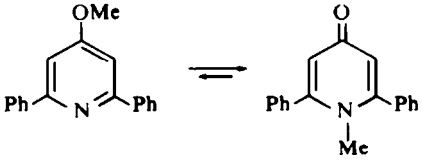
The importance of these different enthalpy values depends, of course, on the context in which the energy differences are to be used. For example, for the prediction of enthalpies in solution or of relative rates of reactions governed by the ground state enthalpy differences, relative liquid state enthalpies and heat of solution data would pertain. For discussion of the energy differences of the isomers devoid of association or solvent effects, the enthalpies in the gas phase would be useful, and for analysis of the fundamental difference in binding energies, such as those obtained from quantum mechanical calculations, the relative chemical binding energies would be of interest. The large estimated errors associated with the latter values seem realistic and reflect the difficulty of accurately gauging differences in kinetic and zero-point energies[3,6] between structurally complex isomers. On the other hand, it has been reasonably suggested that for energy differences of isomeric hydrocarbons effects due to terms other than potential energy are inconsequential in most applications.[7] It was previously noted in a comparison of the relative chemical binding energies of the isomer pairs 2-methoxypyridine (**3**)—1-methyl-2-pyridone (**4**) and 2-methoxyvalerolactim—*N*-methylvalerolactam that errors obtained by summing the estimated errors were too large, since errors made in the original estimates of differences in heats of vaporization and kinetic and zero-point energies for different functionalities would be expected to partially cancel when similar functionalities are compared.[3] Accordingly, gas phase enthalpies will be used for comparison of parent and substituted isomer pairs in the cases considered here. The present work was undertaken to determine the ground state substituent effects of chloro, benzo, methoxy, and methyl groups on methoxypyridine—1-methyl 2- and 4-pyridone equilibria and to obtain quantitative information about the relative enthalpies of 1-methyl 2- and 4-pyridones.

RESULTS

The conversion of 6-chloro-2-methoxypyridine (**7**) to 6-chloro-1-methyl-2-pyridone (**8**) at 130° by the catalytic action of 6-chloro-2-methoxy-1-methylpyridinium fluoroborate is too slow for convenient measurement of the enthalpy of reaction. Accordingly, the ground state enthalpy difference between **7** and **8** was found to be $-4{\cdot}1 \pm 2{\cdot}2$ kcal/mol in favour of **8** (Table 1) from a plot of log K *vs.* $1/T$, with the equilibrium constants being determined by approach to the equilibrium mixture from both sides at 115, 125, and 140°.[4] The entropy difference between the isomers obtained by this analysis is 4 ± 5 eu; in accord with previous estimates for the parent system **3**–**4**,[3] it is likely that the entropy difference between **7** and **8** is actually negligible. It is clear that the enthalpy difference between **7** and **8** is significantly less than for the unsubstituted isomers **3** and **4** and this difference is reflected in the enthalpies given for the gas phase and chemical binding energies in the second and third columns of Table 1.

Equilibration of the quinoline–quinolone isomer pairs was carried out in the previously described calorimeter[3] and the heats of equilibration were measured directly. The relative liquid phase enthalpies obtained, expressed in favour of the quinolones, are $-11{\cdot}5 \pm 0{\cdot}7$ kcal/mol for 2-methoxyquinoline (**9**)—1-methyl-2-quinolone (**10**), and $-13{\cdot}9 \pm 0{\cdot}9$ kcal/mol for 1-methoxyisoquinoline (**11**)—2-methyl-1-isoquinolone (**12**) (Table 1). The conversions of the liquid phase enthalpies

TABLE 1. RELATIVE ENERGY DIFFERENCES FOR THE PYRIDINE–PYRIDONE ISOMER PAIRS IN kcal/mol

Isomer pair	ΔH_l°	ΔH_g°	$\Delta E_{\text{chemical binding}}$
 **3** **4**	− 12·1[a] ± 0·8	− 7·7 ± 2·3	− 7·7 ± 3·8
 **5** **6**	− 8·5[a] ± 0·3	+ 0·1 ± 1·8	+ 0·1 ± 3·3
 **7** **8**	− 4·1 ± 2·2	+ 0·3 ± 3·7	+ 0·3 ± 5·2
 **9** **10**	− 11·5 ± 0·7	− 7·1 ± 2·2	− 7·1 ± 3·7
 **11** **12**	− 13·9 ± 0·9	− 9·5 ± 2·4	− 9·5 ± 3·9
 **19** **20**	+ 1·1[a] ± 1·0	+ 9·7 ± 2·5	+ 9·7 ± 4·0

[a] Data from ref. 3 with the values obtained from mixtures deleted.

to gas phase values and to differences in chemical binding energies given in Table 1 are based on the assumption that the differences in heats of vaporization for the isomers in the present study will be the same as for **3** and **4**.[3] Accordingly, the $\Delta H_g°$ values collected in Table 1 are obtained by subtracting 4·4 ± 1·5 kcal/mol, $\Delta\Delta H_{vap}$, for **3** and **4**, from $\Delta H_l°$, since the pyridine isomers are the more volatile. The difference in the kinetic and zero-point energies of **3** and **4**, previously estimated as 1·5 kcal/mol, is added to $\Delta H_g°$ to give the $\Delta E_{chemical\ binding}$ values. Although the use of **3** and **4** as appropriate models is justified by the reliability of homolog and group increment conversions in standard methods for estimating heats of vaporization,[8] the estimated heats of vaporization remain the weakest point in these estimates.

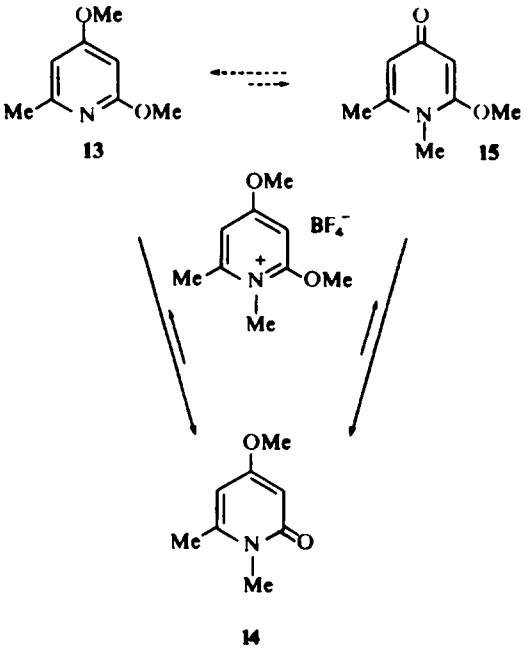
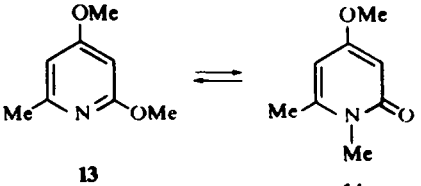
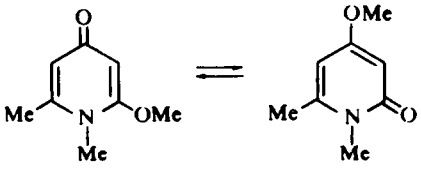
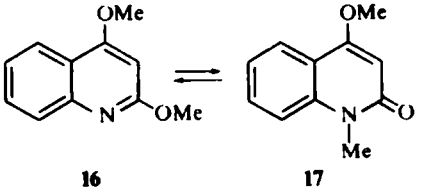
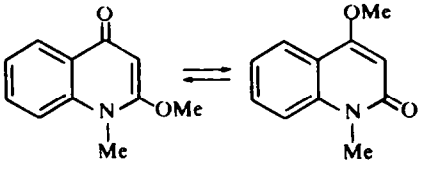


FIG 1. Equilibration of the isomer triad **13**—**14**—**15**

Equilibrations of the 2,4-dimethoxypyridine—2-methoxy-1-methyl-4-pyridone—4-methoxy-1-methyl-2-pyridone isomers **13**–**14**–**15** and **16**–**17**–**18**, summarized in Table 2, provide the first study of isomer triads (Fig. 1) by the alkylated catalyst-calorimetric procedure. The liquid phase enthalpies for the isomer pairs are: 2,4-dimethoxy-6-methylpyridine (**13**)—4-methoxy-1,6-dimethyl-2-pyridone (**14**), −12·1 ± 0·4 kcal/mol; 2-methoxy-1,6-dimethyl-4-pyridone (**15**)–**14**, −4·7 ± 0·3 kcal/mol; 2,4-dimethoxyquinoline (**16**)—4-methoxy-1-methyl-2-quinolone (**17**), −10·5 ± 0·5 kcal/mol; and 2-methoxy-1-methyl-4-quinolone (**18**)—**17**, −5·6 ± 0·6 kcal/mol. Equilibrations of the pairs **15**–**14** and **18**–**17** were carried out in solution in **14** and **17**, respectively, and include a correction for the heat of solution of the less stable isomer in the more stable isomer. This procedure was necessary because the neat isomers **15** and **18** tended to rearrange thermally to **14** and **17** at temperatures above their melting points. The compositions of the mixtures were determined

TABLE 2. RELATIVE ENERGY DIFFERENCES FOR THE METHOXYPYRIDINE–METHOXYPYRIDONE ISOMER PAIRS IN kcal/mol

Isomer pair	ΔH_l°	ΔH_g°	$\Delta E_{\text{chemical binding}}$
 **13** **14**	−12·1 ± 0·4	−7·7 ± 1·9	−7·7 ± 3·4
 **15** **14**	−4·7 ± 0·4	−10·6 ± 1·9	−10·6 ± 3·4
 **16** **17**	−10·5 ± 0·5	−6·1 ± 2·0	−6·1 ± 3·5
 **18** **17**	−5·6 ± 0·7	−11·5 ± 2·2	−11·5 ± 3·7

by withdrawal of a sample just prior to breaking the catalyst bulb, and the heats of solution of **15** and **14** and **18** in **17** were estimated as 0·6 ± 0·1 kcal/mol, since that value is obtained as the heat of solution of 1-methyl-4-pyridone (**6**) in 1-methyl-2-pyridone (**4**) at 130°. Because **15** and **18** are solids at 130°, the standard states for the equilibrations of these isomers are those of the supercooled liquids. The conversions of the liquid phase enthalpies to the gas phase and to chemical binding energies (Table 2) are as outlined above except that the differences in the heats of vaporization of the isomers **15–14** and **18–17** were estimated on the basis of the differences in the estimated heats of vaporization of **4** and **6** as −5·9 ± 1·5 kcal/mol, with **14** and **17** being the more volatile.[3] Measurement of heats of equilibrations in a solution of the more stable isomer with correction for the heat of solution is an extension of the

alkylated derivative-calorimetric method for obtaining energy differences which could prove useful for other thermally unstable isomers.

The structure of **18** was assigned relative to **17** by Arndt *et al.*,[9] on the basis of its higher basicity and its lower yield when produced by reaction of 4-hydroxy-1-methyl-2-quinolone with diazomethane. Both a more efficient synthesis and a definitive structure proof of **17** and **18** were required. The synthesis of **18** from 4-hydroxy-1-methyl-2-quinolone as outlined in Fig 2 proceeds in 27% overall yield.

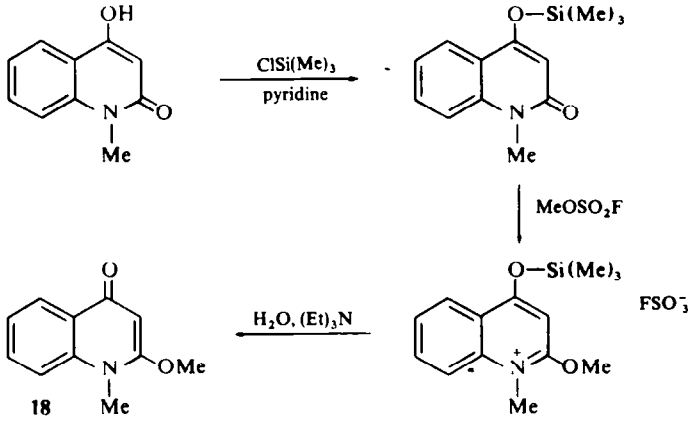


FIG 2. Synthesis of 2-methoxy-1-methyl-4-quinolone (**18**)

The sequential use of the trimethylsilyl group as a blocking group and methyl fluorosulfonate as an efficient methylating agent to produce the previously more difficult to obtain alkyltropic isomer should be a process which conveniently makes available a number of compounds previously obtained only in low yields and usually in admixture with an isomer in syntheses where multiple alkylation sites are available. The same procedure was used to prepare in 37% yield, 2-methoxy-1,6-dimethyl-4-pyridine **15** from 1,6-dimethyl-4-hydroxy-2-pyridone. A structure proof for **17** is outlined in Fig 3. The key compound in this correlation is 2-chloro-4-methoxyquinoline, which is converted to both **17** and 1-methyl-4-quinolone of established structure. The spectral properties[10,11] of **14**, **15**, **17**, and **18** are also consistent with the structures assigned to these compounds. The structures of **14** and **15** follow by synthetic analogy and from the fact that these compounds conform to an ultraviolet spectral correlation which seems reliably diagnostic of isomer type for the pyridones.[11b]

DISCUSSION

The effect of a substituent on pyridine–pyridone equilibria can be gauged by comparison of the enthalpy difference for the substituted isomer pair with the enthalpy differences for the unsubstituted pair. In principle, comparisons should be made only for the differences in chemical binding energies, the last column in both tables. However, as noted heretofore, such a comparison would lead to unrealistically large error estimates, and the gas phase enthalpy differences, column three in Tables 1 and 2, will be used for evaluation of substituent effects.[7]

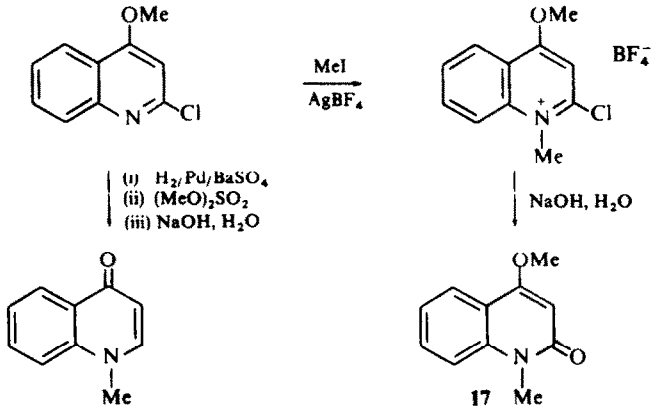


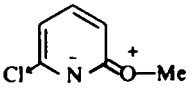
FIG 3. Structure proof for 4-methoxy-1-methyl-2-quinolone (17)

The following conclusions can be drawn by comparing the enthalpy difference of the substituted and unsubstituted pairs: (i) A 6-chloro-substituent shifts the enthalpy from strongly favouring the 1-methyl-2-pyridone system (**3–4**) sufficiently towards the 2-methoxypyridine system that **7** and **8** have comparable enthalpies. (ii) A 6-methyl or 5,6-benzo substituted 4-methoxy-1-methyl-2-pyridone is of lower enthalpy than the isomeric 6-methyl or 5,6 benzo 2-methoxy-1-methyl-4-pyridone by about 11 ± 3 kcal/mol (**15–14** and **18–17**). (iii) Neither benzo conjugation of the quinolone or isoquinolone type nor 4-methoxy or 6-methyl substitution has a major enthalpy effect on methyl pyridone—pyridone or 1-methyl-4-pyridone—2-pyridone enthalpy differences since the differences within the sets (a) **3–4**, **9–10**, and **11–12**; (b) **13–14** and **16–17**; (c) **15–14** and **18–17**; and (d) **3–4** and **13–14** are small. (iv) A substituted 2,4-dimethoxypyridine may be of lower enthalpy than the isomeric 2-methoxy-1-methyl-4-pyridone provided that a cancellation of errors occurs in the heats of vaporization estimates, but the gas phase enthalpy differences for **13–15** and **16–18** of 2·9 ± 3·8 and 5·4 ± 4·2 kcal/mol in favour of the dimethoxypyridine isomer are within experimental errors of the difference for **5–6** of 0·1 ± 1·8 kcal/mol.

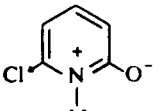
The effect of the 6-chloro substituent in shifting the enthalpy from favouring the 2-pyridone in the unsubstituted pair **3–4** towards the pyridine in the pair **7–8** would be expected *a priori* on the basis of steric, resonance, and inductive effects. However, a steric effect is probably not dominant since a 6-methyl substituent does not seem to have a large effect on the enthalpy differences for the pairs **3–4** and **13–14**† and different evaluations of the relative sizes of chloro and methyl substituents suggest that chloro is slightly the smaller.[12] Consideration of the inductive effect of chlorine on relative resonance energies of **7** and **8** may be seen in the contributors **7a** and **8a**, which suggests that the electron withdrawing effect of the 6-chloro substituent would tend to favour contribution of the dipolar canonical structure **7a**, which places a negative charge on the imidate nitrogen, while the same effect would tend to disfavour contribution of the dipolar canonical structure **8a**, which places a positive charge on the amide nitrogen. A related inductive effect in the sigma framework would focus on the electron demands of nitrogen and suggest that 6-chloro

† It is assumed that the effect of the 4-methoxy group cancels in **13** and **14**.

substitution destabilizes **8** relative to **7** if the amide nitrogen is assumed to be more electronegative than the imidate nitrogen. Paquette *et al.*, suggested the latter type of effect, along with a conjugation effect, to explain the relative stabilities of isomeric cyclopropyl substituted imidates in the azabulvalenes.[13,14,15] Gordon and Katritzky have suggested a resonance effect similar to that above in their study of the protomeric equilibria of the chloropyridones.[16] Other comparisons of protomeric pyridone equilibria in solution which show a linear free energy relationship for substituent effects support the above indication that the effect of the 6-chloro group on the equilibrium of **7–8** is primarily electronic.[17] On the other hand, both steric and electronic effects may be important in the equilibria of the nitrogen and oxygen acyl pyridones.[18]



7a



8a

The enthalpies of the 4-methoxy-1-methyl-2-pyridones **14** and **17** relative to the 2-methoxy-1-methyl-4-pyridones **15** and **18** provide a value of 11 ± 3 kcal/mol for the relative enthalpies of 1-methyl-2-pyridones and 1-methyl-4-pyridones only if the effect of the methoxy group is considered to be independent of its location in the 2- or 4-position. Such independence is not likely for either the electronic or steric effects of the methoxy function. That steric effects can play a major role in 4-methoxypyridine—1-methyl-4-pyridone equilibria is seen by comparing the enthalpy for the unsubstituted isomer pair **5–6** with that for the 2,6-diphenyl substituted isomer pair **19–20** (Table 1). In the unsubstituted case the isomers are of comparable energy, but for the 2,6-diphenyl substituted case the 4-pyridone is disfavoured by 9·7 ± 2·5 kcal/mol. Although estimation of the magnitude of the steric effect in **19** and **20** is complicated by the fact that steric and electronic effects may act in concert to disfavour **20**, it seems clear that a steric effect is important. On the other hand, steric effects do not appear to be dominant in comparisons involving 2-methoxypyridines and 1-methyl-2-pyridones; the gas phase enthalpies for **3–4**, **9–10**, **11–12**, **13–14**, and **16–17** are within experimental error of one another. The apparently minor role of steric effects in these equilibria may reflect the small "size" of the amide carbonyl.[19] In any case, the greater stability of the 1-methyl-2-pyridones **14** and **17** over the isomeric 1-methyl-4-pyridones **15** and **18**, respectively, is best taken as a provisional quantitative indication of relative stabilities of the 1-methyl 2- and 4-pyridones.

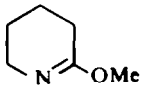
Although the lower enthalpy of a 1-methyl-2-pyridone relative to a 1-methyl—4-pyridone is consistent with qualitative resonance arguments which would depict the dipolar contributors to the 2-pyridone as having less charge separation than the 4-pyridone, such a rationalization should be viewed with considerable skepticism† because of the unknown differences in the sigma bond energies of the isomeric

† For example, extrapolation of these rationalizations to estimates of aromatic character appear unwarranted. Although the relationship between magnetic and thermodynamic criteria of aromatic character is not clear, it has been shown that both 2- and 4-pyrone, which bear the same structural relationship to each other as do 1-methyl 2- and 4-pyridones, appear to be non-aromatic by magnetic criteria.[20]

pyridones. Nonetheless, the lower enthalpy of a 2-one relative to a 4-one appears to be general,[1,21] and it can be suggested that in the absence of dominant perturbations 2-one isomers will generally be of lower enthalpy than isomeric 4-ones for six-membered formally heteroaromatic molecules.

The differences between the liquid and vapor phase enthalpies given in Table 2 for the isomer triads **13–14–15** and **16–17–18** illustrate again[3] the importance of considering heats of vaporization in order to correct for association effects in seeking fundamental information about enthalpy differences. In these instances the enthalpy differences between the 4- and 2-one isomers are increased by conversion to the gas phase, while the differences between the dimethoxy and 2-one isomers are decreased by the same conversion. In fact, comparison of the dimethoxy and 4-one isomers suggests that the latter are of slightly higher enthalpy than the former, a result which is not indicated by the liquid phase data.

That benzo conjugation does not have a major energy effect in these systems is shown by the fact that the enthalpy differences for the isomer pairs **3–4**, **9–10**, and **11–12** are within experimental error of one another, as are the enthalpies of the isomer triads **13–14–15** and **16–17–18**. Since the effect of benzo conjugation is usually considered to attenuate the energy effects associated with aromatic character of the benzo substituted ring[22] and since comparison of the enthalpy difference of $-7{\cdot}7 \pm 2{\cdot}3$ kcal/mol for **3–4** with that of $-14{\cdot}1 \pm 2{\cdot}0$ kcal/mol for the non-aromatic pair **21–22** establishes that participation of an imidate in an aromatic ring lowers its energy relative to that of its isomeric amide, it might have been expected that benzo conjugation would have increased the energy difference between the pyridine and pyridone isomers. In fact, however, comparisons do not even show a trend in this direction, a result which might be attributed to a small steric effect disfavouring the amide isomer in each pair.



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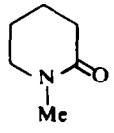

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The effect of substituent changes on energies can be compared meaningfully between alkyltropic and prototropic isomer pairs only if the observed energy differences are suitably corrected for differences in association energies.[3] One method of implicitly making this correction is to limit comparison to structurally related series in the same medium such that association effects would reasonably be expected to cancel.[23,24] Thus, comparison of the equilibria **3–4** and **21–22**, which were used to provide an estimate of the thermodynamic aromatic stabilization of **4** relative to **3**, has been extended to extract similar information from solution protomeric studies of **23–24** and **25–26**.[24] In the same way, the effect of the 6-chloro substituent on the enthalpy of **7–8** relative to **3–4** has been noted as precedented (*vide supra*) by protomeric studies in which the equilibrium **27–28** is shifted toward **27** relative to that for **23–24**.[16,25] Quantitatively for the protomeric systems in water at 20°, the effect of the 6-chloro substituent shifts the free energy towards the imidic acid by *ca.*

2 ± 1 kcal/mol;[25] the same substitution in the alkylomeric series shifts the enthalpy towards the imidate by 8·1 ± 6·0 kcal/mol. The agreement between these values is not impressive, but the large errors associated with the enthalpy value and the fact that solvent has a major effect on the equilibrium **27–28**[25] obscure the quantitative significance of this comparison. Qualitative agreement of problematical quantitative significance is also found in other comparisons. In the case of the quinolone and isoquinolone isomer pairs the protomeric series in solution shows a free energy difference of *ca.* 1 ± 1 kcal/mol in favour of the isoquinolone pair being more in the form of the amide[26] and the alkylomeric series has an enthalpy difference of 2·4 ± 4·6 kcal/mol in the same direction, suggesting in both cases no large enthalpy differences for this comparison. Previous studies on the hydroxypyridone[27] and hydroxyquinolone[28] tautomers have shown that the 2-one form is favoured in solution, but to an unknown degree, so quantitative comparison to the alkylomeric cases is not possible.

23–24, a = b = c = d = CH
25–26, a = b = c = d = CH_2
27–28, a = CCl, b = c = d = CH

The fact that alkylomeric and protomeric equilibria within analogous series do not always exhibit compensation of solvation effects is shown by comparing the first two entries in Table 1 with the corresponding protomeric systems. Thus the 2-pyridone, **3**, is favoured in the isomer pair **3–4** by 7·8 ± 4·1 kcal/mol more than the 4-pyridone, **5**, is favoured in the isomer pair **5–6**; however, for the corresponding protomeric equilibria in water at 20° the 4-pyridone is favoured by a free energy of *ca.* 1 kcal/mol more in equilibrium with 4-hydroxypyridine than is the amide 2-pyridone in equilibrium with 2-hydroxypyridine.[26] The difference in these energies could be attributed to the fact that the requisite heats of vaporization and solution of 2-pyridone and 4-pyridone do not cancel in the protomeric series and thus may be taken to suggest that, for protomeric equilibria in solution, the compounds compared must be quite closely related structurally. Although protomeric equilibria are of considerable interest,[29] the information gleaned from such equilibria about relative stabilities must be implicitly or explicitly corrected for solvent effects, if the values are to be used to estimate energy differences of isolated molecules. This is especially pertinent for evaluations of the different approximate quantum mechanical methods which have been used to predict relative chemical binding energies of heteroaromatic imidate-amide isomer pairs.[30] Alkylomeric equilibria corrected to the gas phase and for kinetic and zero-point energies appear at present to offer the least ambiguous test of such calculations in these systems. On the other hand, predictions of trends by calculations for a series of equilibria using solution data should prove correct if solvent effects are cancelled by the comparison throughout the series.[23]

In conclusion, the isomer pair **3–4** appears to provide a reliable quantitative model for enthalpy differences in similar pyridine–pyridone systems unless a chlorine

atom, or presumably another strongly electron withdrawing group, is substituted at the 6-position. The isomer pair **5–6** appears to provide a useful but less satisfactory quantitative model for related equilibria. The relative insensitivity of the enthalpy difference from the parent systems to substitution suggests that generalization on the basis of the stabilities of the parent systems is warranted for other heteroaromatics, provided that obvious dominant inductive or steric effects are absent.

EXPERIMENTAL

Infrared spectra were obtained on a Perkin–Elmer 521 spectrophotometer. Ultraviolet spectra were taken on a Cary 14 ultraviolet-visible-infrared recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on Varian Associates HR-220, HA-100, A-60A, A-56/60, and T-60 spectrometers and chemical shifts are reported as δ (ppm) relative to the internal TMS. Mass spectra were obtained with Atlas CH4 and CH5 machines. M.ps were determined on a Büchi capillary apparatus and are corrected; b.ps are uncorrected. Elemental analyses were determined by J. Nemeth and associates. The NMR, IR and mass spectral properties of the known compounds are consistent with the assigned structures unless otherwise noted.

All analytical gas chromatography was conducted with a Varian 1800 flame ionization instrument, using a $\frac{1}{8}$ in × $1\frac{1}{2}$ ft. column packed with Carbowax 20 *M* on 60/80 Chromosorb W at column temperatures of 75 and 100°. All preparative GLPC was conducted on a Varian A-90-P thermal conductivity instrument, with a $\frac{3}{8}$ in. × 5 ft. column packed with Carbowax 20 *M* on 60/80 Chromosorb P, at column temperatures of 130 and 160°. Column chromatograms were carried out, as indicated, on Brinkman silica gel (0·05–0·2 mm) or Merck chromatographic alumina, with a 100:1 ratio of adsorbant to mixture unless otherwise indicated. Four column volumes of the following solvent mixtures were used to elute each column: petroleum volumes of the following solvent mixtures were used to elute each column: petroleum ether (30–60°), benzene–petroleum ether, benzene chloroform–benzene, chloroform, ether–chloroform, ether, ethyl acetate–ether, ethyl acetate, methanol–ethyl acetate, and methanol: when mixed solvents were used, 1, 2, 3, 4, 5, 10, 20 and 50% mixtures of the more polar solvent in the less polar solvent were used for elution.

6-Chloro-2-methoxypyridine (7) (Aldrich Chemical Co.) was purified by distillation, b.p., 39–40°, 0·3 Torr (lit.[31] 73–55°, 15 Torr), and by preparative GLPC (130°).

6-Chloro-1-methyl-2-pyridine (**8**) was prepared by heating 14·3 g (0·1 mol) of 6-chloro-2-methoxypyridine with 10% 6-chloro-2-methoxy-1-methylpyridinium fluoroborate at 130° for 22 hr. Chromatography on alumina and elution with petroleum ether gave a white solid which was recrystallized from pentane–ether (3/1) to give needles, 4·54 g (32%), m.p. 62–64° (lit.[31] 63–65°).

6-Chloro-2-methoxy-1-methylpyridinium fluoroborate. To a solution of 7·15 g (0·05 mol) of 6-chloro-2-methoxypyridine (**7**) and 9·0 (0·046 mol) of silver fluoroborate in 125 ml of 1,2-dichloroethane was added 20 ml (0·31 mol) MeI and the mixture was stirred for 24 hr. The precipitate obtained by filtration of the mixture was treated with hot abs MeOH and the solution was combined with the reaction filtrate. Concentration of this solution and dilution with an equal volume of ether gave 7·77 g (69%) of fine white needles, m.p. 152–153°; IR (nujol) 3135 (C—H), 1630 (C=N), 1293 (C—N), 1175 (C—O—C), 1060 (BF_4), and 810 cm^{-1} (C—Cl): NMR (CD_3CN) δ 8·36 (d of d, J_{34} = 8·0 Hz, J_{45} = 8·8 Hz, 1, H-4), 7·62 (d of d, J_{35} = 1·3 Hz, J_{45} = 8·8 Hz, 1, H-5), 7·54 (d of d, J_{34} = 8·0 Hz, J_{35} = 1·3 Hz, 1, H-3), 4·32 (s, 3, O—CH_3), 4·06 (s, 3, N-CH_3). (Calc for $C_7H_9BClF_4NO$: C, 34·26: H, 3·70: N, 5·71: Cl 14·45. Found: C, 34·23: H, 3·68: N, 5·71: Cl, 14·46%). The same compound was obtained in 79% yield in an identical manner from **8**.

2-Methoxyquinoline (**9**) was prepared from 2-chloroquinoline and NaOMe in abs MeOH in 96% yield: b.p., 63–65°, 0·03 Torr (lit.[32] 247°, 760 Torr).

1-Methyl-2-quinolone (**10**) was prepared by heating 2-methoxyquinoline with 10 mol percent methyl tosylate at 130° for 24 hr. Purification by hexane–ether (3/1) recrystallizations yielded 44% crystalline **10**: m.p. 71–72° (lit.[34] 74°).

2-Methoxy-1-methylquinolinium fluoroborate. To a solution of 200 mg (1·26 mmol) of 1-methyl-2-quinolone in 40 ml of 1,2-dichloroethane was added 230 mg (1·20 mmol) of silver fluoroborate and 2·25 g (16 mmol) MeI. The solution was stirred for 24 hr, and the resulting precipitate was collected, washed three times with MeOH, and the filtrate combined with the original filtrate and concentrated. Excess ether was

added, and the resulting mixture was allowed to stand overnight at −15°, then filtered to yield 235 mg (76%) of a white powder: m.p. 130–131° IR (nujol) 1605 (C=N), 1525 (Ar ring), 1280 (C—N), 1160 (C—O—C), and 1050 cm^{-1} (BF_4); NMR (CD_3CN) δ 8·90 (d, J = 5·0 Hz, 1, H-4), 7·79–8·30 (m, 4, ArH), 7·70 (d, J = 5·0 Hz, 1, H-3), 4·45 (s, 3, O-CH_3), 4·20 (s, 3, N—CH_3). (Calc. for $C_{11}H_{12}BF_4NO$: C, 50·62; H, 4·63; N, 5·37. Found: C, 50·33; H, 4·62; N, 5·33%). The same product was obtained in 31% yield in an identical manner from 2-methoxyquinoline.

1-*Methoxyisoquinoline* (**11**) was prepared in 89% yield from 1-chloroisoquinoline and NaOMe in abs MeOH: b.p. 67°, 0·03 Torr (lit.[35] 119°, 8 Torr).

2-*Methyl*-1-*isoquinolone* (**12**) was prepared in 57% yield by the method of Prill and McElvain[36] from isoquinoline: m.p. 35–36° (lit.[37] 38°); after having been dried at 20 Torr for 24 hr, m.p. 56–58°.

1-*Methoxy*-2-*methylisoquinolinium fluoroborate*. To a solution of 500 mg (3·2 mmol) of 2-methyl-1-isoquinolone in 40 ml of 1,2-dichloroethane was added 580 mg (3·0 mmol) silver fluoroborate and 4·5 g (32 mmol) MeI. The solution was stirred for 24 hr and the resulting mixture filtered and MeOH washed. The combined filtrates were reduced to half volume, excess ether was added, and the precipitate was collected after the mixture had been cooled at −15° for 2 hr. Reprecipitation from 1,2-dichloroethane with ether gave 329 mg (42%) of fine white needles: m.p. 85·5–86·5°, IR (nujol) 1640 (C=N), 1290 (C—O—C), and 1050 cm^{-1} (BF_4); NMR (CD_3CN) δ 8·57 (m, 1, H-8), 7·83–8·28 (m, 5, ArH), 4·54 (s, 3, O—CH_3), 4·22 (s, 3, N—CH_3). (Calc. for $C_{11}H_{12}BF_4NO$: C, 50·62; H, 4·63; N, 5·37. Found: C, 50·49; H, 4·54; N, 5·63%). The same product was also obtained in 53% yield from 1-methoxyquinoline.

2,4-*Dimethoxy*-6-*methylpyridine* (**13**) was prepared by the method of Urban and Schneider[36] from 2,4-dichloro-6-methylpyridine[37] in 54% yield: b.p. 56–57°, 0·9 Torr (lit.[36] 87–88°, 17 Torr).

4-*Methoxy*-1,6-*dimethyl*-2-*pyridone* (**14**). A suspension of 5·9 g (42 mmol) of 4-hydroxy-1,6-dimethyl-2-pyridone[38] was methylated twice with equimolar dimethyl sulfate and NaOMe in boiling MeOH. Dilution with water followed by CH_2Cl_2 extraction gave 6·3 g (98%) of crude product, which was chromatographed on 200 g of alumina (25% chloroform–benzene) to give 3·7 g (58%) of colourless powder, m.p. 113–116°. This material was recrystallized twice from benzene–cyclohexane to give 2·0 g (31%) of analytically pure **14**: m.p. 115–116°: IR ($CHCl_3$) 3032, 2960 (C—H), 1660 (C=O), 1589, 1573 (C=C), 1488 (C—H), and 1233 cm^{-1} (C—O—C): NMR ($CDCl_3$) δ 2·30 (d, J = 0·7 Hz, 3, C—CH_3), 3·43 (s, 3, N—CH_3), 3·72 (s, 3, O—CH_3), and 5·78 (m, 2, H-3 and H-5): UV (MeOH) 284 nm (λ_{max}, ε 5940), 228 (sh, 4510), and 210 (λ_{max}, 43,400): *m/e* (70 eV) (rel intensity) 153 (100), 138 (11), 125 (17), 111 (10), 110 (64), 82 (12), 56 (19), and 42 (11). (Calc. for $C_8H_{11}NO_2$: C, 62·73; H, 7·24; N, 9·14. Found: C, 62·60; H, 7·17; N, 9·06%).

2-*Methoxy*-1,6-*dimethyl*-4-*pyridone* (**15**). To a suspension of 16·5 g (119 mmol) of 1,6-dimethyl-4-hydroxy-2-pyridone[38] in pyridine was added 39 g (350 mmol) of chlorotrimethylsilane: the mixture was heated under reflux for an hour. Excess chlorotrimethylsilane and pyridine was distilled to leave a beige solid to which was added 17·1 g (150 mmol) of methyl fluorosulfonate. The mixture was stirred until the mass solidified, and after 1 hr 100 ml of MeOH–H_2O (7:3) was added. The mixture was stirred until homogeneous, neutralized with 5% NaOHaq, and then continuously extracted for 24 hr with CH_2Cl_2. The residue, 15·4 g (85%), obtained after the solvent had been removed under reduced pressure, was chromatographed on 250 g of alumina to give (25% $CHCl_3$–benzene) 8·7 g (48%) of a colourless powder, which was recrystallized from dry benzene under an atmosphere of dry N_2 to give 6·7 g (37%) of pure, hygroscopic **15**: m.p. 170·5–171·5°: IR ($CHCl_3$) 3025, 2975 (C—H), 1641 (C=O), 1566, 1546, 1466 (C—H), and 1224 cm^{-1} (C—O—C): NMR ($CDCl_3$) δ 2·30 (d, J = 1·1 Hz, 3, C—CH_3), 3·43 (s, 3, N—CH_3), 3·80 (s, 3, O—CH_3) (d, J = 2·4 Hz, 1, H-3), and 5·99 (d of q, J = 2·4 Hz, J_q = 1·1 Hz, 1, H-5): UV (MeOH) 253 nm (max, ε 16,000), 223 (sh, 14,600), and 217 (max, 16,500): *m/e* (70 eV) (rel intensity) 153 (70), 125 (13), 110 (100), 82 (14), 56 (18), 55 (12), 42 (14), 41 (11), and 39 (12). (Calc. for $C_8H_{11}NO_2$: C, 62·73; H, 7·24; N, 9.14. Found: C, 62·64; H, 7·25; N, 8·99%).

2,4-*Dimethoxy*-1,6-*dimethylpyridinium fluoroborate*. To a solution of 978 mg (6·45 mmol) of 2,4-dimethoxy-6-methylpyridine (**13**) and 1·27 g (6·50 mmol) of silver fluoroborate in 50 ml of 1,2-dichloroethane was added 4·6 g (32 mmol) of MeI, and the mixture was stirred for 24 hr. The precipitated AgI_2 was washed with five 10 ml portions of MeOH, the combined filtrate and washings were poured into ether, and the colourless precipitate which formed was collected as 1·28 g (77·9%) of colourless powder, m.p. 139–143°. Recrystallization from MeOH–Et_2O gave 999 mg (61%) of pure 2,4-dimethoxy-1,6-dimethylpyridinium fluoroborate; m.p. 148–148·5°; IR (nujol) 2100 (C—H), 1639, 1584, 1503 (Ar ring), 1457 (C—H), 1226 (C—O—C), and 1043 cm^{-1} (BF_4); NMR (CD_3CN) δ 2·61 (s, 3, $ArCH_3$), 3·73 (s, 3, N—CH_3), 4·06 (s, 3, O—CH_3), 4·18 (s, 3, O—CH_3), 6·72 (d, J = 2·8 Hz, 1, H-3), and 6·92 (d, J = 2·8 Hz, 1, H-5). (Calc. for $C_9H_{14}BF_4NO_2$: C, 42·39; H, 5·53; N, 5·49. Found: C, 42·55; H, 5·57; N, 5·48%). The same salt was prepared

by the same procedure from 1,6-dimethyl-2-methoxy-4-pyridone (**15**) in 79% yield and from 4-methoxy-1,6-dimethyl-2-pyridone (**14**) in 79% yield.

4-Methoxy-1-methyl-2-quinolone (**17**) was produced by repetitive methylation of 4-hydroxy-2-quinolone with dimethyl sulfate in 77% yield, m.p. 101–102° (lit.[39] 99·5–100°: lit.[40] 103°).

2,4-Dichloroquinolone was produced by the procedure of Baeyer and Bloem[41] in 49% yield from 4-hydroxy-2-quinolone and PCl_5 and purified by fractional sublimation at 47° and 0·1 Torr: m.p. 64·5–65·5° (lit.[41] 67°). The IR and NMR spectra are consistent with the established structure.

Further sublimation at 47° and 0·1 Torr after collection of the 2,4-dichloroquinoline gave, after recrystallization from MeOH, 13% of colourless needles which were identified as 2,3,4-trichloroquinoline, m.p. 107–108° (lit.[42] 107·5). This material has been previously isolated[42,43] but the location of each of the chlorine atoms was not established. The 220 MHz NMR spectrum shows 4 contiguous aromatic hydrogens: IR ($CHCl_3$) 3103, 3035 (C—H), 1612, 1554, 1551, and 1471 cm^{-1} (Ar ring); (CS_2) 748 cm^{-1} (CCl): NMR ($CDCl_3$), δ 7·58 (d of d of d, J_{67} = 6·5 Hz, J_{78} = 8·5 Hz, J_{57} = 1·3 Hz, 1, H-7), 7·70 (d of d of d, J_{67} = 6·5 Hz, J_{56} = 8·1 Hz, J_{68} = 1·6 Hz, 1, H-6), 7·91 (d of d of d, J_{56} = 8·1 Hz, J_{57} = 1·3 Hz, J_{58} = 0·9 Hz, 1, H-5), and 8·01 (d of d of d, J_{78} = 8·5 Hz, J_{68} = 1·6 Hz, J_{58} = 0·9 Hz, 1, H-8): *m/e* (70 eV) (rel intensity) 235 (32), 233 (97), 231 (100), 198 (28), 196 (47), 161 (45), 98 (22), and 84 (23). (Calc. for $C_9H_4Cl_3N$: C, 46·48; H, 1·73; Cl, 45·74; N, 6·05. Found: C, 46·30; H, 1·64; Cl, 45·46; N, 6·07%).

2,4-Dimethoxyquinoline (**16**) was prepared from 2,4-dichloroquinoline and NaOMe in dry MeOH in 72% yield: m.p. 81–82° (lit.[40] 82°). The IR, NMR, UV, and mass spectral properties and analytical data are consistent with those of the assigned structure.

2-Methoxy-1-methyl-4-quinolone (**18**). To a suspension of 12·5 g (71·3 mmol) of 4-hydroxy-1-methyl-2-quinolone[40] in 200 ml of pyridine was added 15·0 g (138 mmol) of chlorotrimethylsilane: the mixture was heated under reflux for 1 hr and excess chlorotrimethylsilane and pyridine were distilled. After the residue had been dried by addition and distillation of chlorobenzene, 8·0 g (70 mmol) of methyl fluorosulfonate was added and the mixture was stirred until solid. After 1 hr 100 ml of a MeOH–Et_3N–H_2O (5:3:2) solution was added and the mixture was stirred for 1 hr. The volume was reduced to 25 ml under reduced pressure, and 100 ml of water was added, followed by extraction of the solution with CH_2Cl_2. Solvent evaporation gave 8·4 g (62%) of crude **18**, which was chromatographed on 200 g of alumina (50% $CHCl_3$–C_6H_6) to give 5·4 g (40%) of slightly impure **18**, m.p. 186–193°, which was recrystallized from benzene to give 3·7 g (27%) of pure **18**: m.p. 195–195·5° (lit.[40] 195°).

2-Chloro-4-methoxyquinoline was prepared in 34% yield from 4-methoxy-2-quinolone, PCl_5, and $POCl_3$: m.p. 74–75° (lit.[44] 77–77·5°). The IR and NMR spectra are consistent with the assigned structure.

1-Methyl-4-quinolone from 2-chloro-4-methoxyquinoline. A solution of 326 mg (1·68 mmol) of 2-chloro-4-methoxyquinoline in 20 ml of MeOH containing 1·0 g of 5% Pd/$BaSO_4$ was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen had been taken up. Filtration and extraction with CH_2Cl_2 of the solution which had been made basic with 5% NaOH aq, followed by evaporation, gave 255 mg (95%) of 4-methoxyquinoline (NMR). To this unpurified material was added 220 mg of dimethyl sulfate and the mixture warmed at 60° for 5 min. The resulting solid was dissolved in 2 ml of 5% NaOH solution and CH_2Cl_2 extracted. Evaporation gave 230 mg (86%) of colourless solid, m.p. 148–151°. This material was recrystallized from benzene to give 166 mg (62%) of colourless, prismic 1-methyl-4-quinolone: m.p. 152–153° (lit.[45] 152°); m.m.p. 152–153°. The IR and NMR spectra are superimposible onto those of authentic material prepared from 4-methoxyquinoline by methylation followed by aqueous hydrolysis.

4-Methoxy-1-methyl-2-quinolone (**17**) *from 2-chloro-4-methoxyquinoline.* To a solution of 108 mg (0·558 mmol) of 2-chloro-4-methoxyquinoline and 102 mg (0·62 mmol) silver fluoroborate in 25 ml of 1,2-dichloroethane was added 2·3 g (1·0 ml, 16 mmol) of MeI. After the mixture had been stirred for 11 hr, the AgI_2 was collected and washed with two 5 ml portions of MeOH. To the combined filtrate and washings was added 250 ml of ether to give a colourless precipitate which was taken up in 6 ml of 5% NaOH aq. The basic solution was CH_2Cl_2 extracted. Evaporation gave 86 mg (81%) of colourless oily crystals which were recrystallized from benzene–pentane to give 64 mg (61%) of colourless needles of 4-methoxy-1-methyl-2-quinolone: m.p. 100–101° (lit.[40] 103°): m.m.p. 100–101·5°: IR and NMR spectra are superimposible onto those of material produced by the methylation of 4-methoxy-2-quinolone (*vide supra*).

2,4-Dimethoxy-1-methylquinolinium fluoroborate. To a solution of 513 mg (2·71 mmol) of 4-methoxy-1-methyl-2-quinolone and 535 mg (2·74 mmol) of silver fluoroborate in 50 ml of 1,2-dichloroethane was added 2·0 ml (32 mmol) of MeI. After the solution had been stirred overnight the precipitated AgI_2 was collected and washed 10× with MeOH, and the combined filtrate and washings were poured into ether

(400 ml). The colourless precipitate, 633 mg (80%), which formed was recrystallized from MeOH–Et_2O to give 486 mg (62%) of colourless, crystalline 2,4-dimethoxy-1-methylquinolinium fluoroborate: m.p. 187·5–188°: IR (nujol) 3105 (CH), 1606, 1578, 1525, and 1503 (Ar ring), 1 01, 1379, and 1035 cm^{-1} (C—O): NMR (CD_3CN) δ 3·98 (s, 3, N—C<u>H</u>$_3$), 4·30 (s, 3, O—C<u>H</u>$_3$), 4·38 (s, 3, O—C<u>H</u>$_3$), 6·88 (s, 1, <u>H</u>-3), 8·10–7·55 (m, 3, <u>H</u>-6, <u>H</u>-7, <u>H</u>-8), and 8·31 (d of d of d, J_{56} = 7·9Hz, J_{57} = 16 Hz, J_{58} = 1·1 Hz, 1, <u>H</u>-5). (Calc. for $C_{12}H_{14}BF_4NO_2$: C, 49·52: H, 4·84: N, 4·81. Found: C, 49·51: H, 4·86: N, 4·79%). The same salt was prepared in the same manner in 22% yield from 2,4-dimethoxyquinoline and in 55% yield from 2-methoxy-1-methyl-4-quinolone.

Calorimetric determination of the liquid-phase enthalpies of isomerization. The calorimeter and the general procedure used have been previously described[3] and were used as noted except that a Vibro-Mischer was used to stir the calorimeter and the temperature of the oven in which the calorimeter was operated was regulated by a controller described by Anderson.[46]

The general procedure for determination of the enthalpies of isomerization was as follows: a weighed sample of the pure isomer or mixture to be studied was placed in the reaction vessel containing a thin glass bulb containing 10% by weight of catalyst and the vessel was sealed with a solid plunger positioned over and supporting the catalyst bulb. In the cases of the unstable isomers, the plunger was constructed of 3 mm o.d. Pyrex tubing, the end of which was sealed with a serum cap. The assembled calorimeter and its contents were allowed to reach thermal equilibrium with the oven and then a number of electrical calibrations were performed before and after the reaction. No systematic differences in these calibrations could be detected: the average deviation of the calibrations was 2%.

The compounds were tested independently for thermal stability at the temperature of the calorimeter, and the thermally stable compounds were reacted as the pure melts at 140–150°. Since the thermally unstable materials **15** and **18** rearranged appreciably under the conditions of enthalpy measurement, these compounds were studied calorimetrically as mixtures in the stable isomers **14** and **17**, respectively, at 130°. After the initial calibrations, in the cases of the thermally unstable isomers, a sample of the melt was taken from the reaction vessel through the hollow plunger rod by means of a 1·4 mm o.d. Teflon tubing, after which the catalyst bulb was broken and the heat output was measured. The heat output curves were analyzed by the method of Shoemaker and Garland:[47] the recorder deflection was taken as the perpendicular distance between the initial and final slopes extrapolated to the middle of the heating period, and the method of Sturtevant,[48] in which the deflection was obtained by extrapolating the initial and final slopes to the point at which the temperature was the average of the extremes of temperature during the heating period, was shown to give the same result.

The accuracy of the calorimeter was shown to be consistent with values previously reported by measuring the $\Delta H_i°$ of equilibration of 2-methoxypyridine and 1-methyl-2-pyridone. An average of $-11·9 \pm 1·5$ kcal/mol was obtained for four runs. Beak, Bonham, and Lee report a value of $-12·1 \pm 0·8$ kcal/mol.[3] The value of $-12·1$ has been corrected to omit one run which was conducted beginning with a mixture of the compounds. To give correct results, mixture runs must be corrected for the heat of solution of the minor isomer in the major isomer (*vide supra*).

Analysis of the products from the calorimetry experiments by NMR and IR spectroscopy showed, to the limits of detection, complete conversion to the compound designated as the stable isomer, with isolated yields ranging from 84·5–99·7% for all cases. The catalysts were recovered in yields of 56–91·3%.

TABLE 3. CALORIMETRICALLY DETERMINED $\Delta H_i°$ BETWEEN 2-METHOXYQUINOLINE (**9**) AND 1-METHYL-2-QUINOLONE (**10**) AT 150°

Initial mmol **9**	Initial mmol catalyst	*Qe* (cal/cm)	Observed deflection (cm)	Heat evolved (cal)	$\Delta H_i°$ (kcal/mol)
9·43	0·575	8·46	12·98	109·6	− 11·6
9·47	0·575	8·61	12·60	108·3	− 11·5
9·43	0·575	8·68	11·50	100·0	− 10·6
6·39	0·383	9·67	8·10	78·2	− 12·2[a]
					Av. − 11·5 ± 0·7

[a] Calculated from two calibrations only.

The initial mixtures obtained in the cases of the thermally unstable isomers were analyzed by the UV method of Dewar and Urch.[49]

Control experiments showed that no heat of solution of the catalysts in **14** or **17** could be detected, that the heat of stirring the contents of the reaction vessel could not be detected, and that the mixtures studied were homogeneous melts at the time of bulb breakage. The initial amounts of the reactants, the calibration factors, Q_e, the observed pen deflections, the heat liberated, and the $\Delta H_l°$, as well as the average $\Delta H_l°$ for each compound, are listed in Tables 3–8. The errors are standard deviations estimated by the method of Bauer.[50]

TABLE 4. CALORIMETRICALLY DETERMINED $\Delta H_l°$ BETWEEN 1-METHOXYISOQUINOLINE (**11**) AND 2-METHYL-1-ISOQUINOLONE (**12**) AT 150°

Initial mmol **11**	Initial mmol catalyst	Qe (cal/cm)	Observed deflection (cm)	Heat evolved (cal)	$\Delta H_l°$ (kcal/mol)
9·42	0·575	8·46	16·49	139·2	− 14·8
9·48	0·575	9·04	13·12	118·6	− 12·5
6·30	0·383	7·61	12·12	92·3	− 14·7
6·34	0·383	8·47	10·59	89·8	− 14·2
6·26	0·383	9·32	8·92	83·0	− 13·3[a]
6·33	0·383	8·82	10·11	89·2	− 14·1[a]
					Av. − 13·9 ± 0·9

[a] Calculated from two calibrations only

TABLE 5. CALORIMETRICALLY DETERMINED $\Delta H_l°$ BETWEEN 2,4-DIMETHOXY-6-METHYLPYRIDINE (**13**) AND 4-METHOXY-1,6-DIMETHYL-2-PYRIDONE (**14**) AT 150°

Initial mmol **13**	Initial mmol catalyst	Qe (cal/cm)	Observed deflection (cm)	Heat evolved (cal)	$\Delta H_l°$ (kcal/mol)
13·1	0·808	9·00[a]	17·2	155	− 11·8[b]
13·2	0·822	11·4	14·5	165	− 12·5
13·1	0·808	11·5	13·5	156	− 11·9
					Av. − 12·1 ± 0·4

[a] Calculated from three calibrations only
[b] T = 140°.

TABLE 6. CALORIMETRICALLY DETERMINED ΔH_l BETWEEN MIXTURES OF 2-METHOXY-1,6-DIMETHYL-4-PYRIDONE (**15**) AND 4-METHOXY-1,6-DIMETHYL-2-PYRIDONE (**14**) AND PURE **14** AT 130°

Initial mmol **15**	Initial mmol **14**	Initial mmol catalyst	Qe (cal/cm)	Observed deflection (cm)	Heat evolved (cal)	ΔH_l (kcal/mol)
6·76	6·42	0·820	5·50	6·14	33·8	— 5·0
9·74	9·08	0·871	5·26	9·79	51·5	− 5·3
4·98	6·85	0·463	6·24	4·48	28·0	− 5·6
						Av. − 5·3 ± 0·3

TABLE 7. CALORIMETRICALLY DETERMINED ΔH_i° BETWEEN 2,4-DIMETHOXYQUINOLINE (16) AND 4-METHOXY 1-METHYL-2-QUINOLONE (17) AT 140°

Initial mmol 16	Initial mmol catalyst	*Qe* (cal/cm)	Observed deflection (cm)	Heat evolved (cal)	ΔH_i° (kcal/mol)
7·54	0·492	8·45	9·30	78·7	− 10·4
10·8	0·708	9·47	12·3	116	− 10·7
10·4	0·687	8·39	13·0	108	− 10·4
					Av. − 10·5 ± 0·2

TABLE 8. CALORIMETRICALLY DETERMINED ΔH_i BETWEEN MIXTURES OF 2-METHOXY-1-METHYL-4-QUINOLONE (18) AND 4-METHOXY-1-METHYL-2-QUINOLONE (17) AND PURE 17 AT 130°

Initial mmol 18	Initial mmol 17	Initial mmol catalyst	*Qe* (cal/cm)	Observed deflection (cm)	Heat evolved (cal)	ΔH_i (kcal/mol)
3·27	7·28	0·749	7·17	2·53	18·1	− 5·5
1·99	15·62	0·698	6·80	1·97	13·4	− 6·7
2·38	6·66	0·598	7·66	1·95	14·9	− 6·3
						Av. − 6·2 ± 0·6

Estimation of the heats of mixing of isomer pairs. Heats of mixing of the isomer pairs **15** in **14** and **18** in **17** were estimated by measuring the heats of mixing of model **6** in **4** to give mixtures of the average composition obtained in the calorimetric runs. The heats of mixing were measured in the calorimeter in a round-bottomed glass vial which had two compartments separated by a frangible glass partition each containing the pure components to be mixed. After thermal equilibration and calibration, the glass partition was broken, and the heating or cooling of the calorimeter was observed. Values obtained for a 35% mixture of 1-methyl-4-pyridone in 1-methyl-2-pyridone at 130° were +0·5 and +0·7 kcal/mol of 1-methyl-4-pyridone.

GLPC determination of the liquid-phase K_{eq} *for the catalyzed, thermal isomerization of* **7** *and* **8**. Two isomer mixtures which bracketed the equilibrium mixture in initial concentrations of **7** and **8** were used and the change in concentration of **7** and **8** was observed to approach a common value for each mixture.[4]

TABLE 9. GLPC DETERMINED K_{eq}, ΔH_i°, G_i° AND ΔS_e° BETWEEN 2-METHOXY-6-CHLOROPYRIDINE (7) AND 1-METHYL-6-CHLORO-2-PYRIDONE (8)

	115°	125°	140°
Initial **8**/**7** mol ratios	$4{\cdot}11 \times 10^2$	$8{\cdot}08 \times 10^2$	$7{\cdot}48 \times 10^2$
	$5{\cdot}34 \times 10^3$	$3{\cdot}91 \times 10^3$	$5{\cdot}97 \times 10^3$
wt. catalyst (mg)	6·0	6·0	6·0
equilibration time (days)[a]	6·0	1·0	2·0
$Keq \times 10^3$	2·05 ± 0·40	1·75 ± 0·15	1·45 ± 0·50
ΔH_i° (kcal/mol)	−4·05 ± 2·21	−4·05 ± 2·2	4·05 ± 2·2
ΔG_i° (kcal/mol)	−5·90 ± 0·10	−5·94 ± 0·04	−6·01 ± 0·24
ΔS_i° (ev)	4·78 ± 5·35	4·75 ± 5·35	4·63 ± 4·73

[a] **7**, **8**, and the catalyst were shown to be stable individually under the reaction conditions by NMR analysis and by m.p. for the latter two compounds

The ratio of **8**:**7** was between 1×10^3 and 8×10^4 for the more dilute mixture, and between 1×10^2 and 8×10^2 for the more concentrated mixture. Ratios before and after equilibration were determined by GLPC. Equilibrations were carried out in the presence of 10 wt. % of the catalyst in vacuum-sealed thick-walled glass tubes placed in oil baths at the specified temperature $\pm 1°$. After suitable reaction time had elapsed, the tubes were opened and the contents were treated with CCl_4 and filtered. The solvent was carefully evaporated and the residue was dissolved in CH_2Cl_2 for GLPC analysis. Appropriate controls employing known concentrations of the isomer pairs established the accuracy of this procedure. The equilibrium constants obtained at 115°, 125°, and 140° were plotted *vs.* $1/T$ to give ΔG_i°, ΔH_i°, and ΔS_i°. (Table 9).

The final equilibration residue showed the presence of an unidentified impurity by GLPC which increased in magnitude with higher temperatures and longer equilibration time. The amount of the impurity varied from approximately equal magnitude with the minor isomer to twenty times that magnitude. The amount of this material did not appear to influence the magnitude of the equilibrium constants and this material was not identified.

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