Study of the enol–enaminone tautomerism of α-heterocyclic ketones by deuterium effects on ^{13}C chemical shifts

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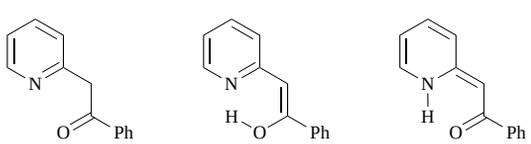
Deuterium isotope effects on ^{13}C chemical shifts have been measured for the enol and enaminone tautomers of a series of α-heterocyclic ketones. Partial deuteration of the exchangeable hydrogen bound to the oxygen atom of the enol or the nitrogen atom of the enaminone leads to deuterium induced shifts of the ^{13}C frequencies (^{2}DIS) which are distinctive for the two types of structures. Thus, 9-methyl-2-phenacyl-1,10-phenanthroline, 2-pyridylacyl- and 2-phenacyl-quinazolines and 2-pyridylacyl- and 2-phenacyl-quinolines, which are known from independent evidence to exist in the enaminone structures, display large and variable negative ^{4}DIS values, −240, −93, −126, −437 and −375, respectively, at the carbon bearing the oxygen atom. By contrast, 2-pyridylacyl- and 2-phenacyl-pyrazines, which are known to exist in the enol form, show large positive ^{2}DIS values, 527 and 479, respectively, for the oxygen bound carbon atom.

Introduction

The tautomeric behavior of heterocyclic ketones containing a CHRCOR′ substituent α to a pyridine-like heterocyclic nitrogen atom differs from that of simple ketones in that a hydrogen atom migration from carbon to nitrogen to form an enaminone provides an alternative to enolisation as a pathway for tautomerisation.[1–7] In contrast to most simple ketones, for aromatic heterocycles with an acylmethyl substituent at the 2-position, either or both of the enol and the enaminone tautomeric forms are sufficiently stable to be observable spectroscopically, if a suitable solvent is chosen.[2,3] As shown for the enol and enaminone tautomers of 2-phenacylpyridine a probable factor contributing to this stabilization is hydrogen bonding.



The relative stabilities of the enol and enaminone tautomers in such systems are quite sensitive both to solvent and to the heterocycle structure.[3] In general, a strongly hydrogen-bonded enol is favored by non-polar solvents. Thus, for 2-phenacylpyridine at equilibrium in aqueous solution, 1 and 12% of enol and enaminone forms are present, respectively,[4] but in dioxane the enol is the dominant tautomer.[2] The enaminone form is favored by factors, such as benzoannelation, which decrease the stability of the fully benzenoid aromatic ring present in the keto and enol tautomers. Thus, for 2-phenacylquinoline the enaminone appears to be favored in all solvents.[5–8] The enaminone is also stabilized by a more basic nitrogen which leads to enhanced resonance between nitrogen and carbonyl groups, and the greater stability of the enol over the enaminone for phenacylpyrazine, even in aqueous solution, can be attributed to the lower basicity of the nitrogen atom in pyrazine than pyridine.[9]

In characterizing tautomerism of this type, spectroscopic distinctions between the enol and enaminone structures are clearly important. Unfortunately, such distinctions are not always easily made. A number of methods have been proposed but, as has been discussed in recent papers,[3,6,9,10] most are either of limited scope or not unambiguous and are summarized below.

UV–VIS spectroscopy

Enaminone and enol tautomers usually differ in their UV–VIS spectra.[2] When an *N*-methylenaminone is available this provides a model for the enaminone structure. Alternatively, if the spectrum of the enolate anion can be measured, *e.g.* in aqueous sodium hydroxide, λ_{max} for the enol normally occurs at a shorter wavelength and for the enaminone at a longer wavelength.[10] UV–VIS spectroscopy is also useful for examining the solvent dependence of tautomerism. Structural assignments may be confirmed by comparison with other spectroscopies in an appropriate solvent (*e.g.* NMR in $CDCl_3$).[3]

IR spectroscopy

IR spectra have been used by Greenhill *et al.* to identify the hydrogen-bonded hydroxy group and carbon–carbon double bond of an enol for 4-quinolylpyruvate in CCl_4 as solvent.[10] Use of IR spectroscopy is restricted to suitable solvents, but correlation with UV–VIS spectra can extend its scope.

^{1}H NMR spectroscopy

Proton chemical shifts fail to distinguish enol and enaminone tautomers.[3,7] The presence of allylic coupling in enols of methyl ketones and the magnitude of coupling constants between hydrogen atoms in the 3- and 4-positions of the aromatic ring are diagnostic but are restricted to ketones possessing these structural features.[7]

^{15}N NMR spectroscopy

Greenhill *et al.*[6] have exploited the large difference in chemical shifts between aromatic and non-aromatic heterocyclic nitrogen atoms to distinguish enol and enaminone tautomers. Due to the high concentrations of substrate required for detection of natural abundance ^{15}N signals, and the less routine character of nitrogen than proton or carbon NMR spectroscopy, this method has not been widely used.

^{13}C NMR spectroscopy

A more generally applicable distinction between enol and

enaminone tautomers is provided by the larger (*ca*. 20 ppm) ^{13}C chemical shift value of carbon bound to oxygen in the carbonyl group of the enaminone than in the enolic function of the enol. However, the individual shifts are influenced by electronegative substituents and these must be taken into account in applying this criterion.[3]

Results and discussion

The above discussion indicates the scope for additional methods for differentiating enol and enaminone tautomers. An attractive possibility is the use of deuterium induced shifts on ^{13}C frequencies (DIS). Replacement of the (O/N)H protons by deuterons induces a secondary isotope effect on the chemical shifts of some ^{13}C atoms in the molecule, which is observed as a 'splitting' of their NMR signals when this replacement is only partial. DIS have provided a wealth of information on hydrogen bonding and tautomerism.[11a–l] We have recently extended the application of DIS to the assignment of heterocyclic tautomerism[12] and developed a method to investigate fast tautomeric equilibria where both tautomers are present in significant amounts.[13]

In the present paper we report independent evidence of enol or enaminone structures for a series of compounds having an acylmethyl group in the α-position to a heterocyclic nitrogen.

The compounds studied in this work were available from a previous investigation of ^{13}C NMR spectra.[3] In that investigation 19 structures were shown to exist partially or completely in enaminone or enol forms. In the present study ^{13}C spectra have been recorded for partially deuterated samples of all of these compounds and their suitability for DIS measurements has been assessed.

The method of partial deuteration is effective when exchange of the isotopically substituted hydrogen is slow enough to allow observation of separate lines for the two isotopomers. This proved to be the case for five of the compounds studied, of which two were known to have enaminone structures, one was an enol, and two were predominantly, but perhaps not exclusively, enaminones.

For the other compounds exchange was too fast for separate peaks to be observed. However, in a number of instances approximate DIS values were obtained by comparison of ^{13}C chemical shifts of deuterated compounds with their protonio counterparts. This method is referred to as 'method B', in contrast to the partial deuteration procedure of 'method A'. The lower precision of method B is partly due to variations of chemical shifts with the concentration of the sample.

The ^{1}H and ^{13}C chemical shifts, together with the DIS values measured for compounds **1**–**6** are shown in Fig. 1. The ^{13}C chemical shifts and the DIS values for compound **7** are given in Fig. 2. For compounds **1**–**4**, 10–30% of the keto forms were also observed as previously reported.[3] The NMR data refer to the other tautomer(s), *i.e.* the enol or the enaminone, or a mixture of the two. Separate signals are not expected for enol and enaminone tautomers because they are rapidly interconverted by intramolecular proton transfer between electronegative atoms.

For structures **1**–**6** the complete assignments of ^{1}H and ^{13}C chemical shifts were made on the basis of ^{1}H–^{1}H (COSY) and ^{1}H–^{13}C direct (HETCOR) and long-range (LRHETC) correlations. The DIS values are recorded as differences in ^{13}C chemical shifts, $DIS = \delta_C(H) - \delta_C(D)$, where $\delta_C(H)$ and $\delta_C(D)$ are the chemical shifts of the carbon atom in the protium and deuterium isotopomers, respectively. The number of bonds n between the carbon measured and the site of deuterium substitution is indicated by a superscript (^{n}DIS). DIS values normally amount to a fraction of a part per million and are conveniently recorded as parts per billion (ppb).

DIS values were measured by method A for compounds **1**, **3**, **5** and **7**, and by method B for compounds **2** and **6**. All the measured DIS values are reported. For compound **4**, which was at the limit of fast exchange, method A was preferred to method B, but the smaller DIS values gave collapsed signals displaying only a shoulder. In these cases, the signs but not the magnitudes of the DIS could be determined and are shown in Fig. 2.

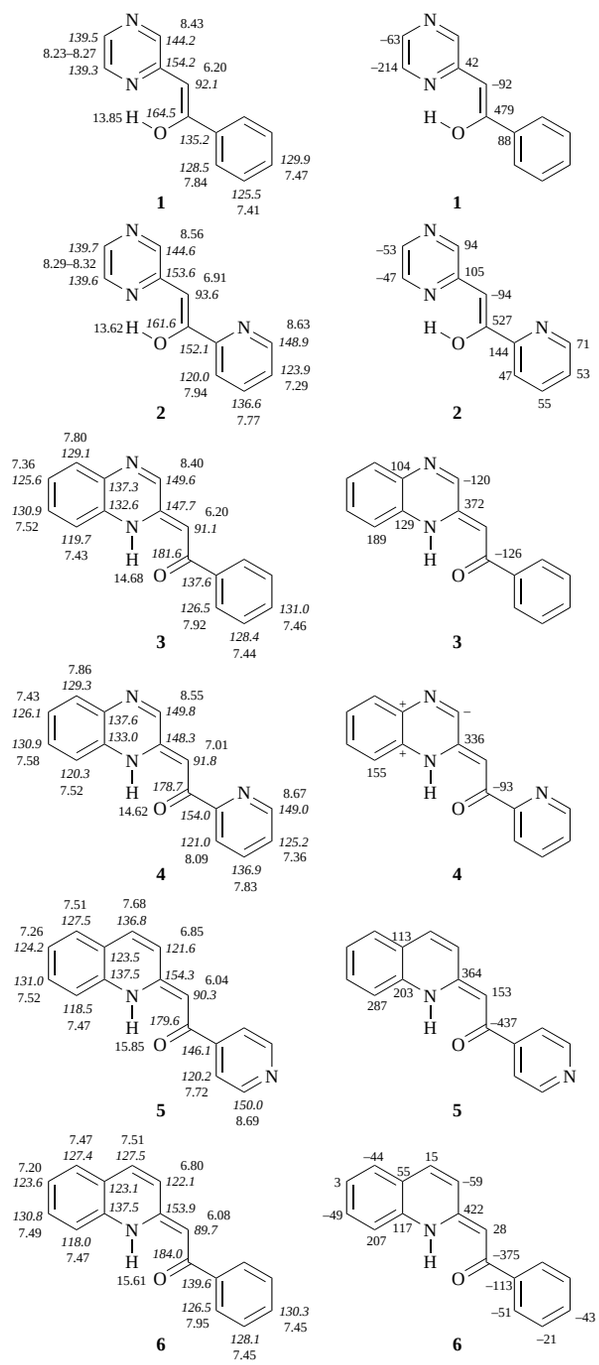


Fig. 1 ^{1}H and ^{13}C chemical shift assignments (left) and DIS in ppb (right) for compounds **1**–**6**

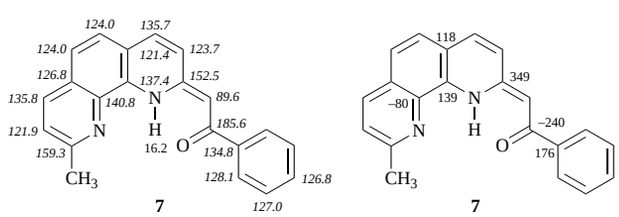


Fig. 2 ^{13}C chemical shift assignments (left) and DIS in ppb (right) for compound **7**

Interpretations of DIS distinguish intrinsic and equilibrium isotope effects.[11a] Substitution of deuterium for hydrogen

causes a change in zero point energy of the bond to the hydrogen which leads to a small decrease in length and increase in electron density. These are the consequences of a reduced anharmonicity and mean square amplitude of vibrations of bonds to deuterium compared with bonds to hydrogen and are believed to be responsible for intrinsic DIS effects. Normally, substitution of deuterium increases electron density in neighbouring bonds and DIS effects are positive. However, negative intrinsic DIS are also observed as long-range DIS (over more than three bonds) in rigid aromatic systems, or in the case of strong hydrogen bonds at the carbon bearing the hydrogen bond acceptor.[11d,e,h,j,l,13]

Equilibrium DIS effects[14] arise where a sample consists of a rapidly equilibrating mixture of isomers. The ^{13}C chemical shifts then represent an average of contributions from the isomers. If the equilibrium is perturbed by isotopic substitution, a different average and a DIS value reflecting this change are observed. Equilibrium DIS provide a potential source of negative values and of values that are larger than expected from intrinsic effects.[15,11i] They may be important in enaminone or enol spectra when there are contributions from major and minor tautomers subject to perturbation by isotopic substitution.

To assess the magnitude of equilibrium DIS effects consider an 80:20 mixture of enaminone and enol which is perturbed to 82:18 by deuterium substitution. This corresponds to an equilibrium isotope effect of 10%. For a carbon atom with chemical shifts of 120 and 110 ppm in enaminone and enol structures, respectively, the deuterium substitution would lead to a change in the observed ^{13}C shift from 118 to 118.2 ppm as a result of the equilibrium isotope effect. The change of 0.2 ppm is comparable to a moderate intrinsic DIS effect. Moreover, intrinsic DIS effects will be superimposed on equilibrium values.

Inspection of the DIS values at the carbon atoms in the 2-position of the heterocycle and the carbon atoms bound to oxygen reveals a very marked difference for structures **1** and **2** compared with structures **3**–**7** (Figs. 1 and 2). As detailed below, the large positive values are ^{2}DIS, whether they are interpreted as intrinsic DIS or equilibrium effects. ^{2}DIS reveal the position of the exchangeable proton, thus allowing the assignment of the major tautomeric form.[11e,g,h,12,13,15] Interpreted as intrinsic DIS, large positive values at the carbon atom bound to the oxygen in pyrazines **1** and **2** (479 and 527 ppb) indicate that these are predominantly in the enol–imine form. The interpretation of these DIS as equilibrium values leads to the same conclusion: because deuterium forms stronger bonds than protium, deuteration shifts the equilibrium towards the most stable form. If this is the enol, positive DIS values are expected at the carbon bound to the oxygen, because the chemical shift of this carbon in the enol is *ca.* 20 ppm lower than in the ketone.[3] It should be stressed however that it is rather uncommon to encounter examples of tautomeric equilibria leading to significant equilibrium DIS effects. The positive DIS values in the 2-position of the pyrazine ring are considerably smaller (42 and 105 ppb) and comparable to the values at the carbon carrying the hydrogen bond acceptor in the resonance assisted hydrogen bond systems of salicyl anilides[13] or β-diketones.[15]

For compounds **3**–**7**, large positive values in the 2-position of the polycyclic heterocycle (372, 336, 364, 422 and 349 ppb, respectively) indicate that these compounds are predominantly in the ketoenamine form. Interpreted as intrinsic DIS, they show that the exchangeable proton is bound to the nitrogen. The same conclusion can be reached if the ^{2}DIS(C2) are interpreted as equilibrium effects, since the chemical shifts of the carbon bound to the nitrogen are larger in enaminones (148–155 ppm[11k] and 151–156 ppm[16]) than in enolimines (160–165 ppm[13]). The negative ^{4}DIS values at the carbon bound to the oxygen in compounds **3**–**7**, are much larger than those encountered in enaminones[11e] and are likely to be equilibrium effects. Interpreted in the same manner as discussed for pyrazines **1** and **2**, these equilibrium effects indicate that the enaminone is the most stable tautomer.

Many of the DIS in other positions serve to confirm the assignments of the dominant tautomer. Thus, in compounds **1** and **2**, DIS(C6) values are similar to those at the carbon bound to the nitrogen in salicyl anilides,[13] which are exclusively enolimines. DIS values at the *ipso* carbon in the aryl of the arylacyl group (88 and 144 ppb) are normal for ^{3}DIS. Interpreted as intrinsic DIS, the values in the 4a-, 8- and 8a-positions of the polycyclic heterocycle in compounds **3**–**6** indicate that in the dominant tautomer the exchangeable proton is bound to the nitrogen. However, in anilines the ^{2}DIS values are larger than for ^{3}DIS,[11f] and the larger values in the 8-position suggest that these may be equilibrium effects. The chemical shifts in the *ortho* position are larger in aromatic enamines (120–122 ppm[13]) than in anilines (113–116 ppm), thus equilibrium ^{3}DIS(C8) would point to the enamine as the most stable tautomer. The DIS values at the methyne carbon in (arylacyl)methyl group are not expected to yield any information about the tautomerism. Even when they are intrinsic DIS, the values at this position of a resonance-assisted hydrogen bond system are determined by the strength of the bonds involved in the transmission pathway.[13]

In conclusion, analysis of the DIS indicates that the dominant tautomer is the enolimine for pyrazines **1** and **2** and the ketoenamine for all of quinoxalines **3** and **4**, quinolines **5** and **6** and phenanthroline **7**. The same conclusion has been reached by previous spectroscopic studies.[3] In our work, no evidence for the presence of a minor isomer was obtained, and while this possibility cannot be excluded for the phenacyl- and pyridylacyl-quinoxalines, **3** and **4**, for the other compounds there seems little reason to doubt that only one tautomer is present in a significant amount, which suggests that the DIS measured are intrinsic.

Experimental

Materials

α-Heterocyclic ketones were prepared from the appropriate methylheterocycle and ester by base-catalyzed condensation, as previously reported.[3] Samples of the deuterium isotopomer were prepared by stirring a chloroform solution of the α-heterocyclic ketone with deuterated water, decanting the water and repeating the deuteration three times. After drying on anhydrous sodium sulfate, the solvent was removed *in vacuo*. Partially deuterated samples were prepared by mixing the two isotopomers in a ratio close to 2:1. The samples used for NMR analysis were solutions of 50–150 mg of α-heterocyclic ketone in 0.8 cm^3 [^{2}H]chloroform.

NMR spectroscopy

Spectra were recorded on a VARIAN Gemini 300 instrument, in [^{2}H]chloroform. Chemical shifts are given in ppm relative to TMS. The ^{13}C spectra used for DIS measurements were recorded using ^{1}H broadband decoupling. The recycling time was set to 10 s and 30 016 data points were acquired for a typical spectral window of 11 500 Hz, recording *ca.* 3000 transients. The FID data points were zero-filled to 32 K prior to Fourier transformation, providing digital resolutions of *ca.* 5 ppb per data point.

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