Substituent and temperature controlled tautomerism: multinuclear magnetic resonance, X-ray, and theoretical studies on 2-phenacylquinolines

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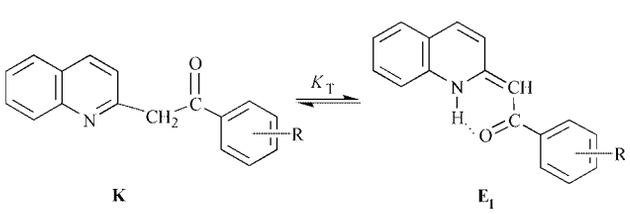
Proton-transfer equilibria in chloroform solution of twelve 2-phenacylquinolines were studied by ^{1}H, ^{13}C and ^{15}N NMR spectroscopies. The (*Z*)-enaminone form stabilized by an intramolecular hydrogen bond was found to prevail in all cases. Electron-donating substituents in the phenacyl part of the molecule lead to an increase of the ketimine form (to 33% for *p*-NMe_2). Variable temperature ^{1}H NMR measurements show that higher temperatures have the same effect. The negative logarithm values of the equilibrium constant, pK_T, were found to be linearly dependent on Hammett σ substituent constants. The pK_T *vs.* temperature correlation also has a linear character. In general, strong electron-withdrawing substituents cause transformation of the ketimine to the enaminone form to become more exothermic but values of the heat of reaction for 2-phenacylquinolines studied are not linearly dependent on σ. X-Ray data show that the strength of the internal hydrogen bond in the enaminone form increases for strong electron-withdrawing substituents. Rough estimation shows this bond to be stronger in chloroform solution than in the crystalline state. π-Electron delocalization in the six-membered quasi-ring involving the H···O bond is very strong. This effect is responsible for the predominance of the tautomeric enaminone form in 2-phenacylquinolines. On the other hand, semiempirical AM1 and PM3 calculations show that in the gas phase the ketimine tautomer is energetically favored in most cases.

Introduction

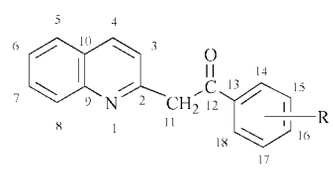
Tautomerism is an interesting phenomenon found in many functionalized nitrogen heterocycles.[1–3] The acidic proton in nitramino- and hydroxy-pyridines is weakly bound which enables fast tautomeric transformations in these compounds.[1–6] Proton transfer from the C–H tautomer is usually much slower.[3]

Enaminones are important organic intermediates and biologically active substances.[7,8] 2-Phenacylquinolines reveal ketimine–enaminone tautomerism, so they are also of considerable interest from that point of view. Enaminone forms were found to dominate in solutions of these compounds.[9–11]



K **E_1**

Various NMR techniques have been used to study the conformation and configuration of enaminones.[7–9,11–13] Similarly, multinuclear magnetic resonance spectroscopic techniques have provided an excellent tool to investigate tautomeric equilibria quantitatively.[4,14,15] It has been reported that protonation-caused chemical shifts of the ring nitrogen atom in aza aromatic compounds are very large.[16] Consequently, ^{15}N NMR spectroscopy provides valuable information on their tautomerism.[17–19] Unfortunately, the chemical shifts of nitrogen can be used to estimate the amount of tautomers only when the tautomeric process is fast.[19,20] Early studies on 2-phenacylquinolines[21] show that substituents affect the positions of their tautomeric equilibria. Other conditions, *e.g.* variable temperature, were also expected to have some effect on the tautomer ratio. The aim of the present paper is to show the substituent and temperature effects on proton transfer in 2-phenacylquinolines. ^{1}H NMR spectroscopy seems to be the best method to evaluate such tautomeric equilibria. Structures for some of 2-phenacylquinolines studied were also determined by single crystal X-ray analysis and related with the results of semiempirical AM1[22] and *ab initio* (STO-3G) MO calculations in order to discover the most important factors that affect the geometry of the molecule.



Compound	R	Compound	R
1	*p*-NMe_2	**7**	*p*-F
2	*p*-NH_2	**8**	*p*-Cl
3	*p*-OMe	**9**	*p*-Br
4	*p*-Me	**10**	*m*-F
5	*m*-Me	**11**	*m*-Br
6	H	**12**	*p*-CF_3

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Table 1 ^{1}H NMR chemical shifts (δ) of 2-phenacylquinoline tautomers for 0.1–0.2 M solutions in $CDCl_3$ at 303 K

Compound	Form[a]	H3[b]	H4[b]	H8	H11[c]	H1[c]	**K** (%)[d]
1	**K**		8.07		4.61		33.0
	E	6.76	7.50	7.37	6.00	15.42	
2	**K**		8.08		4.60		24.6
	E	6.78	7.54	7.39	5.98	15.45	
3	**K**				4.63		11.1
	E	6.77	7.53	7.40	5.99	15.54	
4	**K**				4.65		6.7
	E	6.78	7.55	7.42	6.03	15.64	
5	**K**				4.67		4.8
	E	6.78	7.56	7.42	6.04	15.70	
6	**K**				4.69		4.7
	E	6.83	7.61	7.48	6.07	15.70	
7	**K**				4.64		4.2
	E	6.79	7.58	7.42	5.97	15.59	
8	**K**				4.63		2.1
	E	6.81	7.61	7.44	5.98	15.67	
9	**K**				4.63		2.2
	E	6.80	7.61	7.44	5.98	15.65	
10	**K**				4.62		1.8
	E	6.79	7.58	7.42	5.97	15.66	
11	**K**				4.63		1.5
	E	6.83	7.64	7.50	5.98	15.68	
12	**K**				4.69		1.0
	E	6.87	7.69	7.50	6.06	15.81	

[a] Symbols **K** and **E** refer to ketimine and enaminone forms respectively. [b] ^3J(H3,H4) = 9.0 to 9.2 Hz. [c] Singlet. [d] Contents of the **K** form based on integral intensities of H11 signals in the ^{1}H NMR spectra. Accuracy: ±1%.

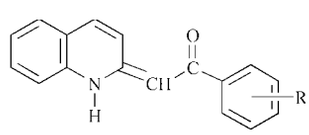
Results and discussion

Three different tautomers should be considered for α-phenacyl derivatives of heterocyclic compounds: ketimine (**K**), enaminone (**E**) and enolimine (**O**). Only two of them were always found in tautomeric mixtures of respective pyridines (**K** and **O**)[10] and quinolines (**K** and **E**).[11]

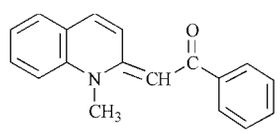
NMR spectra of tautomeric mixtures

All methods utilized in studies on tautomeric equilibria should be used carefully to avoid misinterpretation of the results obtained. One should bear in mind that only one (statistical) signal for each nucleus appears in the NMR spectrum of a tautomeric mixture when the proton exchange between individual forms is fast on the NMR timescale.[4] Single signals are also observed when the system consists practically of only one tautomer. At intermediate rates of the proton exchange broad signals can be seen in the spectrum.[23] Moreover, the electric quadrupole moment of the nitrogen-14 nucleus can also broaden the signal of the N-bound proton even at the low exchange rate.[23] Thus, there are no simple relations between the number of signals in the spectrum, their line shape, and the type of tautomeric process. Since the proton transfer between 2-benzoylmethylquinoline, **K**, and (*Z*)-1,2-dihydro-2-benzoylmethylenequinoline, $\mathbf{E_1}$, is relatively slow, the signals of both tautomeric forms are observed in the NMR spectra. Tautomeric, configurational, and conformational changes are expected to be dependent on substituent R, which should be seen in their NMR spectra. The chemical shifts of H1 (see Table 1) confirm that the enaminone is strongly hydrogen bonded. Thus, it is really the (*Z*) isomer, *i.e.* $\mathbf{E_1}$.[7] This was also proved by detailed analysis of the ^{1}H NMR spectrum of the parent 2-phenacylquinoline, **6**, in chloroform solution.[10] One should bear in mind that due to drastic changes in population of the conformers,[10,24] comparison of the spectral data for tautomeric mixture with those for the fixed (*e.g.* methylated) tautomers may lead to wrong conclusions. Fortunately, slow proton exchange allows observation of the separate signals for each individual form present in the tautomeric mixture. Investigation of these signals enables one to calculate the K_T values with high accuracy.

An intramolecular hydrogen bond stabilizes the $\mathbf{E_1}$ configuration of the 2-phenacylquinoline tautomer. It seems to be the main reason why $\mathbf{E_1}$ is more stable than **K** or $\mathbf{E_2}$ forms in chloroform solution. This is demonstrated by the following observations. *i*. The **E** form non-stabilized by an intramolecular hydrogen bond is always less stable than the **K** form.[25] *ii*. The **K** form of 4-phenacylquinoline (solutions in chloroform, ethanol, and water) is more stable than its **E** form.[25] *iii*. 2-benzoylmethylene-1-methyl-1,2-dihydroquinolines $\mathbf{E_2(Me)}$ have the (*E*) configuration in chloroform solution.[10,11,24]



$\mathbf{E_2}$



$\mathbf{E_2(Me)}$

As it was suggested,[26] the energy (strength) of such an intramolecular hydrogen bond is linearly dependent on the difference between the proton chemical shifts for the compounds considered and that for the model, *i.e.* for hydrogen-bond free compound(s): *E*/kJ mol^{-1} = 4.184[$\Delta\delta$(ppm) +0.4 ± 0.2]. (*E*)-2-Benzoyl-1-(*N*-phenylamino)propene, PhNHCH=C(CH_3)-COPh, seems to be a credible model compound: δ_{NH} 6.6 (in $CDCl_3$).[7] Thus, for unsubstituted compound, **6**, *E* = 39.5 ± 0.8 kJ mol^{-1}. The strongest hydrogen bond was found in **12**. Its energy is by 1.6 kJ mol^{-1} higher than that in **1**.

Population ratios of **K** and **E** tautomers can easily be estimated from the integrals of H11 and H1 signals. Contributions of the **K** form to the mixture of tautomers in chloroform solution of the compounds studied are shown in Table 2. Thus, it can be seen that the enaminone form predominates for all compounds studied. Variable temperature experiments show this to be true in the entire 223–313 K temperature range. ^{1}H and ^{13}C

Table 2 ^{15}N and ^{13}C NMR chemical shifts (δ) of 2-phenacylquinoline tautomers for 0.1–0.2 M solutions in $CDCl_3$ at 303 K

Compound	Form	N1	C2	C3	C4	C8	C11	C12
1 [a]	**K**	−74.7	156.86	126.04	136.52	129.00	49.15	194.61
	E	−237.0	153.22	122.77	135.16	117.44	88.75	184.87
2 [b]	**K**	−73.8	156.53	126.12	136.28	128.99	49.14	194.76
	E	−236.2	153.47	122.64	135.42	117.58	88.77	184.60
3	**K**	−73.7	156.02	126.13	136.27	128.93	49.24	195.16
	E	−233.7	153.69	122.36	135.66	117.70	89.08	183.90
4	**K**	[c]					49.27	196.23
	E	−230.1	153.92	122.23	135.77	117.94	89.56	183.87
5	**K**	−73.8					49.29	
	E	−228.4	154.01	122.13	135.87	118.05	89.90	183.83
6	**K**	−73.8	[d]				49.36	
	E	−228.7	154.14	122.24	136.05	118.18	89.88	183.81
7	**K**	−73.8					49.42	
	E	−231.7	154.01	122.16	136.04	117.94	89.34	182.95
8	**K**	−72.8						
	E	−229.2	154.13	122.08	136.26	118.11	89.59	182.41
9	**K**	−74.7						
	E	−229.2	154.11	122.06	136.33	118.11	89.57	182.48
10	**K**	−72.8						
	E	−229.0	154.13	122.11	136.27	118.11	89.77	181.88
11	**K**	−73.7						
	E	−229.0	154.18	122.05	136.44	118.17	89.75	181.96
12	**K**	−73.1						
	E	−226.2	154.45	122.00	136.66	118.46	90.25	181.65

[a] Chemical shift of the substituent nitrogen atom: −324.5 (**K**), −330.0 ppm (**E**). [b] Chemical shift of the substituent nitrogen atom: −319.6 (**K**), −323.2 ppm (**E**). [c] Not observed. [d] 157.30 ppm in $CDCl_3$ according to ref. 11.

NMR spectra of tautomeric mixtures are usually very complex. Identification of some signals for the **K** tautomer was often not possible,[21] even by comparing the spectra with those of the fixed ketimino form, 2-Qui-CMe_2COAr (Qui = quinolyl).[27] Thus, only some chemical shifts for the ketimino form are mentioned in Tables 1 and 2. It is noteworthy that the missing signals were not necessary for the calculation of tautomeric equilibrium constants.

^{15}N chemical shifts in the NMR spectra of the ketimine forms vary in the range of δ −72.80 to −74.69. They are only slightly affected by substituents (substituent chemical shift, SCS = 1.9 ppm). These shifts are comparable to $\delta^{15}N$ values of the fixed ketimino form, 2-Qui-CMe_2COAr, δ −76.4 to −78.4,[27] and to the value of quinoline itself, δ −63.5.[28] On the other hand, ^{15}N chemical shifts of the enaminone forms are shielded significantly (δ −237.0 to −226.2) from those of the ketimine forms. In addition, a much more distinct substituent effect was also observed in the enaminone forms (SCS = 10.8 ppm). Qualitatively, these findings can be explained by an efficient transmission of the substituent effect in the conjugated double bond system of the quasi-ring in the enaminone form although no regular substituent effect on $\delta^{15}N$ can be seen. In this context, one should remember that $\delta^{15}N$ values are sensitive to solvent, concentration, and temperature effects.[29] Although in the course of this work the temperature and solvent in ^{15}N NMR experiments were always the same, the relative contributions of the ketimine and enaminone forms were not constant owing to their strong dependence on substituents.

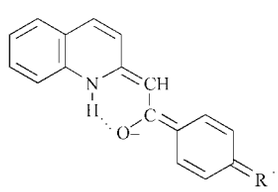
^{13}C NMR spectra (see Table 2) also allow one to distinguish between different tautomers. In general, $\delta^{13}C$ values increase (downfield effect) when R becomes more electron accepting for C11 and C12 in the ketimine and for C2 in the enaminone forms. It is also interesting that comparable SCS values (1.2 ppm) were obtained for the chemical shifts of C2 and C12 in the enaminone form.

UV spectra of tautomeric mixtures

The rate of proton transfer has no effect on UV spectra of a tautomeric mixture. It is known that the **K** form of 2-phenacylquinolines does not absorb light of wavelength above 300 nm.[24,27] On the other hand, 2-benzoylmethylene-1-methyl-1,2-dihydroquinolines are colorful compounds.[24] Thus, similarity of the spectra of a tautomeric mixture of **K** and **E** and that of the **K** form itself is justifiable. This shows that sometimes drastic changes in population of the conformers have negligible effect on UV spectra.[24] In consequence, comparison of the band intensities with those of 1-methyl-1,2-dihydromethylenequinolines can be helpful in estimation of the tautomer ratio.[24]

Substituent effect on tautomeric equilibria

As it can be seen in Table 2, the enaminone form of 2-phenacylquinolines always predominates in chloroform solution. Population ratios of **K** and **E** tautomers were found to be sensitive to the substituent. Increased electron density at the carbonyl oxygen atom strengthens the internal hydrogen bond in the **E**



form. In consequence, electron-donating substituents cause K_T to decrease. For all compounds studied the negative logarithm of the tautomeric equilibrium constants was found to be linearly dependent on Hammett's σ substituent constants:[30] $pK_T = a\sigma + b$. The ranges of a and b are −1.98 to −1.22 and −2.19 to −1.24, respectively for 223–313 K (correlation coefficient R = 0.958–0.996). The slope of that linear dependence becomes less and its quality becomes better at higher temperatures (due to the lower accuracy of **K** determinations at low temperatures), Fig. 1.

Dynamic studies of tautomeric equilibria

The dependence of K_T *vs.* temperature, T, is exponential in character (see Fig. 2). Thus, $\ln K_T = -\Delta H_r^\circ/RT$, where ΔH_r° = heat of reaction, R = gas constant. The quality of the correlations is usually high (see Table 3). In general, the influence of temperature on K_T is more distinct for more electron-

Table 3 Temperature effect on the tautomeric equilibrium constant for 2-phenacylquinolines in chloroform solution

Compound	$\ln K_T = (a/T) + b$ [a]			$\Delta H_r°$/ kJ mol^{-1}
	a [b]	b	R [c]	
1	797.25 ± 60.01	−1.86 ± 0.23	0.978	−6.63
2	825.68 ± 56.49	−1.56 ± 0.21	0.982	−6.86
3	911.49 ± 66.61	−0.89 ± 0.25	0.979	−7.57
4	1725.9 ± 10.71	−3.21 ± 0.04	1.000	−14.34
5	1771.5 ± 74.66	−2.80 ± 0.28	0.993	−14.72
6	1702.1 ± 67.34	−2.56 ± 0.26	0.994	−14.14
7	2615.4 ± 140.11	−5.58 ± 0.53	0.989	−21.73
8	1451.9 ± 132.90	−0.92 ± 0.50	0.968	−12.07
9	2529.5 ± 46.20	−4.56 ± 0.18	0.999	−21.02
10	2453.8 ± 145.80	−4.26 ± 0.55	0.986	−20.39
11	3199.4 ± 157.84	−6.43 ± 0.59	0.992	−26.59
12	2213.4 ± 136.18	−2.69 ± 0.52	0.985	−18.39

[a] Confidence level of calculations 95%. [b] Slope. [c] Correlation coefficient.

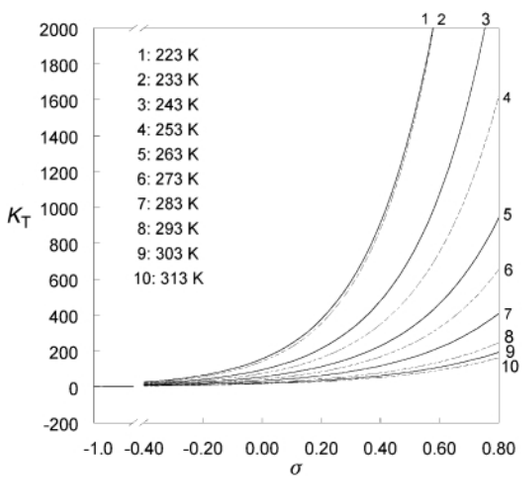


Fig. 1 Substituent effect on the tautomeric equilibria of 2-phenacylquinolines **1**–**12** at different temperatures.

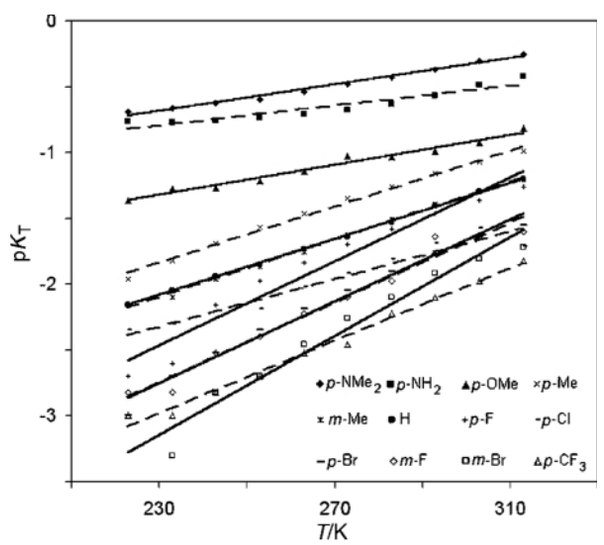


Fig. 2 Temperature effect on the tautomeric equilibria of 2-phenacylquinolines **1**–**12**.

withdrawing substituents. Experimental standard heats of reaction **K** ⟶ **E**, $\Delta H_r° = -RT \ln K_T$, are collected in Table 3. Thus, it can be seen that reaction **K** ⟶ **E** is exothermic for all compounds studied. However, the $\Delta H_r°$'s are not linearly dependent on σ; the exothermic effect is more distinct for strong electron withdrawing substituents.

The dependence K_T *vs.* (σ,T) is shown in Fig. 3. It can be seen that both electron-withdrawing R's and low temperatures cause

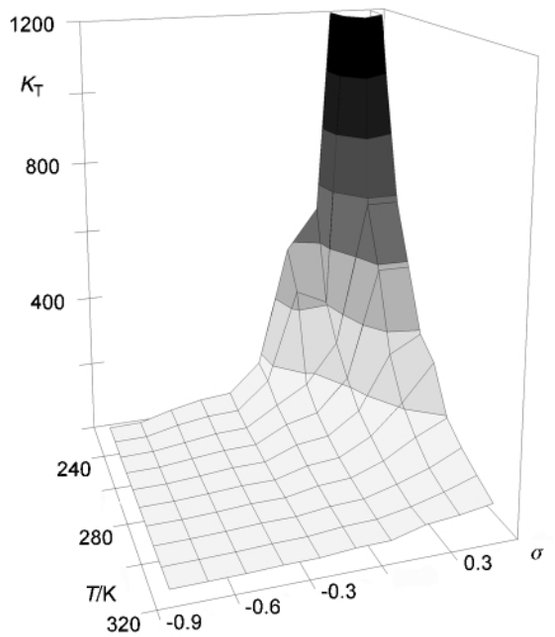


Fig. 3 Effect of temperature and substituents on the population ratio of the tautomeric ketimine and enaminone forms of 2-phenacylquinolines **1**–**12** (solutions in $CDCl_3$).

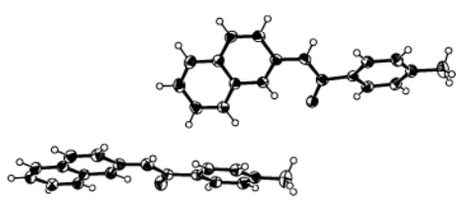
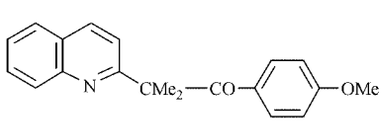


Fig. 4 Crystal structure (ORTEP-III plot[57]) of compound **4**.

K_T to increase. At temperatures above 300 K changes in the amount of the enaminone form become less drastic for all compounds studied in their chloroform solutions. It seems interesting that, with increasing temperature, K_T becomes less dependent on substituents.

X-Ray crystallographic studies

The molecular structure of a compound is always dependent on its physical state. Thus, different tautomeric forms can be preferred in solution, in the crystal, and in the gas phase.[6] X-Ray diffraction studies show that 2-phenacylquinolines exist exclusively in the enaminone form in the crystal at 173 K. As it was shown for compound **5**, the same tautomer prevails at room temperature. The molecular geometry for 2-(*p*-methylphenacyl)quinoline, **4**, is shown in Fig. 4 (positions of hydrogen atoms were found from the electron density map). There are two different molecules of this compound in the unit cell: one is almost planar, **4P**, and another is twisted, **4T**. Molecule **5** is also twisted. On the other hand, *p*-fluoro, **7**, and *m*-bromo derivatives, **11**, exist exclusively in the almost planar enaminone form. All these structures are stabilized by an intramolecular hydrogen bond, N–H···O=C (see $\mathbf{E}_1$). Contrary to the case of 2-nitraminopyridine/2(1*H*)-nitriminopyridine[5,6] and 2-hydroxypyridine/2(1*H*)-pyridone,[31–33] no dimeric forms are present in the crystals of 2-phenacylquinolines. On the other hand, X-ray diffraction studies show that the fixed *p*-methoxy ketimino form **3K** is a strongly twisted molecule.[27]



3K

Table 4 Selected bond lengths (pm) and bond and dihedral angles (°) for compounds **4**, **5**, **7**, and **11** at 173 K

	4P[a]	**4T**[b]	**5**	**5**[c]	**7**	**11**
N1–C2	136.2(3)	136.0(3)	135.6(2)	135.4(2)	136.3(3)	135.1(8)
C2–C3	143.7(3)	143.7(3)	143.7(2)	143.3(2)	143.1(4)	144.1(9)
C2–C11	139.7(3)	139.1(3)	139.8(2)	139.9(2)	140.4(4)	139.7(9)
C11–C12	140.2(3)	141.0(3)	141.1(2)	140.3(2)	140.0(4)	140.7(9)
C12–O	128.2(3)	126.8(3)	127.0(2)	127.2(2)	127.5(3)	126.1(8)
C12–C13	149.6(3)	149.1(3)	149.9(2)	149.6(2)	149.7(3)	150.0(9)
O···H1	167(3)	187(3)	181(2)	172(2)	166(3)	194(7)
C9N1C2	123.3(2)	124.0(2)	124.0(1)	123.5(1)	123.2(2)	124.8(6)
N1C2C3	117.5(2)	116.7(2)	117.0(1)	117.1(1)	117.4(3)	116.5(6)
N1C2C11	119.7(2)	120.6(2)	120.1(1)	119.9(1)	119.8(3)	120.9(6)
C2C11C12	123.1(2)	123.5(2)	122.5(1)	122.9(1)	122.8(3)	121.9(6)
C11C12O	122.1(2)	122.6(2)	123.2(1)	123.0(1)	122.5(2)	123.2(6)
H1N1C2	110(2)	114(2)	113(1)	111(1)	110(2)	117(4)
C11C12C13	121.0(2)	119.2(2)	118.6(1)	119.1(1)	121.1(2)	120.3(6)
N1H1O	142(3)	138(2)	139(2)	141(2)	141(3)	137(6)
C9N1C2C11	177.1(2)	−175.5(2)	171.5(1)	171.7(1)	−178.6(2)	−179.8(5)
N1C2C11C12	−2.7(3)	5.5(3)	−6.3(2)	−6.2(2)	−4.3(4)	−2.7(9)
C2C11C12O	2.2(4)	−3.0(4)	5.6(2)	5.4(2)	−0.7(4)	4.2(10)
C2C11C12C13	−178.1(2)	174.3(2)	−170.7(1)	−170.6(1)	−179.4(2)	−174.0(6)
C11C12C13C14	7.2(3)	34.2(2)	146.0(1)	145.9(2)	6.1(4)	−12.6(9)
C11C12C13C18	−173.3(2)	−147.4(2)	−32.6(2)	−32.8(2)	−175.5(2)	167.0(6)

[a,b] Planar and twisted molecules, respectively (see Discussion). [c] At 293 K.

The data in Table 4 allow us to state that N1–C2, C2–C3 and C12–O bonds in **4P**, **4T**, **5**, **7** and **11** are longer and C2–C11 and C11–C12 bonds are shorter as compared to these in **3K** (complete X-ray data for **3K** are available in ref. 27). On the other hand, the C12–C13 bond has comparable lengths in **4**, **5**, **7**, **11**, and **3K**. C9N1C2, N1C2C11, C11C12O and especially C2C11C12 bond angles are larger in **4**, **5**, **7**, and **11** and N1C2C3 and C11C12C13 bond angles are smaller in these compounds as compared to the same angles in **3K**. Dihedral angles presented in Table 4 for compounds **4**, **5**, **7**, and **11** are quite different from those for **3K**.[27] Thus, substitution of CH_2 by the CMe_2 group in compounds **4**, **5**, **7**, and **11** causes significant conformational changes in their molecules.

It is interesting that angles C11C12O in the almost planar molecules change as follows: **4P** < **7** < **11**. On the other hand, C2C11C12 change in reverse order in those compounds. The intramolecular hydrogen bond C=O···H–N in **7** is almost as long as that in **4P** but it is much longer in **5**, **4T**, and especially in **11**. The H1N1C2 angles change similarly. The benzene ring in **11** is twisted in the opposite direction as compared to other almost planar molecules **4P** and **7**. The N1H1O angle in these compounds decreases as the electron-withdrawing ability of the substituent increases.

Geometrical parameters are approximately the same for molecules **4P** and **4T**. However, the following differences were found: *i* the benzene ring in the phenacyl part of **4T** is more twisted as compared to that in **4P**; *ii* the C12=O bond in **4P** is longer than that in **4T**; *iii* the intramolecular hydrogen bond C=O···H–N in **4P** is shorter by ≈20 pm as compared to that in **4T**; *iv* angle H1N1C2 in **4P** is by ≈4° smaller than that in **4T**; *v* most twist angles in **4P** differ by sign from those in **4T** (twisting in opposite directions); *vi* the N1H1O angle in **4P** is larger as compared to that in **4T**.

Intramolecular hydrogen bonding allows the formation of a six-membered quasi-ring[34] in the tautomeric $\mathbf{E}_1$ enaminone forms of 2-phenacylquinolines. The π-electron delocalization in the N1C2C11C12 spacer of that hydrogen bond seemed worthy of analysis by means of the HOMA model (harmonic oscillator model of aromaticity).[35] The HOMA values for this fragment are always >0.95 (0.952 for **4P** and **4T**, 0.951 for **7**, and 0.963 for **11**), indicating strong delocalization which is comparable with that in typical hetero-aromatic systems such as pyridine (0.998) and pyridazine (0.955), and much better than in pyrylium salts (0.582).[36] The π-electron delocalization in similar hydrogen-bond stabilized six-membered quasi-rings in a series of *N*-salicylideneanilines is much weaker[37] (HOMA = 0.1–0.6). This increased delocalization in 2-phenacylquinolines may be due to rather strong hydrogen bonds. Thus, it is the π-electron delocalization in the hydrogen-bond stabilized ring, reflected in its HOMA value, which is the most important factor responsible for the predominance of the tautomeric enaminone form in these compounds. The approximate energy of the H···O interaction can be estimated by use of the model[38] which was well tested for intramolecular OH···O interactions.[39] The energy values are 9.6 for **11**, 12.8 for **4T**, 16.3 for **5**, 28.5 for **4P**, and 30.7 kJ mol^{-1} for **7**. These data can be compared with an independent measure of the O···H interaction, *i.e.* with the C9N1C2 bond angle shown in Table 4. Analysis based on the Bent–Walsh rule[40] shows that the longer this bond (interatomic distance) the smaller is the bond angle. The resulting scatter graph (see Fig. 5) shows there is a good monotonous dependence. However, it seems worthy of mention that dependences between changes in geometry and changes in energy are either parabolic (harmonic approximation) or exponential, so the plot of *E vs.* angle C9N1C2 is not a straight line.

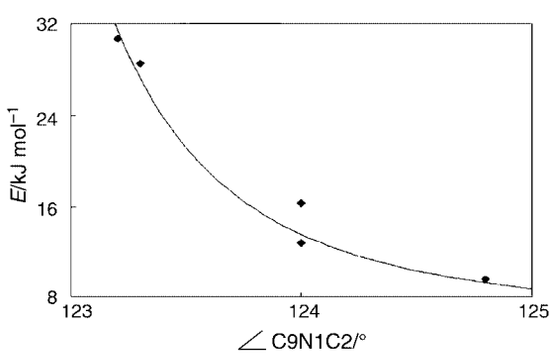


Fig. 5 Plot of the dependence between the O···H interaction energy and C9N1C2 bond angle in 2-phenacylquinolines at 173 K.

Another mutual dependence reflecting hydrogen-bond interaction is that between CO bond length and C9N1C2 bond angle as shown in Fig. 6. The smaller the angle, the longer is the CO bond and the stronger is the hydrogen bond. Thus, CO···H interaction causes the CO bond to be longer.

Table 5 Experimental and calculated geometries [pm or °] of **4P**

Parameter	Exp. (X-ray)	AM1	STO-3G
N1–H1	104.2	100.3	103.8
O···H1	167.1	209.8	162.4
C9N1C2	123.3	122.2	123.9
C1C2C11	119.7	123.1	119.8
C11C12O	122.1	123.8	121.8
H1N1C2	110.4	118.6	111.6
N1H1O	142.2	126.4	141.2

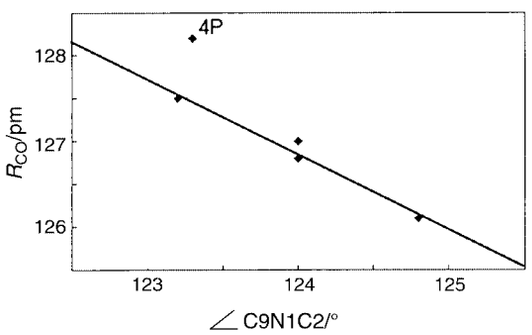


Fig. 6 Plot of the dependence between CO bond length and C9N1C2 bond angle in 2-phenacylquinolines at 173 K.

Electron-donating substituents have a similar influence on the length of that bond. Thus, due to the resonance effect (hyperconjugation) of *p*-methyl in the crystal of **4P** it is considerably longer (as compared to that in **4T**, **5**, **7**, and **11**) and, in consequence, the respective point does not fall on the line in Fig. 6.

Theoretical support

Preliminary theoretical calculations were performed for the compounds studied in order to support the obtained experimental data. Some geometrical parameters obtained for enaminone form **4P** are shown in Table 5. In general, the *ab initio* (STO-3G) method predicts the geometry of the enaminone form more precisely than semi-empirical AM1 and PM3 methods. Moreover, both AM1 and PM3 calculated heats of reaction for 2-phenacylquinolines differ considerably from the experimental data shown in Table 3. The calculations show that the heats of formation for $\mathbf{E}_1$, and especially for $\mathbf{E}_2$, are much higher than for **K**. Unexpectedly, the enaminone form $\mathbf{E}_1$ is preferred in **7**, **8**, **10**, and **12** according to AM1 calculations, which are valid for the isolated molecule in the gas phase.

Conclusions

Multinuclear magnetic resonance shows that proton transfer in chloroform solutions of 2-phenacylquinolines between ketimine and enaminone tautomers is a slow process. This enables quantification of each tautomeric form. The enaminone was found to predominate for all compounds studied. Variable temperature experiments show this to be true in the entire 223–313 K temperature range. The contribution of the ketimine form increases for all compounds that carry electron-donating substituents in the phenacyl part of the molecule. It slightly exceeds 30% for 2-(*p*-dimethylaminophenacyl)quinoline. There is a strong intramolecular hydrogen bond N–H···O=C in the latter tautomer. Rough estimation shows this hydrogen bond to be stronger in chloroform solution than in the crystalline state.

Population ratios of **K** and **E** tautomers were found to be sensitive to the substituent. For all compounds studied the negative logarithm of the tautomeric equilibrium constants were found to be linearly dependent on the Hammett σ substituent constant. In general, influence of temperature on K_T is more distinct for more electron-withdrawing substituents.

Reaction **K** ⟶ **E** is exothermic for all compounds studied. However, standard heats of reaction are not linearly dependent on σ; the exothermic effect is more distinct for strong electron-withdrawing substituents. Both, electron-withdrawing R's and low temperatures cause K_T to increase. At temperatures above 300 K, changes in the amount of enaminone form become less drastic for all compounds studied in their chloroform solutions. At higher temperatures, K_T becomes less dependent on substituents.

X-Ray diffraction studies show that 2-phenacylquinolines exist exclusively in the enaminone form in the crystal at 173 K. As it was shown for 2-(*m*-methylphenacyl)quinoline, **5**, the same tautomer prevails at room temperature. There are two different molecules in the unit cell of 2-(*p*-methylphenacyl)-quinoline: one is almost planar and the other is twisted. Molecule **5** is also twisted. On the other hand, *p*-fluoro, **7**, and *m*-bromo derivatives, **11**, appear exclusively in almost planar enaminone forms. All these structures are stabilized by an intramolecular hydrogen bond, N–H···O=C.

Intramolecular hydrogen bonding allows the formation of a six-membered quasi-ring in enaminone tautomeric forms of 2-phenacylquinolines. The HOMA values for such pseudorings are always >0.95, indicating strong π-electron delocalization. That phenomenon is responsible for the predominance of the enaminone tautomeric form in 2-phenacylquinolines. Analysis based on the Bent–Walsh rule shows that the stronger the hydrogen bond the smaller is the C9N1C2 bond angle, and the longer is the CO bond length.

Experimental

Synthesis

Compounds **1** and **3**–**12** were obtained by treating 2-lithiomethylquinoline with respectively substituted ethyl or methyl benzoates according to known procedures.[41] The reaction products were purified by recrystallization to constant melting point reported earlier for **3**,[21,42] **4**,[21,42] **6**,[12,21,42–47] **8**[21,44] and **9**.[21,42] Satisfactory analytical data (±0.3% for C, H, and N) were obtained for all new compounds. Their mp's are as follows (°C): **1** (205.5–207), **5** (135–137), **7** (137–140), **10** (112–113), **11** (127–129), **12** (151–154). Compound **2** was obtained by hydrolysis of its acetyl derivative.[20]

NMR spectra

All NMR spectra were recorded for 0.1–0.2 M $CDCl_3$ solutions at 303 K (unless otherwise stated) with a Bruker Avance DRX500 FT NMR spectrometer equipped with an inverse detection 5 mm diameter broad band probehead and z-gradient working at 500.13 (^{1}H), 125.76 (^{13}C) and 50.59 MHz (^{15}N). In ^{1}H NMR experiments the spectral width was 10000 Hz (20 ppm) to observe the strongly deshielded protons H1 in enaminone forms, the number of data points 65 K, the flip angle 30°, and the number of scans 8. The FIDs were multiplied by an exponential window function of the digital resolution (0.15 Hz) prior to Fourier Transform (FT). The ^{1}H NMR chemical shifts are referenced to the trace signal of $CHCl_3$ (δ 7.26). In variable temperature (VT) ^{1}H runs the temperature was varied in 10 degree intervals from 223 to 313 K.

In proton composite pulse decoupled (Waltz-16) ^{13}C NMR experiments the spectral width was 33000 Hz (260 ppm), the number of data points 65 K, the flip angle 30°, and the number of scans typically 500–1000. The FIDs were multiplied by an exponential window function of the digital resolution (1.0 Hz) prior to Fourier Transform (FT). The ^{13}C NMR chemical shifts are referenced to the signal of $CDCl_3$ (δ 77.00).

In order to distinguish the spin systems belonging to the different rings and assign the ^{1}H NMR spectra reliably, 2-D double quantum filtered (DQF) ^{1}H,^{1}H COSY[48,49] experiments were run. In these experiments the spectral ranges were limited

Table 6 Experimental data for the X-ray diffraction studies on compounds **4**, **5**, **7**, and **11**

	4	**5**[a]	**5**[b]	**7**	**11**
Formula	$C_{18}H_{15}NO$	$C_{18}H_{15}NO$	$C_{18}H_{15}NO$	$C_{17}H_{12}FNO$	$C_{17}H_{12}BrNO$
Formula weight	261.31	261.31	261.31	265.28	326.19
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/n$ (no. 14)	$P2_1/c$ (no. 14)	$P2_1/c$ (no. 14)	$P2_12_12_1$ (no. 19)	$Pc2_1b$ (no. 29)
a/pm	735.33(2)	728.31(1)	737.19(2)	590.26(4)	447.01(3)
b/pm	1231.33(5)	1445.11(5)	1445.50(4)	765.23(4)	1238.95(7)
c/pm	2934.5(1)	1250.32(4)	1258.37(3)	2843.7(2)	2437.7(2)
β/°	90.488(1)	90.693(2)	90.736(3)		
$V/10^6$ pm^3	2656.9(2)	1315.85(6)	1340.82(6)	1284.5(1)	1350.1(2)
Z	8	4	4	4	4
μ(Mo-Kα)/mm^{-1}	0.081	0.082	0.080	0.095	3.039
No. measured reflections	14072	7149	8737	6653	5904
No. independent reflections	6164	3102	3084	2994	2889
R_{int}	0.052	0.025	0.031	0.053	0.053
R (%)[b]	6.37	4.56	4.88	5.29	4.77
R_w (%)[b]	13.15	10.68	11.47	9.69	9.25
GOF	1.084	1.016	1.032	1.009	1.020

[a] Measured at 173.0 K. [b] Measured at 293.0 K.

in aromatic parts (typically less than 1000 Hz), the data matrix size was 256 points (f_2-axis) × 128 points (f_1-axis), which was zero filled to 256 points along the f_1-axis prior to FT. Eight scans were accumulated for every f_1-increment (f_2-spectrum). A shifted sine-bell window function was used along both axes prior to FT.

2-D z-pulsed field gradient (PFG) selected ^{1}H,^{13}C heteronuclear multiple quantum correlation (HMQC),[50,51] and ^{1}H,^{13}C heteronuclear multiple bond correlation (HMBC)[52] experiments were run to assign reliably the ^{13}C NMR spectra. In HMQC the matrix size typically was 2500 Hz/512 points (^{1}H = f_2-axis) × 10000 Hz/512 points (^{13}C = f_1-axis), which was multiplied by a sine-bell window function along both axes prior to FT. The number of scans was 8 and a composite pulse decoupling (garp) was used to remove proton couplings. In HMBC measurements the spectral range at the ^{13}C = f_1-axis was expanded to include also quaternary C12 resonating in the range 195–181 ppm. In this case the data matrix was zero filled to 1024 points along the f_1-axis and windowed as in the case of HMQC prior to FT. 64 scans were accumulated for each f_1-increment. A 50 ms delay for an evolution of ^nJ(C,H) couplings was included in the pulse sequence.

In order to determine ^{15}N NMR chemical shifts, z-PFG ^{1}H,^{15}N HMBC experiments were run. In these experiments the size of the data matrix was 2500 Hz/512 points (^{1}H) × 22500 Hz/1024 points (^{15}N-axis). The ^{15}N NMR chemical shifts were referenced to an external neat ^{15}N-enriched nitromethane (δ 0.0) sample in a 1 mm diameter capillary tube inserted coaxially inside the 5 mm NMR sample tube. A sine-bell multiplication was done along both axes prior to FT. 64 scans were accumulated for every ^{15}N f_1-increment. A 100 ms delay for an evolution of ^nJ(N,H) couplings was included in the pulse sequence.

X-Ray crystallographic studies

Crystals of compounds **4**, **5**, **7**, and **11** were obtained by slow evaporation of the solvent from their chloroform solutions. The crystal structure data were recorded with a Nonius KappaCCD diffractometer using graphite monochromatized Mo-Kα radiation (λ = 71.073 pm). An oscillation angle of 1° was used in all cases. All measurements were carried out at 173.0 ± 0.1 K and for compound **5** additionally at 293.0 ± 0.1 K. Data were processed by DENZO-SMN.[53] The structures were solved by direct methods (SHELXS 97)[54] and refined on F^2 (SHELXL 97).[55]

For all compounds reflections were corrected for Lorentz polarization effects. The hydrogen atoms were located from the difference Fourier map and refined with isotropic thermal parameters except for methyl hydrogens in **4** and H4 in **11** which were calculated to their idealized positions with isotropic thermal parameters (1.2–1.5 times the C thermal parameter) and refined as riding atoms. Other experimental X-ray data are in Table 6.

CCDC reference number 188/239.

See http://www.rsc.org/suppdata/p2/a9/a908874a/ for crystallographic files in .cif format.

Theoretical calculations

Semiempirical AM1 and PM3 calculations were performed with the HYPERCHEM 3.0 program (Hypercube, Waterloo, Ontario, Canada). *Ab initio* calculations were carried out with the GAMESS 4.3 program[56] using the STO-3G basis set at the Hartree–Fock level.

References

1 J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, *The Tautomerism of Heterocycles* (*Adv. Heterocycl. Chem.*, *Supplement 1*), Academic Press, New York, 1976.
2 A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, 1963, **1**, 339.
3 A. R. Katritzky, M. Karelson and P. A. Harris, *Heterocycles*, 1991, **32**, 329.
4 R. Gawinecki, E. Kolehmainen and D. Rasała, *J. Phys. Org. Chem.*, 1995, **8**, 689.
5 T. M. Krygowski, D. Pawlak, R. Anulewicz, D. Rasała, R. Gawinecki, G. Häfelinger, M. N. Homsi and F. K. H. Kuske, *Acta Chem. Scand.*, 1996, **50**, 808.
6 R. Gawinecki, E. D. Raczyńska, D. Rasała and S. Styrcz, *Tetrahedron*, 1997, **53**, 17211.
7 J.-C. Zhou, *Magn. Reson. Chem.*, 1998, **36**, 565.
8 L. Kozerski, K. Kamieńska-Trela, L. Kania and W. von Philipsborn, *Helv. Chim. Acta*, 1983, **66**, 2113.
9 A. R. Katritzky, I. Ghiviriga, D. C. Oniciu, R. A. More O'Ferrall and S. M. Walsh, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, 2605.
10 R. A. More O'Ferrall and B. A. Murray, *J. Chem. Soc.*, *Perkin Trans. 2*, 1994, 2461.
11 J. V. Greenhill, H. Loghmani-Khouzani and D. J. Maitland, *Tetrahedron*, 1988, **44**, 3319.
12 P. E. Hansen, R. Kawecki, A. Krówczyński and L. Kozerski, *Acta Chem. Scand.*, 1990, **44**, 826.
13 V. V. Lapachev, I. Ya. Mainagashev, S. A. Stekhova, M. A. Fedetov, V. P. Krivopalov and V. P. Mamaev, *J. Chem. Soc.*, *Chem. Commun.*, 1985, 494.
14 M. Witanowski, L. Stefaniak and G. A. Webb, *Annu. Rep. N.M.R. Spectrosc.*, 1977, **7**, 117; 1981, **11B**, 1; 1986, **18**, 1.
15 P. Dobrowolski, B. Kamieński, J. Sitkowski, L. Stefaniak and Y. Chun, *Bull. Acad. Pol. Sci.*, *Chem.*, 1988, **36**, 203.
16 G. C. Levy and R. L. Lichter, *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*, Wiley, New York, 1979, p. 80.
17 L. Stefaniak, *Org. Magn. Reson.*, 1979, **12**, 379.
18 L. Stefaniak, M. Witanowski and G. A. Webb, *Pol. J. Chem.*, 1981, **55**, 1441.

19 J. Llor, O. Lopez-Mayorga and L. Munoz, *Magn. Reson. Chem.*, 1993, **31**, 552.
20 L. Stefaniak, *Tetrahedron*, 1976, **32**, 1065.
21 M. Yamazaki, K. Noda and M. Hamana, *Chem. Pharm. Bull.*, 1970, **18**, 908.
22 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
23 R. M. Silverstein, G. C. Bassler and T. C. Morrill, *Spectrophotometric Identification of Organic Compounds*, 5th edn., Wiley, New York, 1991, pp. 183 and 185.
24 R. Gawinecki, B. Ośmiałowski, E. Kolehmainen and M. Nissinen, *J. Mol. Struct.*, in the press.
25 J. V. Greenhill, H. Loghmani-Khouzani and D. J. Maitland, *Can. J. Chem.*, 1991, **69**, 696.
26 T. Schaefer, *J. Phys. Chem.*, 1975, **79**, 1888.
27 R. Gawinecki, E. Kolehmainen, B. Ośmiałowski and P. Palkovič, *Heterocycl. Commun.*, 1999, **5**, 549.
28 L. Stefaniak, J. D. Roberts, M. Witanowski and G. A. Webb, *Org. Magn. Reson.*, 1984, **22**, 201.
29 G. C. Levy and R. L. Lichter, *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*, Wiley, New York, 1979, pp. 32–33.
30 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
31 D. W. Aksnes and H. Kryvi, *Acta Chem. Scand.*, 1972, **26**, 2255.
32 R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, 1969, **73**, 2465.
33 B. R. Penfold, *Acta Crystallogr.*, 1953, **6**, 591.
34 D. Lloyd and D. R. Marshall, *Proceedings of an International Symposium Aromaticity, Pseudo-aromaticity and Anti-aromaticity*, *Jerusalem*, *1970*, eds E. D. Bergmann and B. Pullman, The Israel Academy of Science and Humanities, Jerusalem, 1971, pp. 85–90.
35 T. M. Krygowski, *J. Chem. Inf. Comput. Sci.*, 1993, **33**, 70.
36 T. M. Krygowski and M. Cyrański, *Tetrahedron*, 1996, **52**, 10255.
37 T. M. Krygowski, B. Stępień, R. Anulewicz-Ostrowska and T. Dziembowska, *Tetrahedron*, 1999, **55**, 5457.
38 T. M. Krygowski, M. K. Kalinowski, I. Turowska-Tyrk, Ph. C. Hiberty, P. Milart, A. Silvestro, R. D. Topsom and S. Daehne, *Struct. Chem.*, 1991, **2**, 71.
39 T. Dziembowska, B. Szczodrowska, T. M. Krygowski and S. J. Grabowski, *J. Phys. Org. Chem.*, 1994, **7**, 142.
40 K. Woźniak, T. M. Krygowski, H. Kariuki, W. Jones and E. Grech, *J. Mol. Struct.*, 1990, **240**, 119.
41 G. Fukata, C. O'Brien and R. A. More O'Ferrall, *J. Chem. Soc.*, *Perkin Trans. 2*, 1979, 792.
42 F. W. Bergstrom and A. Moffat, *J. Am. Chem. Soc.*, 1937, **59**, 1494.
43 N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, 1952, **74**, 5217.
44 E. H. Sund and W. D. Lowe, *J. Chem. Eng. Data*, 1983, **28**, 137.
45 M. J. Weiss and Ch. R. Hauser, *J. Am. Chem. Soc.*, 1949, **71**, 2023.
46 J. F. Wolfe, D. E. Portlock and D. J. Feuerbach, *J. Org. Chem.*, 1974, **39**, 2006.
47 P. E. Wright and W. E. McEwen, *J. Am. Chem. Soc.*, 1954, **76**, 4540.
48 M. Rance, O. W. Srensen, G. Bodenhausen, G. Wagner, R. R. Ernst and K. Wüthrich, *Biochem. Biophys. Res. Commun.*, 1984, **117**, 479.
49 A. Derome and M. Willamson, *J. Magn. Reson.*, 1990, **88**, 177.
50 A. Bax, R. H. Griffey and B. L. Hawkins, *J. Magn. Reson.*, 1983, **55**, 301.
51 A. Bax and S. Subramanian, *J. Magn. Reson.*, 1986, **67**, 565.
52 A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, 1986, **108**, 2093.
53 Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307.
54 G. M. Sheldrick, *Acta Crystallogr.*, *Sect. A*, 1990, **46**, 467.
55 G. M. Sheldrick, SHELXL 97, A program for crystal structure refinement, University of Göttingen, 1997.
56 M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.*, 1993, **14**, 1347.
57 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.