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Tautomeric 2-arylquinolin-4(1*H*)-one derivatives- spectroscopic, X-ray and quantum chemical structural studies

Malose J. Mphahlele[a,*], Ahmed M. El-Nahas[b,*]

[a]*Department of Chemistry, University of South Africa, P.O. Box 392, UNISA, Pretoria 0003, South Africa*
[b]*Department of Chemistry, Faculty of Science, El-Menoufia University, Shebin El-Kom, Egypt*

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Abstract

A convenient method for the synthesis of 2-aryl-1-methylquinolin-4(1*H*)-ones is described. Spectroscopic and X-ray crystallographic techniques as well as quantum chemical calculations have been used to probe the structure of potentially tautomeric 2-arylquinolin-4(1*H*)-ones in solution phase, gas phase and solid state. The exclusive NH-4-oxo nature of the title compounds in solution phase (NMR) and solid state (IR and X-ray) is also corroborated by comparison of their spectroscopic data with those of the corresponding 2-aryl-1-methylquinolin-4(1*H*)-one and 2-aryl-4-methoxyquinoline derivatives. Results from mass spectrometric analysis confirm the coexistence of the 4-quinolinone and 4-hydroxyquinoline isomers in the gas phase and this is supported by quantum chemical computations.

Keywords: 2-Arylquinolin-4(1*H*)-ones; Solution phase, solid state and gas phase studies

1. Introduction

Our research interest currently focuses on the synthesis and structural property studies of the medicinally important 2-arylquinolin-4(1*H*)-one derivatives with potential to exist in tautomeric equilibrium with the 2-aryl-4-quinolinol isomers [1,2]. Understanding of tautomeric equilibria of heterocyclic compounds is critical in the rationalization of chemical and physical properties, reactivity of heterocycles, the mechanism of enzymatic catalysis and drug-receptor interaction [3]. Recently, we have reported the synthesis [1] and tautomeric studies of 2-aryl-3-bromoquinolin-4(1*H*)-ones [2], which are found to exist exclusively in solution phase (NMR) and solid state (IR and X-ray) as the NH-4-oxo derivatives. The coexistence of the 4-quinolinone and 4-hydroquinoline isomers in the gas phase was confirmed by mass spectrometry and this was supported by B3LYP gas phase calculations [2]. Most of the studies on the tautomeric equilibria of 2-substituted-4-quinolinols *versus* 2-substituted-4-quinolone isomers carried out to-date are based largely on the UV, IR and NMR spectroscopic data, quantum chemical calculations (semi-empirical and ab initio methods) and to a lesser extend on X-ray crystallography [3,4]. In spite of the extensive synthetic [5] and pharmacological investigations of the 2-aryl-4-quinolones as antibacterial [4] and antitumour agents [5], to our knowledge, the tautomerism of these compounds has not been documented. We therefore investigated the geometry of the title compounds in solution, gas and solid state using spectroscopic, X-ray crystallographic and quantum chemical techniques to provide a more focused qualitative structural analysis of these systems. The results of spectroscopic and X-ray crystallographic methods have been interpreted in combination with results of computer modelling and by comparison with spectroscopic data of the corresponding fixed derivatives (NMe and OMe).

2. Results and discussion

Compounds **4** used as substrates in this investigation were prepared by cyclization of systems **3** which were, in turn, prepared by condensing 2-aminoacetophenones **1** with benzoyl chloride derivatives **2** following literature procedure (Scheme 1) [5b]. The antitumour activity of the 2-aryl-4-quinolin-4(1*H*)-ones appears to be influenced by

* Corresponding authors.
Tel.: +27-12-429-8805; fax: +27-12-429-8549 (M.J. Mphahlele).
E-mail address: mphahmj@unisa.ac.za (M.J. Mphahlele).

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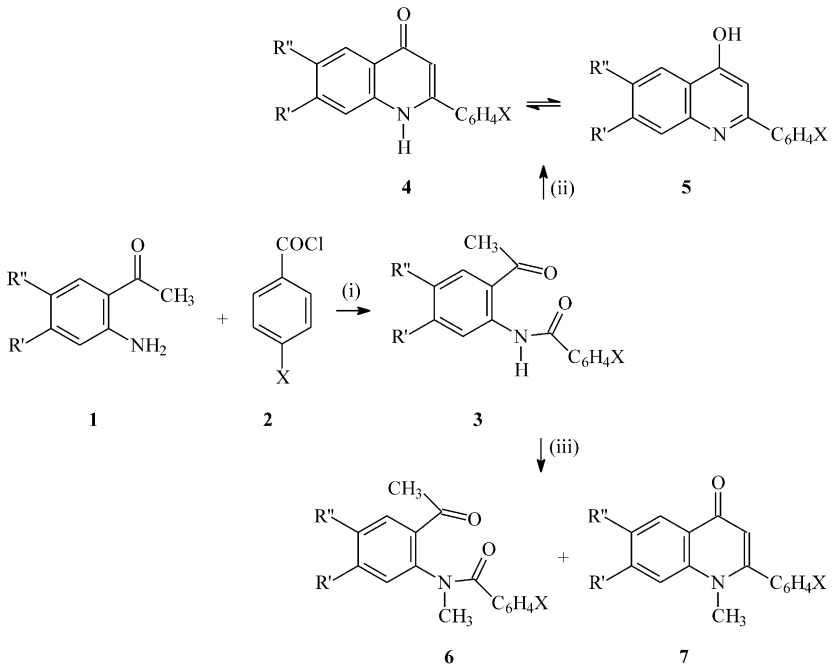

(i) NEt_3, THF, 0° C – r.t; (ii) ^{tert}ButOK, ^{tert}BuOH, heat; (iii) NaH, THF then CH_3I, r.t.

Scheme 1.

the change in substituents on the heterocyclic ring [6,7]. In order to obtain qualitative information on the tautomeric structure prevailing in solution, gas and solid state, we required model molecules in which the potential for prototropic shift is eliminated. Consequently we prepared the corresponding *N*-methyl derivatives **7** to compare their spectroscopic data with those of precursors **4** and the isomeric 2-aryl-4-methoxyquinolines. Previous synthetic routes leading to the 2-substituted 1-methylquinolin-4(1*H*)-one derivatives either involve multiple steps with reduced overall yields [8] or produce mixtures of *O*-methylated and *N*-methylated derivatives that are difficult to separate by conventional column chromatographic techniques [5,9]. Graveoline has been isolated in 87% yield as a sole product from the reaction of norgraveoline and methyl iodide-potassium carbonate mixture in refluxing acetone [10], however, the generality of this observation has not been demonstrated. The reaction of methyl iodide with 2-phenyl-4-quinolone, on the other hand, is reported to yield the *N*-methyl phenylquinolinium iodide [11]. To our knowledge, the shortest route (one-step synthesis) reported to-date for the synthesis of 2-aryl-1-methyl-4-quinolones in appreciable yields involves the condensation of lithium enolates of acetophenone derivatives with substituted *N*-methylisatoic anhydrides [8]. Although the reaction is high yielding, each reaction when using different substrates has its unique temperature requirements for completion [8].

In order to circumvent the problem of non-regioselectivity of direct methylation of **4**, we attempted to convert substrates **3** to their *N*-methyl derivatives **6** with the aim of cyclizing the latter to **7**. Systems **3** were treated with 1.2–1.5 equiv. of sodium hydride in dry THF followed by quenching with 1.2–1.5 equiv. of methyl iodide to afford after 18 h traces of the starting material, the expected derivative **6** (minor) and **7** (major), respectively (Scheme 1). The ^{1}H NMR spectra of compounds **6** are characterized by the presence of two sets of methyl signals at δ ca. 1.80 ppm ($COCH_3$) and δ ca. 3.38 ppm (NCH_3) and a group of signals in the aromatic region. In view of the ready availability of the substrates and the mild reaction conditions, the generalized approach reported in this paper represents a convenient alternative to existing methods for the synthesis of *N*-methyl 2-aryl-4-quinolones. A three-step synthetic approach leading to the formation of analogous *N*-benzyl-2-arylquinolin-4(1*H*)-ones had been reported before [12]. The isomeric 2-aryl-4-methoxyquinolines are well known natural products some of which have been found to possess antimalarial activity and for this reason, numerous methods have been developed for their synthesis [13]. Hitherto this investigation, we also reported the synthesis and characterization of the 2-aryl-4-methoxyquinolines obtained *via* iodine-methanol promoted oxidation of the 2-aryl-1,2,3,4-tetrahydro-4-quinolinones [14].

3. Solution phase studies using NMR spectroscopy

The ^{1}H NMR spectra of the compounds **4** are characterized by the olefinic proton (3-H) signal, aromatic signals and the imine proton signal at δ ca. 6.32–6.50 ppm,

Table 1
^{13}C NMR chemical shifts (ppm) of systems **4** and **7** (in DMSO-d_6, 75 MHz)

4/7	R	R′, R″	X	CH_2O_2	NCH_3	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
4a	H	H	H	–	–	150.0	107.3	176.9	124.9	123.2	124.7	131.8	118.7	140.5
4b	H	H	F	–	–	149.0	107.3	176.8	125.0	123.3	124.7	131.8	118.7	140.4
4c	H	H	Cl	–	–	150.1	106.5	175.8	125.1	122.8	124.5	131.1	120.6	142.5
4d	H	H	OCH_3	–	–	150.4	107.1	177.5	126.9	123.8	125.3	132.3	119.4	141.2
7a	CH_3	H	H	–	37.2	154.8	112.6	177.6	126.8	123.7	126.7	132.3	115.9	141.9
7b	CH_3	H	F	–	37.2	153.6	112.8	177.5	126.8	123.7	126.7	132.4	115.9	141.9
7c	CH_3	H	Cl	–	39.4	156.9	108.9	171.0	124.3	124.5	126.7	134.6	118.8	141.2
7d	CH_3	H	OCH_3	–	37.3	154.7	112.7	177.6	126.7	123.5	128.1	132.2	115.9	142.0
7e	CH_3	OCH_2O	H	102.0	37.8	152.2	112.1	176.2	122.7	103.7	145.3	153.3	95.5	139.1
7f	CH_3	OCH_2O	F	102.1	37.7	152.2	112.1	176.9	122.6	103.5	145.3	152.2	95.5	139.0
7g	CH_3	OCH_2O	Cl	102.1	37.8	152.3	112.1	176.1	122.6	103.6	145.4	152.0	95.5	139.1

For atom labeling see Fig. 1. For the sake of clarity, the chemical shift values of the aryl substituent have not been included.

δ ca. 6.50–8.20 ppm and δ ca. 11.71 ppm, respectively. Their ^{13}C NMR spectra are characterized by a group of resonances in the aromatic region and the carbonyl carbon signal at δ ca. 175.0–176.5 ppm. The ^{1}H NMR spectra of **7**, on the other hand, are characterized by the presence of the *N*-methyl signal at δ ca. 3.51 ppm, the vinylic proton (3-H) signal at δ ca. 6.51 ppm and the aromatic proton signals. Their ^{13}C NMR spectra are characterized by the *N*-methyl signal in the region δ 37.2–39.0 ppm, signals corresponding to aromatic carbons and the carbonyl carbon at δ ca. 171.0–178.0 ppm (Table 1). The *O*-methyl and C-4 signals of the 2-aryl-4-methoxyquinolines, on the other hand, resonate at δ_C ca. 58.0 ppm (δ_H ca. 4.50 ppm) and δ_C ca. 168.0 ppm, respectively [14]. The NMR spectral data of systems **4** differ from those of the 2-aryl-4-methoxyquinoline derivatives [14] and are comparable to those of compounds **7**. The striking similarity between the NMR spectral data of **4** and **7** rules out the possibility of **5** and confirms the carbonyl nature of the title compounds. Thus compounds **4** exist exclusively as the NH-4-oxo tautomers in a polar solvent such as DMSO in analogy with the structures of the 2-aryl-3-bromoquinolin-4(1*H*)-ones [2] and 4-quinolinone [3,4].

4. Solid state studies using IR spectroscopy and X-ray crystallography

The solid state structures of the title compounds were investigated using FT-IR spectroscopy (Table 2) and X-ray crystallography. Their carbonyl nature was confirmed in the solid state by their IR frequencies [ν_{max} (cm^{-1}) ca. 1632–1643 (C=O)] that are comparable to those of the corresponding derivatives **7** (Table 2).

Despite the enormous chemical [5] and pharmacological interest [4,5] in systems **4**, to our knowledge, no information has been published on their X-ray crystal data [2,4a]. The scarcity of X-ray crystallographic data for systems **4** can be attributed to their amorphous nature in the solid state [4]. Single crystals of the 2-(4′-fluorophenyl) derivative suitable for X-ray crystallographic analysis were obtained by slow evaporation of the ethanol solution and the compound is found to exist exclusively as the NH-4-oxo derivative **4b**. In the crystal lattice (Fig. 1a) compounds **4** adopt a conformation in which the B-ring lies at 157.3° relative to the co-planar A- and C-rings (see Table 3 for torsion angles). At the B3LYP/3-21G level, the computed values for N1-C2-C1′-C2′ and C3-C2-C1′-C2′ torsion angles are 140.3° and 41.0°, respectively. The difference between computed and observed torsion angles may be attributed to crystal packing which tends to give wider angles. In general, the geometry optimized enol forms **5a–d** are planar whereas the corresponding keto forms **4a–d** deviate from planarity due to the repulsion between hydrogen atoms attached to N-1 and

Table 2
IR frequencies for compounds **4** and **7**

4, **7** (X)	ν_{max} (cm^{-1}) (KBr pellet)
4a (H)	3423, 1636, 1581, 1545, 1516, 1470, 1404, 1256, 840, 772, 689, 524
4b (F)	3400, 2970, 1633, 1604, 1591, 1548, 1507, 1164, 852, 796, 570, 515
4c (Cl)	3420, 3087, 2930, 1642, 1598, 1500, 1424, 1331, 1098, 828, 532
4d (OMe)	3412, 1613, 1591, 1569, 1542, 1291, 1276, 1250, 1017, 849, 757
7a (H)	1636, 1594, 1583, 1547, 1474, 1356, 1256, 840, 529, 524
7b (F)	1623, 1601, 1550, 1509, 1223, 1136, 851, 806, 774
7c (Cl)	1620, 1582, 1534, 1467, 1169, 1032, 965, 847, 727
7d (OMe)	1618, 1600, 1512, 1496, 1402, 1295, 1181, 1031, 840, 758
7e (H)	1626, 1585, 1495, 1472, 1286, 1273, 1250, 1097, 1037, 890, 702
7f (F)	1626, 1581, 1510, 1498, 1482, 1272, 1033, 934, 841
7g (Cl)	1626, 1581, 1511, 1498, 1448, 1286, 1273, 1162, 1034

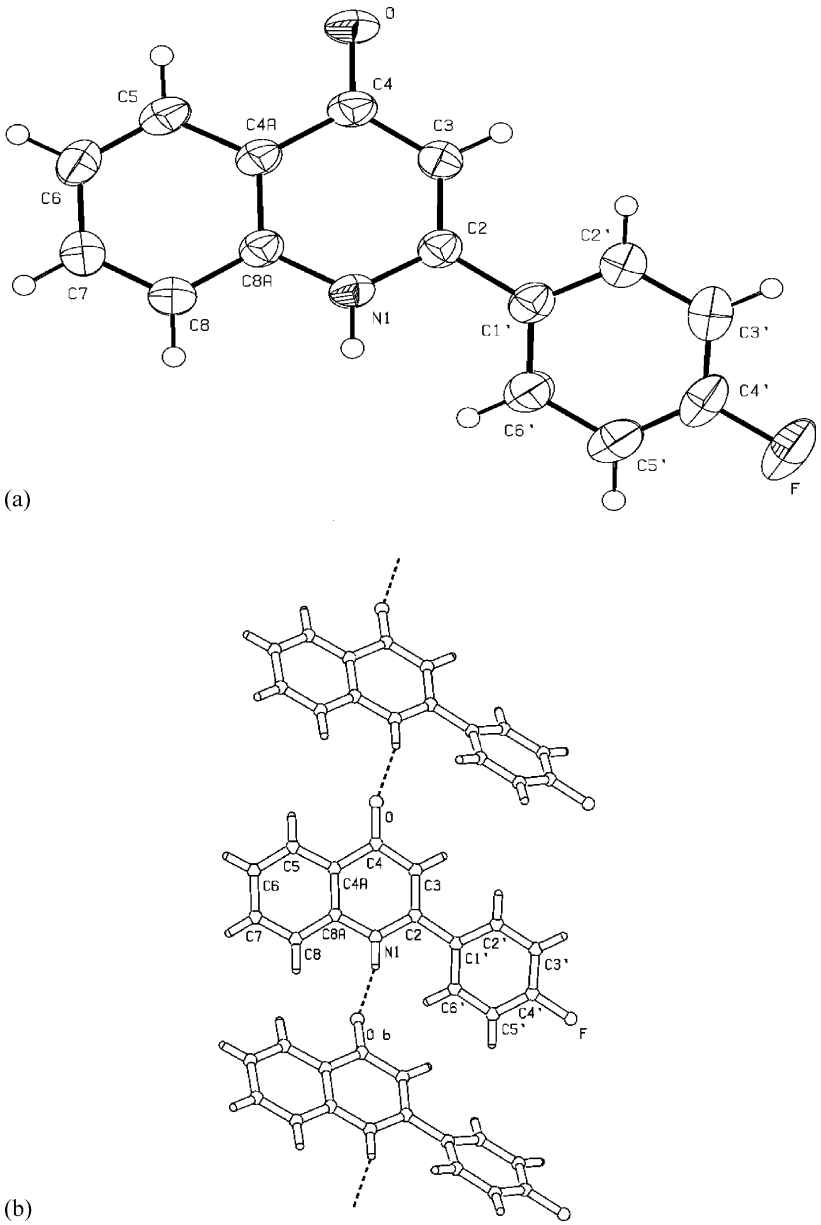

Fig. 1. (a) ORTEP diagram of **4b**, showing crystallographic labeling. Thermal ellipsoids are drawn at the 50% probability level. (b) X-Ray crystal structure for **4b**, showing the hydrogen bonding pattern.

C-6′ (Fig. 1a). The observed geometry of systems **4** differs remarkably from that of the 2-aryl-3-bromoquinolin-4(1*H*)-ones described before [2] in which the aryl substituent deviates considerably (125.9°) from co-planarity probably to relieve steric interaction between 1-H and Br and the *ortho* hydrogens (2′-H and 6′-H).

Table 3
Selected torsion angles [°] for compound **4b**

C1′-C2-C3-C4	− 178.22(13)
N1-C2-C1′-C6′	23.52(19)
C3-C2-C1′-C6′	− 155.71(14)
N1-C2-C1′-C2′	− 157.29(13)
C3-C2-C1′-C2′	23.5(19)

Systems **4** exhibit strong intermolecular hydrogen bonding with the O···H and N−H interatomic distances of 1.914 and 0.898 Å, respectively (Fig. 1b).

5. Gas phase studies using mass spectrometry

The C-ring of the molecular ions of systems **4** and **7** fragment by elimination of CO (M-28) to afford radical-cations in relatively high abundance (Table 4). The 2-aryl-4-methoxyquinolines, on the other hand, are known to undergo fragmentation pattern typical for ether derivatives [14]. The presence of **5** in the gas phase is confirmed by the cation fragments corresponding to the extrusion of hydroxyl

Table 4
Selected mass fragments of systems **4** and **6** with relative intensities in parentheses

Compounds	Molecular formula	M^+ (%)	*m/z* (%)	*m/z* (%)
4a	$C_{15}H_{11}NO$	221 (94.8)	204 (M-OH, 16.1)	193 (M-CO, 100)
4b	$C_{15}H_{10}NOF$	239 (85.7)	222 (M-OH, 30.1)	211 (M-CO, 100)
4c	$C_{15}H_{10}NO^{35}Cl$	255 (100)	238 (M-OH, 19.1)	227 (M-CO, 70.9)
4d	$C_{16}H_{13}NO_2$	251 (100)	236 (M-OH, 20.1)	223 (M-CO, 93.7)
7a	$C_{16}H_{13}NO$	235 (88.9)	–	207 (M-CO, 100)
7b	$C_{16}H_{12}NOF$	253 (83.0)	–	225 (M-CO, 100)
7c	$C_{16}H_{12}NO^{35}Cl$	269 (75.2)	–	241 (M-CO, 100)
7d	$C_{17}H_{15}NO_2$	265 (100)	–	237 (M-CO, 72.9)
7e	$C_{17}H_{13}NO_3$	279 (74.4)	–	251 (M-CO, 68.6)
7f	$C_{17}H_{13}NO_3F$	297 (63.1)	–	269 (M-CO, 100)
7g	$C_{17}H_{13}NO_3^{35}Cl$	313 (55.6)	-	285 (M-CO, 100)

radical [M-17] in 16–31% relative abundance. Although tautomerism is a difficult subject to study in the gas phase using spectroscopic methods, quantum chemical calculations became a valuable tool for determination of structures and energies of molecules in the gas and solution phases to complement experimental data.

6. Quantum chemical calculations

Geometry optimization of **4a–d** and **5a–d** were first accomplished using PM3 with the MOPAC program as implicated in Alchemy 2000 software package [15]. The small energy differences between **4** and **5** (Scheme 1, Table 5) as determined by PM3 indicate the predominance of the NH-4-oxo form. This energy difference may be significantly affected by inclusion of zero-point energy (ZPE) correction and, therefore, ZPE calculation seems to be necessary for accurate estimation of tautomerization energies. Calculations were carried at higher levels of theory, namely B3LYP hybrid density functional method [16] and Moller Plesset perturbation theory [17] at second order. Full geometry optimizations have been carried out without symmetry constraints using the three-parameter hybrid density functional theory (DFT) functional of Becke (B3LYP) [16] with the 3-21G basis set. Frequency calculations were done at the HF/3-21G level and indicate that all of the investigated forms are minima (no imaginary

Table 5
Calculated energies (kcal/mol and a.u.) and dipole moments (μ) for the quinolone **4** and quinolinol **5** forms at different levels of theory

Compounds			PM3					B3LYP/6-31 + G(d), MP2/6-31 + G(d)				
4/5	R′, R″	X	ΔH_f (**4**)	ΔH_f (**5**)	ΔH_f (**5**–**4**)	μ (**4**)	μ (**5**)	E_{abs} (**4**)	E_{abs} (**5**)	E_{rel} (**4**–**5**)[a]	μ (**4**)	μ (**5**)
a	H	H	27.9	28.6	0.7	4.85	1.75	−708.24337[b] −708.25657[a] −706.08105[c] 0.23757[d]	−708.23621[b] −708.24450[a] −706.07882[c] 0.23638[d]	4.5[b] 7.6[a] 1.4[c] 0.7[e]	6.698[b]	2.168[b]
b	H	F	−15.3	−15.0	0.3	4.06	2.52	−807.48221[b] −807.49497[a] −805.09057[c] 0.22917[d]	−807.47817[b] −807.48572[a] −805.08930[c] 0.22804[d]	3.8[b] 5.8[a] 0.8[c] 0.7[e]	5.665[b]	2.961[b]
c	H	Cl	21.4	21.9	0.5	4.34	2.06	−1167.83820[b] −1167.85030[a] −1165.10456[c] 0.22736[d]	−1167.83237[b] −1167.83943[a] −1165.10381[c] 0.22622[d]	3.7[b] 6.8[a] 0.5[c] 0.7[e]	5.634[b]	3.105[b]
d	H	OMe	−10.4	−9.6	0.8	5.76	1.63	−822.76990[b] −822.78260[a] −820.28458[c] 0.27239[d]	−822.76238[b] −822.77186[a] −820.28199[c] 0.27120[d]	4.7[b] 6.7[a] 1.6[c] 0.7[e]	6.803[b]	3.756[b]

[a] Uncorrected absolute (a.u.) and relative (kcal/mol) energies from PCM-B3LYP/6-31 + G(d)//B3LYP/3-21G.
[b] Uncorrected absolute (a.u.) and relative (kcal/mol) energies and dipole moments (Debye) from B3LYP/6-31 + G(d)//B3LYP/3-21G.
[c] Uncorrected absolute (a.u.) and relative (kcal/mol) energies from MP2/6-31 + G(d)//B3LYP/3-21G.
[d] Zero-point energies (ZPE, a.u.) from HF/3-21G.
[e] ZPE, correction (kcal/mol).

eigenvalues of the Hessian matrix). The zero-point vibrational energy corrections were retrieved from the frequency calculations and used to correct the tautomerization energies. Single point energy calculations in the gas phase have been carried out at the B3LYP and MP2 levels of theory using the 6-31 + G(d) basis set at the B3LYP/3-21G geometries. Solvation in DMSO has been modelled at the B3LYP/6-31 + G(d)//B3LYP/3-21G level using the Polarized Continuum Model (PCM) of Tomasi and coworkers [18]. DFT and Hartree–Fock (HF) calculations were carried out with GAUSSIAN 98 program [19] and MP2 calculations were performed using the PC GAMESS version [20a] of the GAMESS (US) QC package [20b]. The results of quantum chemical calculations are listed in Table 5.

ZPE correction adds 0.7 kcal/mol to the stability of **5a–d**. DFT calculations at the B3LYP level indicate that the stability of **4a–d** increases to 3–4 kcal/mol even after the inclusion of ZPE correction. On the other hand, corrected MP2 energies give small energy difference between **4** and **5** in favor of the NH-4-oxo isomers in the gas phase except for **5c**, which is 0.2 kcal/mol more stable. The small energy differences between **4** and **5** observed using PM3 and MP2 calculations explain the coexistence of both tautomers in the gas phase as determined by mass spectrometry. The overall dipole moments of systems **4** calculated using PM3 and B3LYP methods are higher than those of the corresponding isomers **5** thus predicting the greater stability of the NH-4-oxo form in polar media. PCM-B3LYP/6-31 + G(d) calculations in DMSO reveal that systems **4** are more stable than **5** by 5–7 kcal/mol after ZPE correction (Table 5). The tautomerization energies in DMSO correlate linearly with the difference in dipole moments between keto and enol isomers.

7. Conclusion

A comparison of spectroscopic data of 2-aryl-4-methoxyquinolines [14] and *N*-methyl isomers **7** with those of **4** provides qualitative information on the tautomer that exists in solution and solid state. DFT results modelled in DMSO and X-ray data all point to the exclusive carbonyl nature of the title compounds in solution and solid state in agreement with spectroscopic data, respectively. In the gas phase where solvent-assisted stabilization and intermolecular hydrogen bond are absent, both tautomers coexist as confirmed by mass spectrometry and supported by PM3, B3LYP, and MP2 gas phase calculations. Conjugative effects of the 2-aryl substituent as well as electronic effects of the substituents at its *para* position appear not to influence the tautomeric equilibrium. Our results which incorporate X-ray data of the 2-aryl-4-quinolones complement previously reported spectroscopic and computational data of 4-quinolone *versus* 4-quinolinol equilibrium [2–4].

8. Experimental

Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets at the University of Pretoria's Raman and Infrared Facility using Bruker IFS 113V FT-IR spectrometer (number of scans = 32, resolution = 2 cm^{-1}). NMR spectra were obtained as DMSO-d_6 solutions using Varian Mercury 300 MHz NMR spectrometer and the chemical shifts are quoted relative to the solvent peaks. The low-resolution mass spectra were recorded at Rhodes University using Finnigan Mat GCQ instrument. XRD data collection and solution were carried out at the Jan Boeyens Structural Chemistry Laboratory (University of the Witwatersrand). The synthesis and characterization of **4a** and **7a** have been described before [5]. Analytical data for new compounds **4b–d**, **6a–g** and **7b–g** which were prepared following literature method [5] are as follows:

2-(*p*-Fluorophenyl) derivative **4b**. Solid (55%); m.p. 322–325 °C (AcOH) and δ_H (300 MHz, DMSO-d_6) 6.32 (1H, s, 3-H), 7.33 (1H, t, *J* 7.5 Hz, 6-H), 7.42 (2H, t, *J* 8.2 Hz, 2′-H and 6′-H), 7.66 (1H, t, *J* 7.7 Hz, 7-H), 7.75 (1H, d, *J* 8.3 Hz, 8-H), 7.91 (2H, t, *J* 7.5 Hz, 3′-H and 5′-H), 8.09 (1H, d, *J* 8.1 Hz, 6-H) and 11.71 (1H, s, NH).

2-(*p*-Chlorophenyl) derivative **4c**. Solid (65%); m.p. 270–273 °C (AcOH) and δ_H (300 MHz, DMSO-d_6) 6.41 (1H, s, 3-H), 7.28 (1H, t, *J* 7.5 Hz, 6-H), 7.57-7.62 (3H, m, 2′-H, 6′-H and 7-H), 7.74 (1H, d, *J* 7.8 Hz, 8-H), 7.90 (2H, d, *J* 7.8 Hz, 3′-H and 5′-H), 8.09 (1H, d, *J* 7.5 Hz, 6-H) and 11.76 (1H, brs, NH).

2-(*p*-Methoxyphenyl) derivative **4d**. Solid (80%); m.p. 290–293 °C (AcOH) and δ_H (300 MHz, DMSO-d_6) 3.84 (3H, s, OCH_3), 6.31 (1H, s, 3-H), 7.12 (2H, d, *J* 8.5 Hz, 2′-H and 6′-H), 7.31 (1H, t, *J* 7.5 Hz, 6-H), 7.64 (1H, t, *J* 7.5 Hz, 7-H), 7.76 (1H, d, *J* 8.4 Hz, 8-H), 7.80 (2H, d, *J* 8.4 Hz, 3′-H and 5′-H), 8.07 (1H, d, *J* 7.5 Hz, 6-H) and 11.46 (1H, brs, NH).

8.1. Synthesis of 2-aryl-1-methylquinolin-4(1H)-one derivatives. General procedure

A stirred suspension of **3** (1 equiv.) in dry THF (5 ml per mmol of **3**) was treated with NaH (1.2 equiv.) at room temperature. After 1 h at room temperature, the mixture was treated with methyl iodide (1.2 equiv.) and stirring continued for 18 h. The mixture was quenched with ice-cold water and then extracted with chloroform. The combined chloroform solutions were dried over Na_2SO_4, filtered and then evaporated under reduced pressure. The residue was purified by column chromatography (elution with hexane–EtOAc, 3:2 v/v) to afford

N-Methyl 2-phenyl derivatives (R′, R″ = H): **6a** brown syrup (12%) and δ_H (300 MHz, $CDCl_3$) 1.82 (3H, s, $COCH_3$), 3.43 (3H, s, NCH_3), 7.20–7.66 (8H, m, C_6H_5, 3-H, 4-H and 5-H) and 8.52 (1H, dd, *J* 1.5 and 8.1 Hz, 6-H);

and **7a** Solid (75%); m.p. 143–145 °C (EtOH) (Lit., [5] 145–147 °C).

N-Methyl 2-(*p*-fluorophenyl) derivatives (R′, R″ = H): **6b** Solid (10%); m.p. 168–170 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 1.86 (3H, s, $COCH_3$), 3.48 (3H, s, NCH_3), 7.22–7.28 (4H, m, C_6H_4F), 7.41 (1H, t, *J* 7.5 Hz, 4-H), 7.50 (1H, d, *J* 8.7 Hz, 3-H), 7.78 (1H, t, *J* 7.5 Hz, 5-H), 8.55 (1H, d, *J* 8.1 Hz, 6-H); and **7b** Solid (70%); m.p. 178–180 °C (EtOH) and δ_H (300 MHz, DMSO-d_6) 3.59 (3H, s, CH_3), 6.23 (1H, s, 3-H), 7.19 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.37–7.44 (3H, m, 3′-H, 5′-H and 6-H), 7.53 (1H, d, *J* 8.4 Hz, 8-H), 7.70 (1H, t, *J* 8.1 Hz, 7-H) and 8.47 (1H, d, *J* 8.0 Hz, 5-H).

N-Methyl 2-(*p*-chlorophenyl) derivatives (R′, R″ = H): **6c** Solid (15%); m.p. 108-111 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 1.85 (3H, s, $COCH_3$), 3.47 (3H, s, NCH_3), 7.24 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H), 7.40 (1H, t, *J* 7.5 Hz, 4-H), 7.49 (1H, d, *J* 8.7 Hz, 3-H), 7.54 (2H, d *J* 8.4 Hz, 3′-H and 5′-H), 7.68 (1H, t, *J* 7.8 Hz, 5-H) and 8.54 (1H, d, *J* 8.1 Hz, 6-H); and **7c** Solid (80%); m.p. 174–178 °C (EtOH) and δ_H (300 MHz, DMSO-d_6) 3.90 (3H, s, CH_3), 7.71 (4H, s, C_6H_4Cl), 7.78 (1H, t, *J* 8.0 Hz, 6-H), 8.09 (1H, t, *J* 8.1 Hz, 7-H), 8.22 (1H, d, *J* 8.4 Hz, 8-H) and 8.40 (1H, d, *J* 8.1 Hz, 5-H).

N-Methyl 2-(*p*-methoxyphenyl) derivatives (R′, R″ = H): **6d** Solid (20%); m.p. 179–182 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 1.85 (3H, s, $COCH_3$), 3.45 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 7.03 (2H, d, *J* 8.7 Hz, 2′-H and 6′-H), 7.16 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H), 7.34 (1H, t, *J* 7.6 Hz, 4-H), 7.46 (1H, d, *J* 8.7 Hz, 3-H), 7.62 (1H, t, *J* 7.5 Hz, 5-H) and 8.52 (1H, d, *J* 8.1 Hz, 6-H); and **7d** Solid (56%); m.p. 144–146 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 3.61 (3H, s, NCH_3), 3.86 (3H, s, OCH_3), 4.27 (1H, s, 3-H), 6.99 (2H, d, *J* 8.7 Hz, 3′-H and 5′-H), 7.33 (2H, *J* 7.8 Hz, 2′-H and 6′-H), 7.39 (1H, dt, *J* 0.9 and 7.5 Hz, 7-H), 7.52 (1H, d, *J* 8.2 Hz, 8-H), 7.68 (1H, dt, *J* 1.5 and 7.8 Hz, 6-H) and 8.47 (1H, dd, *J* 1.5 and 8.1 Hz, 5-H).

N-Methyl 2-phenyl derivatives (R′, R″ = OCH_2O): **6e** Solid (17%); m.p. 178–181 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 1.80 (3H, s, $COCH_3$), 3.37 (3H, s, CH_3), 6.04 (2H, s, CH_2O_2), 6.85 (1H, s, 3-H), 7.24 (2H, dd, *J* 1.8 and 7.9 Hz, 2′-H and 6′-H), 7.48 (3H, m, 2′-H, 3′-H and 5′-H) and 7.84 (1H, s, 6-H); and **7e** Solid (60%); m.p. 210-212 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 3.52 (3H, s, CH_3), 6.08 (2H, s, CH_2O_2), 6.20 (1H, s, 3-H), 6.93 (1H, s, 8-H), 7.35–7.48 (5-H, m, C_6H_5) and 7.81 (1H, s, 5-H).

N-Methyl 2-(*p*-fluorophenyl) derivatives (R′, R″ = OCH_2O): **6f** Solid (10%); m.p. 226–228 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 1.80 (3H, s, $COCH_3$), 3.38 (3H, s, NCH_3), 6.07 (2H, s, CH_2O_2), 6.86 (1H, s, 3-H), 7.21 (2H, d, *J* 8.4 Hz, 2′-H and 6′-H), 7.51 (2H, d, *J* 8.4 Hz, 3′-H and 5′-H) and 7.84 (1H, s, 6-H); and **7f** Solid (70%); m.p. 240-242 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 3.52 (3H, s, CH_3), 6.09 (2H, s, OCH_2O), 6.18 (1H, s, 3-H), 6.92 (1H, s, 8-H), 7.18 (2H, t, *J* 8.4 Hz, 2′-H and 6′-H), 7.38 (2H, t, *J* 8.4 Hz, 3′-H and 5′-H) and 7.80 (1H, s, 5-H).

N-Methyl 2-(*p*-chlorophenyl) derivatives (R′, R″ = OCH_2O): **6 g** Solid (10%); m.p. 212–213 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 1.81 (3H, s, $COCH_3$), 3.39 (3H, s, NCH_3) 6.08 (2H, s, CH_2O_2), 6.87 (1H, s, 3-H), 7.26 (4H, s, C_6H_4Cl) and 7.86 (1H, s, 6-H); and **7 g** Solid (55%); m.p. 247–248 °C (EtOH) and δ_H (300 MHz, $CDCl_3$) 3.51 (3H, s, CH_3), 6.08 (2H, s, CH_2O_2), 6.15 (1H, s, 3-H), 6.90 (1H, s, 8-H), 7.33 (2H, d, *J* 8.2 Hz, 3′-H and 5′-H), 7.46 (2H, d, *J* 8.1 Hz, 2′-H and 6′-H) and 7.77 (1H, s, 5-H).

8.2. X-Ray crystallographic data collection and processing [21]

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program SAINT + [21a] and absorption corrections were made using the program SADABS [21b]. The crystal structure was solved by direct methods using SHELXTL [21c]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on F^2 using SHELXTL. With the exception of H1, atoms were located from the difference map then positioned geometrically and allowed to ride on their respective parent atoms. H1 was located from the difference map and refined isotropically without restraints. Diagrams and publication material were generated using SHELXTL and PLATON [21d]. Crystal data for **4b**, $C_{15}H_{10}NOF$, $M_r = 239.24$, monoclinic, *a*/Å 11.776(2), *b*/Å 7.2064(14), *c*/Å 13.322(3), $\alpha = \gamma = 90°$, $\beta = 92.263(4)°$, *V*/Å [3] 1129.6(4), temperature (K) 293(2), $P2_1/c$, $Z = 4$, μ/mm^{-1} 0.100, number of reflections measured = 7298 and number of independent reflections = 2790 [R(int) = 0.0238]. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference number 210421).

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