Synthesis of Pyrazoloquinolines as Gastric H^+/K^+-ATPase Inhibitors[1]

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A series of 1-aryl-1*H*-pyrazolo[4,3-*c*]quinolines and 2-aryl-2*H*-pyrazolo[4,3-*c*]quinolines are prepared by reacting 3-acyl-4-chloroquinolines in ethanol or 3-acyl-4(1*H*)-quinolone in acetic acid with appropriate hydrazines as possible anti-ulcer agents. A regiospecific synthesis of 1-aryl-1*H*-pyrazolo[4,3-*c*]quinolines is also achieved. The central pyridine ring could be easily reduced by catalytic hydrogenation.

Introduction

Pyrazoloquinolines are interesting compounds because of their possible biological activity since they are isosteric to 5,6,6-ring systems.[3,4,5]

The area of anti-ulcer research has changed dramatically over the past several years due to the introduction of reversible proton pump inhibitors, *e.g.* SK & F 96067.[6] The interest in 1*H*-pyrazolo[4,3-*c*]quinoline structure was drawn on the basis of speculation that the carbonyl group in SK & F 96067 (Figure 1) is responsible for restricting the conformation of the arylamino group, both by forming a hydrogen bond to NH and by increasing the conjugation between the nitrogen and quinoline ring due to its electron-withdrawing effect.[7] Therefore it was decided to put the conformational constraint covalently by forming of an additional ring.

A series of 1-aryl-1*H*-pyrazolo[4,3-*c*]quinolines and 2-aryl-2*H*-pyrazolo[4,3-*c*]-quinolines with rigid conformation were prepared by reacting 3-butyryl-4-chloro-8-methoxyquinoline (**3a**) or 3-acetyl-4-chloro-8-methoxyquinoline (**3b**) with appropriate hydrazines[8] in ethanol (Method A). Key intermediates **3a-b** were obtained using modified literature procedures (Scheme 1).[9] In brief, *o*-anisidine was refluxed with ethyl 2-butyryl-3-ethoxyacrylate (**1a**), ethyl 2-acetyl-3-ethoxyacrylate (**1b**) or ethyl 2-butyryl-3-ethoxy-2-butenoate (**1c**) in diphenyl ether to give 3-butyryl-8-methoxy-4(1*H*)-quinolone (**2a**), 3-acetyl-8-methoxy-4(1*H*)-quinolone (**2b**) and 3-butyryl-2-methyl-8-methoxy-4(1*H*)-quinolone (**2c**), respectively. Treatment of **2a-b** with phosphorus oxychloride led to the corresponding chloro derivatives **3a-b**.

As most syntheses of pyrazole rings use hydrazines and 1,3-difunctional compounds, the mechanism of the reaction is still only partially understood.[3] If the nucleophilicity of the two nitrogen atoms of the hydrazine is different, the more abundant isomer corresponds to the addition at the more nucleophilic nitrogen of the hydrazine to the more electrophilic center of the 1,3-dicarbonyl compound, or to a precursor of such a species.[7] Thus unless the nucleophilicity of the two nitrogen atoms of the hydrazines is very different, they give both of the isomers.

As expected, coupling of **3a** with the phenylhydrazine gave a separable mixture of isomers **4a** and **5a**. The structures of isomers were determined by interpretation of phase-sensitive NOESY spectra of **4a** and **5a** (Figure 2). While the interaction of side chain methylene protons with H_4 and phenyl protons was evident in the spectrum of **5a**, similar interaction between phenyl protons and H_9 was evident in **4a**.

Coupling of **3a-b** with the appropriately substituted hydrazines usually gave a separable mixture of isomers **4b-h** and **5b-g**. In most cases, undesirable N_2-substituted isomers **5** were the major products (Table 1). For 4-nitrophenylhydrazine with electron-withdrawing substituent, only **5e** was obtained. In case of benzylhydrazine, the isomer **4g** was the major product. With sterically hindered *o*-tolylhydrazine, the hydrazone **6** was isolated as a major product, which was cyclized by refluxing in dioxane to afford **4h** in 60% yield (Scheme 1).

The structures of isomers were determined by comparison of NMR spectra and chromatographic behavior, which were very consistent over the series. The characteristic feature was downfield shifts of alkyl protons of **4** compared to those of **5**, probably due to steric congestion.[10] Another characteristic of **5** was the H_9 doublet at δ 8.08.[11] The isomers **4** moved faster on silica gel plates (ethyl acetate-hexane). The assignments were later confirmed by the trend in biological activity, the isomers **4** consistently showed better activity compared to undesired isomers **5**.

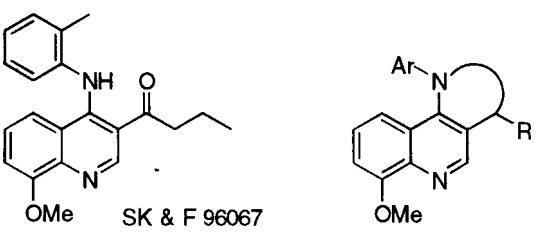
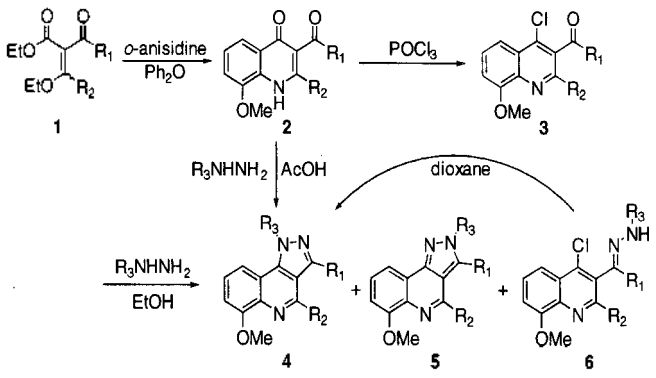


Figure 1



Scheme 1

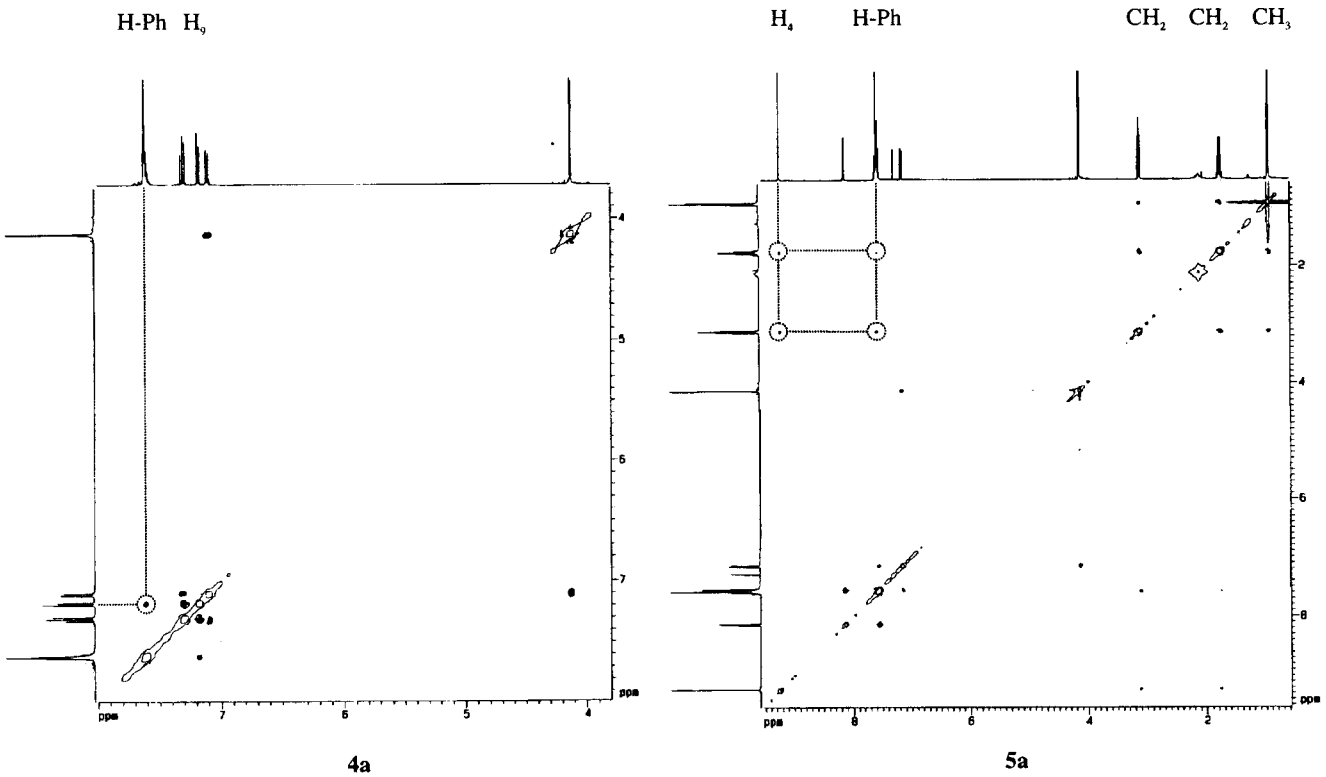


Figure 2. NOESY Spectra of **4a** and **5a**.

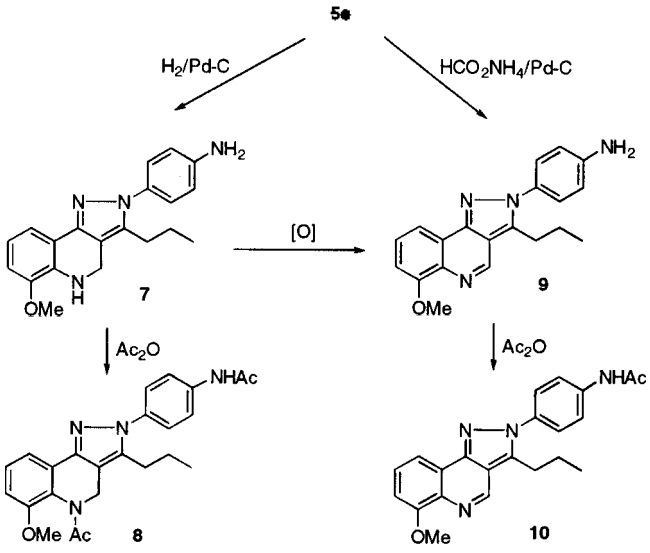
A remarkable regioselectivity for 1-aryl-1*H*-pyrazolo[4,3-*c*]quinolines was achieved by reacting arylhydrazines with 3-butyryl-8-methoxy-4(1*H*)-quinolone **2a** in acetic acid (Method B). Only N_1-substituted isomers **4** were obtained in all cases (Table 1, Scheme 1). A complete reversal of regioselectivity was observed for 4-nitrophenylhydrazine.

Table 1. Comparison of Synthetic Methods

No	R_3	R_1	R_2	Yield (%)*, 4 : 5	
				Method A	Method B
a	Ph	n-Pr	H	17:33	–
b	2-F-Ph	n-Pr	H	8:77	–
c	4-MePh	n-Pr	H	36:30	–
d	4-MeOPh	n-Pr	H	30:40	59:0
e	4-NO_2Ph	n-Pr	H	0:76	65:0
f	2-MePh	n-Pr	H	17:32	50:0
g	$PhCH_2$	n-Pr	H	47:8	–
h	2-MePh	Me	H	17:9	–
i	2-MePh	n-Pr	Me	–	57:0

*The yields are isolated yields.

Reduction of nitro compound **5e** with ammonium formate and 10% palladium on carbon led to the corresponding amino derivative **9**. However, the product of a catalytic hydrogenation of **5e** over 10% palladium on carbon at 40 psi was not amino derivative **9**, but a dihydroquinoline **7**, which was unstable and spontaneously oxidized to the compound **9**.[12,13] In order to avoid oxidation, the dihydroquinoline **7** was acylated with acetic anhydride to afford diacetyl derivative **8**. Acetylation of **9** with acetic anhydride gave compound **10** (Scheme 2).



Scheme 2

All synthesized compounds were tested for their ability to inhibit H^+/K^+-ATPase activity.[14] The activity of all synthesized compounds was lower than activity of SK & F 97067. The compounds **4a**, **4f** and **5f** showed IC_{50} of 25, 93 and 47 μM, respectively.

Experimental Section

Melting points were taken on the Mel-Temp apparatus

and were uncorrected. ^{1}H NMR spectra were taken on a Varian Gemini-200 MHz spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were taken on a Bruker 300 spectrometer at 75.5 MHz. 2D NMR experiments were carried out on a Bruker AMX-500 MHz spectrometer. Mass spectra were obtained with a Shimadzu QP 100 GC/MS mass spectrometer. Elemental analyses were done at Analytical Laboratory of KRICT.

General Procedure for Coupling of 3-Butyryl-4-chloro-8-methoxyquinoline and Hydrazines (Method A). A mixture of **3a** (0.79 g, 3 mmol), appropriately substituted hydrazine R_3NHNH_2 (3.6 mmol) and acetic acid (0.216 g, 3.6 mmol) in ethanol (80 mL) was stirred at ambient temperature for 48 h (72 h for 4-nitrophenylhydrazine). The ethanol was removed *in vacuo*. The residue was dissolved in dichloromethane and washed with aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated. Flash chromatographic separation yielded two isomers, **4** and **5**.

General Procedure for Regioselective Synthesis of N_1-Substituted Pyrazoloquinolines 4 (Method B). A mixture of **2** (3 mmol) and appropriately substituted hydrazine R_3NHNH_2 (3.6 mmol) in acetic acid was refluxed for 2 h. The acetic acid was removed *in vacuo*. The residue was dissolved in dichloromethane and washed with aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated. Purification by column chromatography (silica gel, ethyl acetate) yielded N_1-substituted isomers **4**.

1-Phenyl-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4a): mp 157-159 °C; ^{1}H NMR ($CDCl_3$) δ 9.23 (s, 1H, H_4), 7.58 (s, 5H, ArH), 7.27 (m, 1H, ArH), 7.11 (m, 2H, ArH), 4.10 (s, 3H, OCH_3), 3.21 (t, 2H, *J*=7.4 Hz, CH_2), 1.92 (m, 2H, CH_2), 1.11 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 317 (M^+, 92), 316 (M^+-H, 100), 288 (62), 287 (40), 286 (26), 258 (20), 257 (25), 128 (15).

2-Phenyl-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (5a): mp 189-191 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1H, H_4), 8.08 (d, 1H, *J*=8.0 Hz, ArH), 7.55 (s, 5H, ArH), 7.50 (m, 1H, ArH), 7.12 (d, 1H, *J*=8.0 Hz, ArH), 4.10 (s, 3H, OCH_3), 3.08 (t, 2H, *J*=7.4 Hz, CH_2), 1.73 (m, 2H, CH_2), 0.91 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 318 (M^+, 13), 317 (M^+-H, 66), 316 (100), 288 (49), 287 (23), 286 (21), 258 (21), 257 (23), 128 (6).

1-(2-Fluorophenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4b): mp 149-150 °C; ^{1}H NMR ($CDCl_3$) δ 9.26 (s, 1H, H_4), 7.65 (m, 2H, ArH), 7.36 (m, 3H, ArH), 7.12 (m, 2H, ArH), 4.11 (s, 3H, OCH_3), 3.14 (t, 2H, *J*=7.4 Hz, CH_2), 1.96 (m, 2H, CH_2), 1.08 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 335 (M^+, 78), 334 (M^+-H, 100), 306 (55), 305 (30), 276 (12), 275 (7), 257 (4).

2-(2-Fluorophenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (5b): mp 164-167 °C; ^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1H, H_4), 8.12 (d, 1H, *J*=8.0 Hz, ArH), 7.56 (m, 3H, ArH), 7.38 (m, 2H, ArH), 7.13 (d, 1H, *J*=8.0 Hz, ArH), 4.12 (s, 3H, OCH_3), 3.00 (t, 2H, *J*=7.4 Hz, CH_2), 1.75 (m, 2H, CH_2), 0.92 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 335 (M^+, 90), 334 (M^+-H, 100), 306 (52), 305 (31), 286 (20), 276 (15), 275 (16), 258 (14), 257 (18).

1-(4-Methylphenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4c): mp 183-184 °C; ^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1H, H_4), 7.47-7.03 (m, 7H, ArH), 4.87 (s, 3H, OCH_3), 3.10 (t, 2H, *J*=7.4 Hz, CH_2), 2.49 (s, 3H, CH_3Ar), 1.93 (m, 2H, CH_2), 1.06 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 331 (M^+, 65), 330 (M^+-H, 100), 302 (46), 301 (28), 300 (12), 272 (13), 271 (5), 257 (10), 256 (10).

2-(4-Methylphenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (5c): mp 124-125 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1H, H_4), 8.12 (d, 1H, *J*=8.0 Hz, ArH), 7.59 (t, 1H, *J*=8.0 Hz, ArH), 7.39 (m, 4H, ArH), 7.13 (d, 1H, *J*=8.0 Hz, ArH), 4.11 (s, 3H, OCH_3), 3.08 (t, 2H, *J*=7.4 Hz, CH_2), 2,47 (s, 3H, CH_3Ar), 1.74 (m, 2H, CH_2), 0.93 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 331 (M^+, 64), 330 (M^+-H, 100), 302 (41), 301 (23), 300 (19), 272 (16), 271 (13), 257 (14), 256 (10), 228 (10).

1-(4-Methoxyphenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4d): mp 187-188 °C; IR (KBr) 1605, 1558, 1532 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.23 (s, 1H, H_4), 7.50 (d, 2H, *J*=9.0 Hz, ArH), 7.30 (m, 1H, ArH), 7.07 (m, 4H, ArH), 4.11 (s, 3H, 6-OCH_3), 3.94 (s, 3H, OCH_3), 3.12 (t, 2H, *J*=7.4 Hz, CH_2), 1.94 (m, 2H, CH_2), 1.08 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 347 (M^+, 100), 346 (76), 320 (10), 318 (32), 317 (16), 288 (16); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.3, 27.7, 56.0, 56.4, 109.0, 114.5, 114.9, 116.2, 121.7, 127.6, 128.0, 132.6, 135.8, 141.0, 146.1, 147.5, 156.2, 160.5.

Anal Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.09; O, 9.21. Found: C, 72.22; H, 6.13; N, 12.14; O, 9.43.

2-(4-Methoxyphenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (5d): mp 168-169 °C; IR (KBr) 1607, 1581, 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.18 (s, 1H, H_4), 8.12 (d, 1H, *J*=8.0 Hz, ArH), 7.45 (m, 3H, ArH), 7.09 (m, 3H, ArH), 4.10 (s, 3H, 6-OCH_3), 3.88 (s, 3H, OCH_3), 3.05 (t, 2H, *J*=7.4 Hz, CH_2), 1.72 (m, 2H, CH_2), 0.91 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 347 (M^+, 100), 346 (60), 320 (14), 318 (46), 317 (24), 288 (16); ^{13}C NMR ($CDCl_3$) δ 14.5, 23.2, 29.3, 56.0, 56.5, 108.3, 114.1, 115.0, 117.69, 117.74, 126.7, 128.9, 133.9, 137.3, 140.6, 144.5, 148.9, 156.4, 160.6.

Anal Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.09; O, 9.21. Found: C, 72.21; H, 6.17; N, 12.17; O, 9.45.

1-(4-Nitrophenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4e): mp 206-208 °C; ^{1}H NMR ($CDCl_3$) δ 9.26 (s, 1H, H_4), 8.47 (d, 2H, *J*=9.0 Hz, ArH), 7.87 (d, 2H, *J*=9.0 Hz, ArH), 7.44-7.13 (m, 3H, ArH), 4.14 (s, 3H, OCH_3), 3.14 (t, 2H, *J*=7.4 Hz, CH_2), 1.96 (m, Hz, CH_2), 1.10 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 363 (16), 362 (M^+, 100), 361 (M^+-H, 98), 333 (63), 332 (67), 315 (45), 303 (29), 287 (36), 286 (39), 258 (16), 257 (25), 256 (36), 216 (11), 129 (19).

2-(4-Nitrophenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (5e): mp 174-176 °C; ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1H, H_4), 8.45 (d, 2H, *J*=9.0 Hz, ArH), 8.08 (d, 1H, *J*=8.0 Hz, ArH), 7.82 (d, 2H, *J*=9.0 Hz, ArH), 7.55 (t, 1H, *J*=8.0 Hz, ArH), 7.16 (d, 1H, *J*=8.0 Hz, ArH), 4.11 (s, 3H, OCH_3), 3.17 (t, 2H, *J*=7.4 Hz, CH_2), 1.78 (m, 2H, CH_2), 0.95 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 363 (43), 362 (M^+, 100), 361 (M^+-H, 99), 333 (54), 315 (45), 287 (36), 286 (39), 258 (16), 257 (25), 256 (36).

1-(2-Methylphenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4f): mp 106-109 °C; IR (KBr) 1610, 1582, 1521, 1236, 1199, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.28 (s, 1H, H_4), 7.46 (m, 4H, ArH), 7.24 (d, 1H, *J*=8.0 Hz, ArH), 7.07 (d, 1H, *J*=8.0 Hz, ArH), 6.85 (d, 1H, *J*=8.0 Hz,

ArH), 4.08 (s, 3H, OCH_3), 3.15 (t, 2H, *J*=7.4 Hz, CH_2), 1.96 (m with s, 5H, CH_3Ar+CH_2), 1.07 (t, 3H, *J*=7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 14.5, 21.8, 23.3, 29.3, 56.5, 108.3, 114.2, 117.7, 117.9, 126.7, 127.4, 130.5, 137.3, 138.6, 139.8, 140.4, 144.5, 149.0, 156.4; MS (EI) *m/z* 331 (M^+, 65), 330 (M^+-H, 100), 302 (49), 301 (33), 300 (11), 286 (20), 258 (17), 257 (18), 256 (14).

2-(2-Methylphenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (5f): mp 163-164 °C; IR (KBr) 1596, 1559, 1529, 1172, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.22 (s, 1H, H_4), 8.11 (d, 1H, *J*=8.0 Hz, ArH), 7.53 (t, 1H, *J*=8.0 Hz, ArH), 7.38 (m, 4H, ArH), 7.13 (d, 1H, *J*=8.0 Hz, ArH), 4.11 (s, 3H, OCH_3), 2.91 (t, 2H, *J*=7.4 Hz, CH_2), 2.05 (s, 3H, CH_3Ar), 1.66 (m, 2H, CH_2), 0.91 (t, 3H, *J*=7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.7, 23.3, 27.7, 56.4, 109.0, 114.5, 116.3, 121.7, 126.5, 127.1, 127.6, 130.4, 137.3, 139.9, 140.9, 146.1, 147.6, 156.2; MS (EI) *m/z* 331 (M^+, 81), 330 (M^+-H, 100), 302 (44), 301 (47), 300 (17), 286 (9), 270 (10), 258 (19), 257 (12), 256 (23).

1-Benzyl-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4g): mp 116-117 °C; ^1H NMR ($CDCl_3$) δ 9.21 (s, 1H, H_4), 7.67 (d, 1H, *J*=8.0 Hz, ArH), 7.44 (t, 1H, *J*=8.0 Hz, ArH), 7.28 (m, 3H, ArH), 7.11 (m, 2H, ArH), 6.00 (s, 2H, CH_2Ph), 4.11 (s, 3H, OCH_3), 3.12 (t, 2H, *J*=7.4 Hz, CH_2), 1.95 (m, 2H, CH_2), 1.08 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 331 (M^+, 100), 330 (68), 302 (48), 211 (11), 182 (11), 91 (80).

2-Benzyl-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (5g): mp 157-160 °C; ^1H NMR ($CDCl_3$) δ 9.10 (s, 1H, H_4), 8.09 (d, 1H, *J*=8.0 Hz, ArH), 7.51 (t, 1H, *J*=8.0 Hz, ArH), 7.30-7.11 (m, 5H, ArH), 5.64 (s, 2H, CH_2Ph), 4.04 (s, 3H, OCH_3), 2.99 (t, 2H, *J*=7.4 Hz, CH_2), 1.68 (m, 2H, CH_2), 0.92 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 331 (M^+).

1-(2-Methylphenyl)-4-methyl-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (4i): mp 146-153 °C; ^1H NMR ($CDCl_3$) δ 7.50-7.38 (m, 4H, ArH), 7.18-6.98 (m, 2H, ArH), 6.74 (dd, 1H, *J*=1.2, 8.1 Hz, ArH), 4.05 (s, 3H, OCH_3), 3.17 (t, 2H, *J*=7.5 Hz, CH_2Et), 3.07 (s, 3H, 4-CH_3), 1.93 (s, 3H, $PhCH_3$), 1.88 (m, 2H, CH_2), 1.13 (t, 3H, *J*=7.2 Hz, CH_3).

2-(2-Methylphenyl)-3-methyl-6-methoxypyrazolo[4,3-c]quinoline (5h), 1-(2-Methylphenyl)-3-methyl-6-methoxypyrazolo[4,3-c]quinoline (4h) and *o*-Tolylhydrazone of 3-Acetyl-4-chloro-8-methoxyquinoline (6). A mixture of **3b** (0.9 g, 3.8 mmol), *o*-tolylhydrazine hydrochloride (0.73 g, 4.6 mmol) and anhydrous sodium acetate (0.38 g, 4.6 mmol) in ethanol (100 mL) was stirred for 72 h. Work up is given in general example. Separation by column chromatography (silica gel, ethyl acetate) gave 0.1 g (9%) of compound **5h**, 0.2 g (17%) of compound **4h** and 0.45 g (35%) of uncyclized hydrazone **6**. Cyclization of hydrazone **6** by refluxing in dioxane gave **4h** in 60% yield.

4h: mp 285-287 °C; ^1H NMR ($CDCl_3$) δ 9.24 (s, 1H, H_4), 7.44 (m, 4H, ArH), 7.26 (m, 1H, ArH), 7.09 (m, 1H, ArH), 6.82 (m, 1H, ArH), 4.10 (s, 3H, OCH_3), 2.78 (s, 3H, 3-CH_3), 1.96 (s, 3H, CH_3Ar); MS (EI) *m/z* 303 (M^+, 71), 302 (M^+-H, 100), 274 (24), 273 (27), 258 (9), 231 (11).

5h: mp 202-204 °C; ^1H NMR ($CDCl_3$) δ 9.18 (s, 1H, H_4), 8.12 (d, 1H, *J*=8.0 Hz, ArH), 7.54 (t, 1H, *J*=8.0 Hz, ArH), 7.50-7.37 (m, 4H, ArH), 7.14 (d, 1H, *J*=8.0 Hz, ArH), 4.13 (s, 3H, OCH_3), 2.56 (s, 3H, 3-CH_3), 2.07 (s, 3H, CH_3Ar); MS (EI) *m/z* 303 (M^+, 61), 302 (M^+-H, 100), 274 (61), 273 (31), 258 (11), 257 (12), 231 (7), 91 (10).

6: oil; ^1H NMR ($CDCl_3$) δ 9.04 (s, 1H, H_2), 7.62-7.10 (m, 6H, ArH+NH), 6.85 (t, 1H, ArH); MS (EI) *m/z* 341 (M^+, 5), 339 (M^+, 24) , 304 (M^+-HCl, 30), 303 (56), 302 (M^+-HCl, 100), 274 (64), 233 (37), 106 (44), 77 (41).

2-(4-Aminophenyl)-3-propyl-4,5-dihydro-6-methoxypyrazolo[4,3-c]quinoline (7). A solution of **4h** (0.3 g, 0.8 mmol) in methanol (50 mL) was hydrogenated over 10% palladium on carbon (0.1 g) at 40 psi and ambient temperature for 16 h. The catalyst was filtered off, and filtrate was concentrated under reduced pressure to give oil. Purification by flash column chromatography (ethyl acetate) gave **7** as an oil (0.18 g, 65%): ^1H NMR (DMSO-d_6) δ 7.06 (m, 3H, ArH), 6.72-6.47 (m, 4H, ArH), 5.33 (s, 2H, NH_2), 5.23 (s, 1H, NH), 4.41 (s, 2H, 4-CH_2), 3.77 (s, 3H, OCH_3), 2.48 (t, 2H, *J*=7.4 Hz, CH_2), 1.35 (m, 2H, CH_2), 0.75 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 334 (M^+, 55), 333 (M^+-H, 100), 318 (18), 303 (11), 289 (12).

2-(4-Acetylaminophenyl)-3-propyl-5-acetyl-4,5-dihydro-6-methoxypyrazolo[4,3-c]quinoline (8). A solution of **7** (0.1 g, 0.3 mmol) and acetic anhydride (0.3 mL, 3 mmol) in CH_2Cl_2 (20 mL) was stirred at ambient temperature for 4 h. Excess acetic anhydride was hydrolyzed with aqueous sodium bicarbonate. The organic layer was washed with aqueous sodium bicarbonate, dried over sodium sulfate and filtered. Flash chromatographic purification using ethyl acetate yielded **8** (0.08 g, 64%): mp 213-215 °C; ^1H NMR ($CDCl_3$) δ 7.81 (br. s, 1H, NH), 7,62 (m, 3H, ArH), 7.33 (m, 3H, ArH), 6.95 (d, 1H, *J*=7.5 Hz, ArH), 5.94 (br. d, 1H, 4-CH_2), 3.93 (m, 4H, 4-CH_2+OCH_3), 2.63 (m, 2H, CH_2), 2.23 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 1.51 (m, 2H, CH_2), 0.86 (t, 3H, *J*=7.3 Hz, CH_3); MS (EI) *m/z* 418 (M^+, 22), 375 (M^+-Ac, 66), 360 (8).

Anal Calcd for $C_{24}H_{26}N_4O_3$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.64; H, 6.33; N, 13.35.

2-(4-Aminophenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (9). To a stirred suspension of **4h** (0.3 g, 0.8 mmol) and 10% Pd-C (0.1 g) in methanol (50 mL) anhydrous ammonium formate (0.26 g, 4 mmol) was added in a single portion. The resulting reaction mixture was stirred at room temperature for 3 h. The catalyst was removed by filtration and washed with methanol (10 mL). The filtrate was evaporated *in vacuo*. The resulting residue was treated with water, and the product was extracted with chloroform and dried over sodium sulfate. Recrystallization from ethyl acetate gave **9** (0.25 g, 91%): mp 211-214 °C; ^1H NMR (DMSO-d_6) δ 9.17 (s, 1H, H_4), 7.89 (d, 1H, *J*=8.0 Hz, ArH), 7.51 (t, 1H, *J*=8.0 Hz, ArH), 7.22 (m, 3H, ArH), 6.71 (d, 2H, *J*=8.6 Hz, ArH), 5.56 (br. s, 2H, NH_2), 3.99 (s, 3H, OCH_3), 3.06 (t, 2H, *J*=7.4 Hz, CH_2), 1.66 (m, 2H, CH_2), 0.83 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 332 (M^+, 100), 331 (M^+-H, 85), 303 (55), 273 (21).

2-(4-Acetylaminophenyl)-3-propyl-6-methoxypyrazolo[4,3-c]quinoline (10). It was prepared as described for **8** in a yield of 76%; mp 225-226 °C; ^1H NMR ($CDCl_3$) δ 9.20 (s, 1H, H-4), 8.13-8.07 (d+s, 2H, ArH+NH), 7.77 (d, 2H, *J*=8.8 Hz, ArH), 7.53 (m, 3H, ArH), 7.16 (d, 1H, *J*=8.0 Hz, ArH), 4.12 (s, 3H, OCH_3), 3.10 (t, 2H, *J*=7.4 Hz, CH_2), 2.24 (s, 3H, CH_3CO), 1.75 (m, 2H, CH_2), 0.95 (t, 3H, *J*=7.4 Hz, CH_3); MS (EI) *m/z* 374 (M^+, 100), 373 (M^+-H, 99), 345 (35), 315 (6).

Anal Calcd for $C_{22}H_{22}N_4O_2$: C, 70.56; H, 5.92; N, 14.96; O, 8.55. Found: C, 70.01; H, 5.98; N, 15.04; O, 8.71.

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Formation and Dissociation Kinetics of Tetraaza-Crown-Alkanoic Acid Complexes of Cerium(III)

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The formation and dissociation rates of Ce^{3+} Complexes of the 1,4,7,10-tetraaza-13,16-dioxacyclooctadecane-N,N', N",N"'-tetraacetic acid (**1**), 1,4,7,10-tetraaza-13,16-dioxacyclooctadecane-N,N',N",N"'-tetramethylacetic acid (**2**), and 1,4,7,10-tetraaza-13,16-dioxacyclooctadecane-N,N',N",N"'-tetrapropionic acid (**3**) have been measured by the use of stopped-flow spectrophotometry. Observations were made at 25.0±0.1 °C and at an ionic strength of 0.10 M $NaClO_4$. The complexation of Ce^{3+} ion with **1** and **2** proceeds through the formation of an intermediate complex $(CeH_3L^{2+})^*$ in which the Ce^{3+} ion is incompletely coordinated. This may then lead to be a final product in the rate-determining step. Between pH 4.76 and 5.76, the diprotonated (H_2L^{2+}) from is revealed to be a kinetically active species despite of its low concentration. The stability constants ($\log K_{(CeH_3L^{2+})^*}$) and specific water-assisted rate constants (k_{OH}) of intermediate complexes have been determined from the kinetic data. The dissociation reactions of Ce^{3+} complexes of **1**, **2**, and **3** were investigated with Cu^{2+} ions as a scavenger in acetate buffer. All complexes exhibit acid-independent and acid-catalyzed contributions. The effect of buffer and Cu^{2+} concentration on the dissociation rate has also been investigated. The ligand effect on the dissociation rate of Ce^{3+} complexes is discussed in terms of the side-pendant arms and the chelate ring sizes of the ligands.

Introduction

In recent years, there has been growing interest in the macrocyclic receptors containing in their framework both oxygen and nitrogen atoms.[1,2] The molecular recognition and activation of anionic or neutral substrates has led to a further development in the chemistry of such macrocycles.[3,4] Several factors influence the kinetics of formation and dis-

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