Molecular Design of pH-Sensitive Spin Probes in the 2,3,4,6,7,8-Hexahydroimidazo[1,5-*a*]pyrimidine Series with Different Lipophilic/Hydrophilic Properties

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Received 6 April 2005; revised 29 June 2005

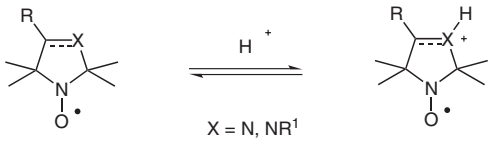
Abstract: New pH-sensitive spin probes – 2,3,4,6,7,8-hexahydroimidazo[1,5-*a*]pyrimidines – were synthesized by the reaction of 4-amino-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-imidazol-1-oxyl with aminomethylated α,β-unsaturated carbonyl methiodides or hydrochlorides. Introduction of hydrophilic (COOH) or lipophilic ($C_{10}H_{21}$) groups in the aminomethylated compounds allowed the synthesis of pH-sensitive spin probes with different solubilities.

Key words: radicals, enone, Mannich bases, spin probes, amidine

Stable nitroxides have been used intensively for the last forty years and have become a powerful tool for the design of new materials,[1] in the development of new synthetic methods,[2] and for measuring certain physical and biological properties.[3]

Local pH is a very important characteristic of living organisms including the human body. The measurement of pH in biological organells and organs should allow the early diagnosis of some diseases that cause changes in pH.[4]

The use of 3-imidazolines or imidazolidines nitroxyl radicals for in vitro and in vivo pH measurements is based on the noticeable changes in ESR spectra of a spin probe molecule due to the contribution of both protonated and unprotonated forms (Scheme 1).[4]



Scheme 1 Protonation/deprotonation of 3-imidazoline and imidazolidine nitroxides

Previous advances in pH-sensitive nitroxides were surveyed.[5] In recent times research has been directed towards pH-sensitive nitroxides which are lipophylic,[6] stable towards reduction,[7] also the synthesis of two pK pH-sensitive[8] nitroxides have been published by our group.

SYNTHESIS 2005, No. 20, pp 3649–3653
Advanced online publication: 25.10.2005
DOI: 10.1055/s-2005-918432; Art ID: Z06705SS

The measurement of pH in vivo puts some limitations on spin probe properties. In most cases the probe should have a pK_a value near the physiological one, i.e. 7 and significant changes should be visible in the ESR spectra (difference in the hyperfine coupling constant of the protonated and unprotonated form Δa_N).[9] A spin probe which is to be used inside a cell in aqueous media should be hydrophilic, while a probe for the measurement of pH at the membrane surface should be lipophilic.

The design of biologically applicable pH-sensitive spin probes includes the construction of the following blocks in the molecule: source of the ESR signal (A), which interacts with the pH-sensitive block (B), and a regulator (C) of the physical properties of the probe (for example, lipophilic/hydrophilic properties) (Figure 1).

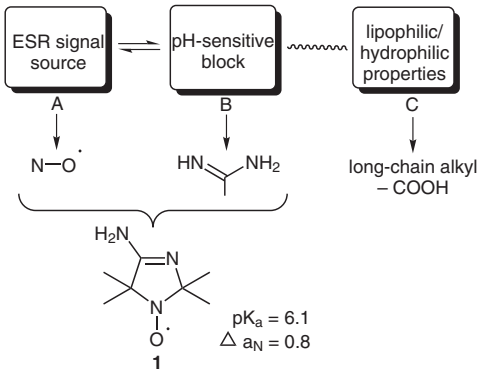


Figure 1 Important components for a pH-sensitive spin probe with different lipophilic/hydrophilic properties

The ESR signal of the nitroxyl group of cyclic amidine 4-amino-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-imidazol-1-oxyl (**1**), depends on the proton concentration in the solution. The pK_a value of **1** (6.1) is close to the physiological one.[9] Amidine bicyclic systems based on **1** are known to be more basic than monocyclic amidines.[10] Recently we have shown[11] that reaction of amidine **1** with enone Mannich base methiodides leads to pH-sensitive nitroxides 2,3,4,6,7,8-hexahydroimidazo[1,5-*a*]pyrimidines **2** and **3** (Figure 2). The structure of **3** was determined by X-ray crystal analysis.[12] The reactivity of **1** differs from that of diamagnetic amidines due to the influence of the nitroxyl group on the properties of the amidine moiety and this is

the only known method for the direct modification of **1** (for synthesis of **1**[13]). Previously alkylated paramagnetic amidines have been prepared via other pathways.[14]

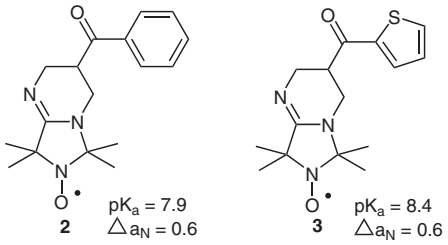


Figure 2 Imidazopyrimidine pH-sensitive nitroxides

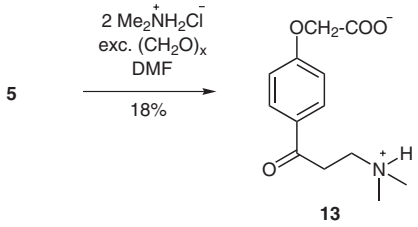
Herein, we report the application of the reaction of **1** with enone Mannich base methiodides and 2-dimethylaminomethylacrylic acid hydrochloride to obtain pH-sensitive nitroxides with different lipophilic/hydrophilic properties.

In general, the synthesis of enone Mannich bases[15] and their methiodides[11] starts from acetophenones. So, the most obvious approach is to synthesize methiodides, modified with a long alkyl chain group for lipophilic probes and carboxyl or ester group for hydrophilic probes.

Double aminomethylation of decyloxyacetophenone **4** in DMF followed by the elimination of dimethylamine lead to 2-(4-decyloxybenzoyl)allyldimethylamine **6** (Scheme 2). Compound **6** was reacted with iodomethane to afford 2-(4-decyloxybenzoyl)allyltrimethylammonium iodide **8**. It should be noted that this compound was the only methiodide we were able to purify by crystallization owing to the presence of the decyl group. All other methiodides were not stable to recrystallization.

The reaction of the iodide **8** with the amidine **1** in isopropanol in the presence of triethylamine at room temperature resulted in the formation of imidazopyrimidine **10** in 50% yield as an orange oil, which was soluble in hexane and other organic solvents and insoluble in water.

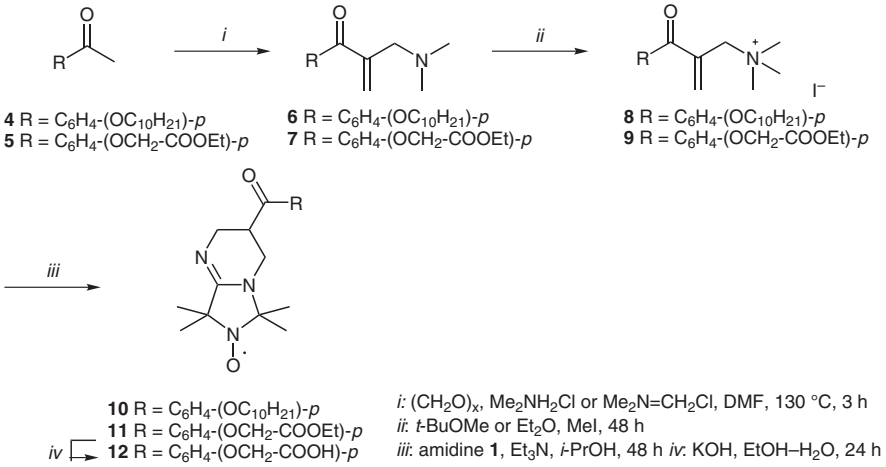
To introduce the ester group in the spin probe we started from ester **5**. Mannich reaction of **5** under standard conditions [DMF (2 equiv), $Me_2NH{\cdot}HCl$, excess $(CH_2O)_x$, 125 °C, 3 h] failed to give enone Mannich base **7**. The only isolated product contained no ethoxy group and only one dimethylaminomethyl group (according to NMR data), which we deduced to be amino acid **13**.



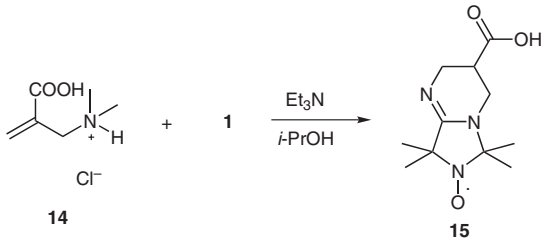
Scheme 3 Aminomethylation of (4-acetylphenoxy)acetic acid

This result may be rationalized as resulting from the hydrolysis of the ester group by water formed during the reaction of formaldehyde with dimethylamine. To avoid hydrolysis and to shift the equilibrium towards the formation of the target product we performed aminomethylation of ketone with Eschenmoser's salt and obtained enone Mannich base **7** as the hydrochloride. Reaction of the hydrochloride with amidine **1** under the conditions used previously for the reaction of enone Mannich bases with binucleophiles[16] gave a complex mixture of products, containing only small amounts of desired spin probe **11**. Conversion of the hydrochloride **7** into methiodide **9**, and further reaction of **9** with amidine **1** resulted in **11** in 41% yield. Hydrolysis of ester **11** with an excess of potassium hydroxide in water–ethanol gave water soluble spin probe **12** (isolated as highly hygroscopic hydrochloride).

The carboxyphenyl group in **12** decreased the solubility of the spin probe in water. In connection with this, a water soluble spin probe without a phenyl group using aminomethylated acrylic acid **14**[17] was synthesized.



Scheme 2 Synthesis of new imidazopyrimidine pH-sensitive spin probes



Scheme 4 Synthesis of water-soluble spin probe **15**

Thus, refluxing amidine **1** with an excess of hydrochloride **14** after reverse phase TLC gave acid **15** as a yellowish solid which was highly water soluble and hygroscopic.

Both the pK_a and partition coefficients of the probes synthesized were estimated according to the previously described procedures[18] and are summarized in Table 1.

Table 1 Titration Data and Partition Coefficients (Kp) of the Spin Probes Synthesized

Probe	pK_a	Δa_N, G	Kp (octanol–water)
10[a]	8.5 ± 0.1	0.55	No radical was found in buffer
11	8.85 ± 0.05	0.59	6.5
11·HCl	8.82 ± 0.05	0.57	0.042
12·HCl	8.67 ± 0.05	0.6	0.027
15	9.4 ± 0.05 5.05 ± 0.15	0.5 0.1	0.12

[a] Titration in 10% acetone solution in buffer.

Several 2,3,4,6,7,8-hexahydroimidazo[1,5-*a*]pyrimidines, new pH-sensitive spin probes, were synthesized via reaction of aminomethylated salts of α,β-unsaturated carbonyl compounds with paramagnetic 4-amino-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-imidazol-1-oxyl. The introduction of different groups was responsible for the lipophilic/hydrophilic properties of the molecule, which allowed the preparation of probes which are soluble in both water or lipids.

IR spectra were recorded on Bruker Vector 22 as KBr disks or neat. UV spectra were recorded on a HP Agillent 8453. ^{1}H NMR spectra were carried out on a Bruker AM-400 (400.13 MHz), Bruker WP-200SY (200.2 MHz), and Bruker AC-200 (200.2 MHz) spectrometers. HRMS were obtained using a Finnigan MAT 8200 mass spectrometer. EPR spectra were recorded on a Bruker ER-200D-SRC spectrometer using a 10 μL quartz capillary. Mps were measured on a Kofler plate and are uncorrected. Analytical and preparative TLC was performed on Silufol UV_{254} plates (Cavalier, CSFR), Polygram sil N-HR/UV_{254} (Macherey-Nagel Co., Germany), and silica gel (Lachema, CSFR). Decyloxyacetophenone **4** and ester **5** were synthesized by the alkylation of 4-hydroxyacetophenone, whose analytical data are in accordance with that previously reported.[19,20]

2-(4-Decyloxy)benzoylallyltrimethylammonium Iodide (8)

A solution of 4-decyloxyacetophenone (2 g, 7 mmol), Me_2NH·HCl (1.2 g, 15 mmol), and paraformaldehyde (0.7 g, 24 mmol) in DMF (15 mL) was stirred at 125 °C for 3 h. DMF was removed by passing a stream of air over the mixture. The residue was dissolved in H_2O (20 mL) and the resulting solution was washed with *t*-BuOMe (10 mL). The pH was adjusted to 9 by the addition of NaOH and the phenylpropenone **6** was extracted with *t*-BuOMe (3 × 10 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give crude phenylpropenone **6**, which was used without further purification.

Yield: 9.4 g (60%); colorless oil.

^{1}H NMR (CCl_4, HMDS): δ = 0.88 (3 H, t, *J* = 6 Hz, CH_3), 1.20–1.58 (14 H, m, 7 × CH_2), 1.77 (2 H, m, OCH_2CH_2), 2.21 [6 H, s, $N(CH_3)_2$], 3.19 (2 H, s, NCH_2), 3.96 (2 H, t, *J* = 6.5 Hz, OCH_2), 5.51 (1 H, s, =CH), 5.76 (1 H, s, =CH′), 6.82 (2 H, d, *J* = 8.3 Hz, ArH), 7.73 (2H, d, *J* = 8.3 Hz, ArH).

MeI (0.07 mL, 1.2 mmol) was added to a solution of the phenylpropenone (**6**; 0.22g, 0.6 mmol) in *t*-BuOMe (3 mL). After 24 h the resulting precipitate was filtered off, washed with *t*-BuOMe (3 mL), and dried in air to give **8**.

Yield: 0.22 g (76%); colorless crystals; mp 135–138 °C (*i*-PrOH).

IR (KBr): 1650, 1600 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 0.85 (3 H, t, *J* = 6 Hz, CH_3), 1.20–1.58 (14 H, m, 7 × CH_2), 1.73 (2 H, m, OCH_2CH_2), 3.07 [9 H, s, $N(CH_3)_3$], 4.08 (2 H, t, *J* = 6.5 Hz, OCH_2), 4.39 (2 H, s, NCH_2), 6.31 (1 H, s, =CH), 6.61 (1 H, s, =CH′), 7.07 (2 H, d, *J* = 8.5 Hz, ArH), 7.91 (2 H, d, *J* = 8.5, ArH).

UV (EtOH): λ_{max} (log ε) = 299 nm (4.12).

Anal. Calcd for $C_{23}H_{38}INO_2$: C, 56.67; H, 7.86; N, 2.87; I, 26.03. Found: C, 56.92; H 7.82; N 2.83; I 26.29.

[4-(3-Dimethylaminopropionyl)phenoxy]acetic Acid (13)

A solution of acetophenone **5** (2.22 g, 10 mmol), Me_2NH·HCl (1.63 g, 20 mmol), and paraformaldehyde (1.05 g, 35 mmol) in DMF (20 mL) was stirred at 125 °C for 3 h. DMF was removed by passing a stream of air over the mixture. The residue was dissolved in H_2O (20 mL) and the resulting solution was washed with *t*-BuOMe (10 mL). The pH was adjusted to 9 by the addition of NaOH and extracted with *t*-BuOMe (3 × 10 mL). The organic layer contained only a small quantity of unidentified compounds. The aqueous layer was neutralized with HCl, evaporated under reduced pressure to dryness, and treated with EtOH (3 mL). The precipitated NaCl was filtered, the filtrate was evaporated under reduced pressure, treated with hot EtOAc (3 mL), and EtOH (3 mL) was added to give a solution. The solution was allowed to sit at 5 °C for 48 h from which **13** precipitated.

Yield: 0.46 g (18%); colorless crystals; mp 168–170 °C (EtOAc–EtOH); recrystallization gave alcoholate (signals of EtOH appeared in NMR spectra).

IR (KBr): 1675, 1601 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.36 [6 H, s, $N(CH_3)_2$], 2.83 (2 H, t, *J* = 5.8 Hz, CH_2), 3.19 (2 H, t, *J* = 5.8 Hz, CH_2), 4.47 (2 H, s, OCH_2), 6.92 (2 H, d, *J* = 8.7 Hz, ArH), 7.87 (2 H, d, *J* = 8.7 Hz, ArH).

HRMS: *m*/*z* calcd for $[M - N(CH_3)_2]^+$: 206.0579; found: 206.0568.

[4-(2-Dimethylaminomethylacryloyl)phenoxy]acetic Acid Ethyl Ester Hydrochloride (7·HCl)

A solution of 4-acetylphenoxyacetic acid ethyl ester (**5**; 3.11 g, 14 mmol) and Eschenmoser's salt (30 mmol; prepared in situ from $Me_2NCH_2NMe_2$ and CH_3COCl) in DMF (12 mL) was stirred at 125 °C for 3 h. DMF was evaporated under reduced pressure and

the residue was treated with acetone (50 mL) to give the ethyl ester hydrochloride of **7**.

Yield: 4.2 g (92%); colorless crystals; mp 158–160 °C (acetone–EtOH).

IR (KBr): 1760, 1660, 1590 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.22 (3 H, t, *J* = 7 Hz, CH_2CH_3), 2.75 (6 H, s, 2 × NCH_3), 4.07 (2 H, s, NCH_2), 4.16 (2 H, q, *J* = 7 Hz, CH_2CH_3), 4.93 (2 H, s, OCH_2), 6.12 (1 H, s, =CH), 6.62 (1 H, s, =CH′), 7.10 (2 H, d, *J* = 9 Hz, ArH), 7.82 (2 H, d, *J* = 9 Hz, ArH).

UV (EtOH): λ_{max} (log ε) = 290 nm (4.03).

Anal. Calcd for $C_{16}H_{22}ClNO_4$: C, 58.62; H, 6.76; N, 4.27; Cl, 10.82. Found: C, 58.62; H 6.74; N 4.39; Cl, 11.10.

[2-(4-Ethoxycarbonylmethoxybenzoyl)allyl]trimethylammonium Iodide (9)

A solution of the ethyl ester hydrochloride of **7** (0.26 g, 0.8 mmol) in H_2O (3 mL) was neutralized with Na_2CO_3 and extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and filtered. MeI (0.055 mL, 0.88 mmol) was added to the resulting solution. After 48 h an oil formed, which was treated with Et_2O (2 × 3 mL) to give the solid iodide **9.**

Yield: 0.27 g (77%); decomposes upon recrystallization.

IR (KBr): 1755, 1647, 1597 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.22 (3 H, t, *J* = 7 Hz, CH_2CH_3), 3.36 (9 H, s, 3 × NCH_3), 4.18 (2 H, q, *J* = 7 Hz, CH_2CH_3), 4.40 (2 H, s, NCH_2), 4.94 (2 H, s, OCH_2), 6.33 (1 H, s, =CH), 6.63 (1 H, s, =CH′), 7.08 (2 H, d, *J* = 9 Hz, ArH), 7.92 (2 H, d, *J* = 9 Hz, ArH).

UV (EtOH): λ_{max} (log ε) = 222 (4.29), 290 (4.03).

(4-Decyloxyphenyl)-(6,6,8,8-tetramethyl-7-oxyl-2,3,4,6,7,8-hexahydroimidazo[1,5-*a*]pyrimidin-3-yl)methanone (10)

Amidine **1** (0.11 g, 0.72 mmol) was added to a stirred suspension of iodide **8** (0.35 g, 0.72 mmol) in *i*-PrOH (5 mL). After 48 h, the solution was filtered, solvent was evaporated under reduced pressure, the resulting oil was treated with an aq solution of $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. TLC (Al_2O_3) gave **10** as an orange oil.

Yield: 0.15 g (47%); yellow oil.

IR (KBr): 1670, 1600 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 280 (4.15).

HRMS: *m*/z calcd for $[M - NO]^+$: 426.3220; found: 426.3220.[21]

[4-(6,6,8,8-Tetramethyl-7-oxyl-2,3,4,6,7,8-hexahydroimidazo[1,5-*a*]pyrimidine-3-carbonyl)phenoxy]acetic Acid Ethyl Ester (11)

This was carried out starting from **9** according to the procedure described for the synthesis of **10**.

Yield: 0.1 g (42%), yellow oil.

IR (KBr): 1756, 1670, 1600 cm^{-1}.

HRMS: *m*/*z* calcd for $[M + H]^+$: 403.2107; found: 403.2124.

[4-(6,6,8,8-Tetramethyl-7-oxyl-2,3,4,6,7,8-hexahydroimidazo[1,5-*a*]pyrimidine-3-carbonyl)phenoxy]acetic Acid Hydrochloride (12·HCl)

A solution of KOH (0.15 mmol, 0.008 g) and ethyl ester **11** (0.1 mmol, 0.04 g) in H_2O–EtOH (1 mL) was kept at r.t. for 24 h. An excess of HCl in EtOH (sat., 3 mL) was added. The reaction mixture was evaporated to dryness, *i*-PrOH (2 mL) was added, KCl was filtered off, and the filtrate was evaporated in vacuo. The residue was treated with Et_2O (2 mL) to give the hydrochloride of **12**.

Yield: 0.04 g (100%); slightly yellow hydroscopic crystals; mp 149–151 °C (EtOH).

IR (KBr): 1740, 1684, 1667 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}N_3O_5 \cdot HCl \cdot 1.5H_2O$: C, 52.11; H, 6.45; N, 9.60. Found: C, 52.44; H 6.56; N 9.10.

6,6,8,8-Tetramethyl-7-oxyl-2,3,4,6,7,8-hexahydroimidazo[1,5-*a*]pyrimidine-3-carboxylic Acid (15)

A solution of amidine **1** (0.77 mmol, 0.12 g), aminoacrylic acid **14** (1.16 mmol, 0.19 g), and Et_3N (1.54 mmol, 0.21 mL) in *i*-PrOH (3 mL) was refluxed for 4 h, another portion of aminoacrylic acid (0.1 g) was added and the reaction was refluxed for a further 2 h. The resulting mixture was concentrated in vacuo, the residue was treated with a hot mixture of *t*-BuOMe–*i*-PrOH (5:1, 2 mL), the precipitated salts were filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in H_2O (2 mL) and washed with $CHCl_3$ (2 mL). The aqueous layer was concentrated in vacuo to give a hygroscopic solid (0.12 g). Reverse phase TLC (water, MeOH) gave the carboxylic acid **15**.

Yield: 0.06 g (32%); colorless highly hydroscopic solid; mp 113–115 °C (MeOH).

IR (KBr): 1683, 1588 cm^{-1}.

HRMS: *m*/*z* calcd for $[M + H]^+$: 241.1426; found: 241.1421.

Anal. Calcd for $C_{11}H_{18}N_3O_3 \cdot 1.5H_2O \cdot 1.5MeOH$: C, 47.61; H, 8.63; N, 13.32. Found: C, 47.52; H, 8.10; N, 13.01.

Acknowledgment

The authors would like to thank INTAS (grant N 99-1086), the Russian Foundation of Basic Research (grant no. 04-03-32563), Science Support Foundation, and President Council on Young Scientists Support (grant MK-4029.2004.3) for financial support.

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(12) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic

Data Centre as supplementary publication no. CCDC-149032. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(1223)336033, e-mail: deposit@ccdc.cam.ac.uk].

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