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Preparation and Properties of *N,N,N′,N′*-Tetrasubstituted 1,4-Benzenediamines

Jørn B. Christensen,*[,a] Niels-Christian Schiødt,[a] Klaus Bechgaard[b] and Thomas Buch-Rasmussen[c]

[a]Department of Chemistry, University of Copenhagen, Symbion Science Park, Fruebjergvej 3, DK-2100 Copenhagen Ø, Denmark, [b]Department of Solid State Physics, Risø National Laboratory, DK-4000, Roskilde, Denmark and [c]Novo Nordisk A/S, Roskildevej 56, DK-2400 Hillerød, Denmark

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The synthesis of nine different *N,N,N′,N′*-tetrasubstituted 1,4-benzenediamines is described. These compounds are of interest as mediators for glucose oxidase based biosensors and as donor molecules for conducting molecular solids. The electrochemical behaviour and the electronic absorption spectra have been investigated.

Glucose sensors have attracted a lot of attention in recent years, especially because of their potential application in controlling insulin dosage in diabetes patients.[1] One of the strategies for construction of a glucose sensor relies on the enzymatic oxidation of glucose to δ-gluconolactone with glucose oxidase, which is readily available from the fungus *Aspergillus niger*. The reaction occurring under aerobic conditions is shown in Fig. 1.

The concentration of glucose can be measured by amperometric detection of the hydrogen peroxide formed. However this method suffers from the disadvantage that in order to oxidize the H_2O_2 at a reasonable rate, a large overpotential is necessary, and thus interference from other compounds, such as ascorbic acid[2] or drugs like paracetamol[3] in the blood, becomes possible. A solution to this problem is the use of a mediator, which is a redox-active molecule capable of oxidizing the reduced enzyme back to the active state.[4,5] The concentration of glucose can then be measured by monitoring the redox pair formed by the mediator in its reduced and oxidized state. A perfect mediator should undergo fast electron transfer with the enzyme and should be stable in both the reduced and oxidized forms.

Our attention was drawn to tetrasubstituted 1,4-benzenediamines because *N,N,N′,N′*-tetramethyl-1,4-benzenediamine (TMBD) was a known mediator for glucose oxidase.[6] Thus TMBD served as a starting point for refinement of the redox and physical properties. Since only few *N,N,N′,N′*-tetrasubstituted 1,4-benzenediamines were known outside the patent literature, and almost nothing had been described about their redox behavior, the purpose of this work became the development of a general method for the synthesis of *N,N,N′,N′*-tetrasubstituted 1,4-benzenediamines and an investigation of their redox properties. Furthermore, a literature search revealed that a large body of work had been reported on the radical cation salts of TMBD,[7–18] but nothing had been described regarding conducting molecular solids based on analogues to TMBD.

Some of the results based on this synthetic work regarding the use of *N,N,N′,N′*-tetrasubstituted 1,4-benzenediamines as mediators have been published.[19–21]

The synthetic methods employed earlier included: 1, alkylation of 1,4-benzenediamine with cyclic ethers;[22–25] 2, alkylation of 1,4-benzenediamine with alkyl halides;[26–29] 3, reaction of 1,4-cyclohexanedione with secondary amines followed by oxidation;[30–32] and 4, reaction of sodium salts of secondary amines with fluorobenzenes.[33]

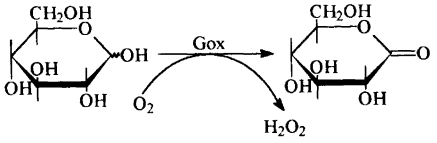


Fig. 1.

* To whom correspondence should be addressed.

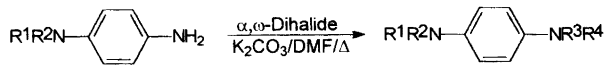
Results and discussion

Synthesis. We chose to look closer at the alkylation of 1,4-benzenediamines with alkyl halides (method 2), because this method would allow the preparation of unsymmetrically substituted derivatives via *N,N*-disubstituted 1,4-benzenediamines. We found that the alkylation

Table 1. The synthesized benzenediamines.

No.	Name	Yield (%)
1a	1,4-Bis(1-pyrrolidinyl)benzene	29
1b	1,4-Bis(1-piperidinyl)benzene	70
1c	1,4-Bis(1-morpholinyl)benzene	50
1d	1-[4-(1-Pyrrolidinyl)phenyl]morpholine	62
1e	1-[4-(1-Piperidinyl)phenyl]morpholine	76
1f	1-{4-[Ethyl(methyl)amino]phenyl}morpholine	43
1g	1-(4-Dimethylaminophenyl)morpholine	57
1h	1-(4-Dimethylaminophenyl)pyrrolidine	21
1i	1-(4-Dimethylaminophenyl)piperidine	52

could be performed in satisfactory yields by using alkyl bromides/chlorides and K_2CO_3 in DMF as outlined in Scheme 1. The compounds synthesized are shown in Table 1.



1a-1e, 1g-1i

α,ω-Dihalide = $Br(CH_2)_4Br$, $Br(CH_2)_5Br$, $(ClCH_2CH_2)_2O$

Scheme 1.

Compound **1f** was prepared as shown in Scheme 2. The two-step conversion of **5** into **1f** was chosen, since all attempts to convert the secondary amine **5** into **1f** by methylation with CH_3I gave a mixture of **1f** and **1g**, the latter being formed by quaternization of **1f** followed by de-ethylation via nucleophilic attack of iodide. This was evident from cyclic voltammetry from the large difference (60 mV) in oxidation potential for the two compounds.

The starting material 1-(4-acetamidophenyl)morpholine (**6**) was obtained by two routes, either from commercially available 4-aminoacetanilide or from 1-(4-nitrophenyl)morpholine[34] (**3**) by reduction with iron–acetic acid utilizing the method of Owsley and Bloomfield.[35]

Cyclic voltammetry. The electrochemical properties of the benzenediamines **1a–1i** were investigated by cyclic voltammetry. All the benzenediamines undergo two reversible one-electron oxidations in acetonitrile. The halfwave potentials are given in Table 2. We note that the first oxidation potential is very sensitive to the nature of the substituents. Thus oxidation potentials in the range 60–410 mV are accessible simply by changing the substituents on the nitrogen.

Table 2. Oxidation potentials[a] for the benzenediamines **1a–1i.**

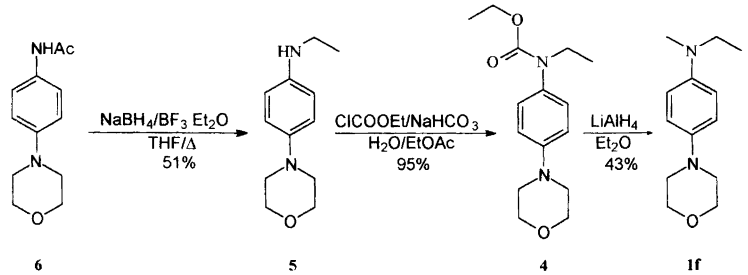
Compound	$E_{1/2}{}^1$/mV	$E_{1/2}{}^2$/mV	ΔE/mV
TMBD	140	610	470
1a	60	730	670
1b	240	730	490
1c	410	820	410
1d	340	780	440
1e	330	780	450
1f	270	790	520
1g	330	810	480
1h	120	740	620
1i	210	750	540

[a] Potentials were measured at a scan rate of 200 mV s^{-1} using Pt versus SCE in 0.1 M Bu_4NPF_6–CH_3CN.

Electronic absorption spectra. The electronic absorption spectra of the *N,N,N',N'*-tetraalkyl-1,4-benzenediamines **1a–1i** are very similar to each other and to TMBD itself.[36,37] They consist of two bands in the UV-region (see Table 3). The more intense band is well shaped and does not vary much throughout the series either in position or in intensity. It is an allowed transition of the π–π^* type. A weaker, broad band seems to be more sensitive to the alkyl substituents. Two general features are presented by this band: 1, the lower the energy of the observed band maximum, the more intense is this band; 2, the observed band maximum correlates to a certain degree (qualitatively) with the energy of the potential for the first reversible oxidation as measured

Table 3. Absorption maxima, λ_{max} and molar absorption coefficients, ε of the neutral benzenediamines.

No.	$\lambda_{max}1$/nm (ε_1/M^{-1} cm^{-1})	$\lambda_{max}2$/nm (ε_1/M^{-1} cm^{-1})
1a	269 (23100)	345 (2800)
1b	262 (17250)	311 (1700)
1c	262 (17550)	305 (1900)
1d	266 (19800)	328 (2350)
1e	265 (17600)	321 (2150)
1f	266 (18400)	324 (2150)
1g	264 (17400)	321 (2150)
1h	268 (19650)	337 (2650)
1i	265 (17600)	321 (2150)



Scheme 2.

by CV. For the latter reason, this band must be at least partly an n–π* transition. It is quite probable however, that this band consists of more than one transition.[38]

The spectra of the oxidized species were obtained by mixing solutions of the phenylenediamines with a solution of Bu_4NBr_3 in a molar ratio of 2:1 according to eqn. (1), dilution of the resulting blue solution to 10^{-4} M with respect to the substrate and recording as described in the Experimental section.

$$2R_2N\text{–}C_6H_4\text{–}NR_2 + Br_3^- \rightarrow 2[R_2N\text{–}C_6H_4\text{–}NR_2]^+ + 3Br^- \quad (1)$$

This procedure was initially carried out with CH_2Cl_2 as the solvent but the spectra proved to be concentration dependent, presumably because of self-aggregation and/or complex formation with the bromide ion. Indeed $TMBD^+$ has been found to dimerize in solution at low temperatures.[39,40] For the characterization of $\mathbf{1a}^+$–$\mathbf{1i}^+$, acetonitrile proved to be a better choice since the molar absorption coefficients were concentration independent (measured in the range 5×10^{-5} M to 2×10^{-4} M). The absorption maxima and molar absorption coefficients are listed in Table 4.

The spectral data of $\mathbf{1a}^+$–$\mathbf{1i}^+$ in Table 4 reveal little variation among the groups. Assignments of the bands in the parent compound *N,N,N',N'*-tetramethylbenzenediamine perchlorate (Wursters blue perchlorate) has been done in early work by Albrecht and Simpson.[36] The bands in the visible region (which we call $\lambda_{max}4$–$\lambda_{max}7$) were assigned as one single electronic transition with vibrational structure stemming from large differences in nuclear geometry between the ground and excited states. This was proved by the mirror image relationship between the absorption and emission spectra (recorded at low temperature). This assignment seems to be further confirmed by the fact, that the largest difference in the spectra of $\mathbf{1a}^+$–$\mathbf{1i}^+$ is the broadness of the bands, where the spectrum of the vibrationally more restricted species, $\mathbf{1a}^+$ (see Fig. 2) and $\mathbf{1h}^+$ are the best resolved.

The possibility of complex formation with bromide ion was briefly explored by recording spectra of $\mathbf{1h}^+$ with varying amounts (0–10 equiv.) of Bu_4NBr, but they were found to be identical. Experiments with excess Bu_4NBr_3 were also carried out. The spectrum of $\mathbf{1h}^+$ was recorded with substrate/oxidant ratios of 1:0.5, 1:0.75 and 1:1. These spectra are identical except for a small red-shift and a strongly increasing absorbance of $\lambda_{max}1$ upon increasing the excess of Bu_4NBr_3, owing to the strong absorption of this compound at 269 nm (ε = 40 000 $M^{-1}\,cm^{-1}$ in acetonitrile). Bu_4NBr_3 does not have other bands above 250 nm in acetonitrile solution. For substrate/oxidant ratios 1:0.5 and 1:0.75, the spectrum of $\mathbf{1d}^+$ does not change (again except for $\lambda_{max}1$). However, when the ratio was set to 1:1, all the absorption bands increased without changing the form of the spectrum, but after a few minutes, the solution was completely decolorized. Since the solution arising from stoichiometric oxidation of **1d** is stable for days, this

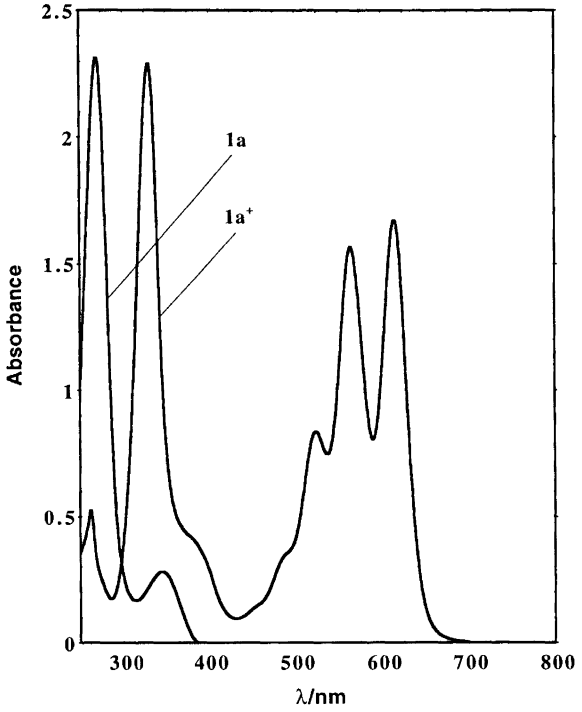


Fig. 2. Electronic absorption spectra of **1a** and $\mathbf{1a}^+$ each in 10^{-4} M acetonitrile solution.

Table 4. Absorption maxima λ_{max}/nm and molar absorption coefficients $\varepsilon/M^{-1}\,cm^{-1}$ of oxidized benzenediamines in acetonitrile solution.

No.	$\lambda_{max}1$ (ε_1)	$\lambda_{max}2$ (ε_2)	$\lambda_{max}3$ (ε_3)	$\lambda_{max}4$ (ε_4)	$\lambda_{max}5$ (ε_5)	$\lambda_{max}6$ (ε_6)	$\lambda_{max}7$ (ε_7)
$\mathbf{1a}^+$	263 (7300)	330 (19750)	sh 374 (5000)	sh 489 (2500)	524 (6450)	565 (12400)	615 (13300)
$\mathbf{1b}^+$	259 (10900)	335 (6650)	sh 385 (1600)		sh 537 (2850)	578 (5400)	623 (5750)
$\mathbf{1c}^+$ [a]	256 (10050)	333 (4800)	sh 377 (1650)		sh 536 (2000)	576 (3700)	620 (3800)
$\mathbf{1d}^+$	261 (6300)	333 (13600)	sh 379 (4450)	sh 489 (1800)	sh 533 (4700)	570 (8500)	619 (8950)
$\mathbf{1e}^+$	258 (9050)	336 (12300)	sh 386 (2750)		sh 533 (4550)	573 (8300)	617 (8750)
$\mathbf{1f}^+$	259 (6100)	332 (15550)	sh 381 (3550)	sh 485 (1900)	sh 532 (6150)	569 (10750)	617 (11100)
$\mathbf{1g}^+$	259 (7050)	331 (13150)	sh 379 (3250)	sh 485 (1650)	sh 533 (5300)	570 (9150)	617 (9400)
$\mathbf{1h}^+$	262 (5950)	329 (18550)	sh 372 (4800)	sh 487 (2350)	527 (6000)	564 (11100)	614 (11650)
$\mathbf{1i}^+$	262 (7100)	332 (18650)	sh 378 (3950)	sh 482 (2000)	sh 529 (6250)	567 (10800)	613 (11150)

sh: Shoulder. [a] Decomposes quickly; molar absorption coefficients are only tentative for this compound.

behavior does not seem to stem from an equilibrium redox reaction [eqn. (1)] but rather from complex formation of $\mathbf{1d}^+$ with Br_3^- leading to enhanced intensity of the absorption bands, followed by collapse of the complex to a colorless product. Alternatively, a small amount of the dication may be formed which, if this species coincidentally has absorptions in the same regions as the monocation, may lead to enhanced absorption without necessarily changing the form of the spectrum. However, the ratios between the observed absorbances are constant for all three concentrations of Bu_4NBr_3 so the former explanation seems more plausible. It is well known that dioxane forms a complex with Br_2[41,42] and similar complex formation can be imagined with the morpholine groups on $\mathbf{1d}^+$ and $\mathbf{1e}^+$ acting as ligands towards bromine. That the spectrum of $\mathbf{1h}^+$ does not change upon addition of as much as 100% excess Bu_4NBr_3 may well be due to the lack of morpholine groups in this molecule. The fact that the spectra of $\mathbf{1d}^+$ with substrate/oxidant ratios 1:0.5 and 1:0.75 are identical with each other, but different from that with substrate/oxidant ratio 1:1, may point towards different types of complex with different stability, but we found this subject to be too complicated to be included in this work. For $\mathbf{1e}^+$, a decrease in all the absorption bands was found upon addition of two oxidation equivalents (ratio 1:1) reflecting the faster decomposition of $\mathbf{1e}^+$ than $\mathbf{1d}^+$ with excess Br_3^-.

Preliminary experiments were also done with a solution of CF_3CO_2Ag in acetonitrile as the oxidant. The same procedure was used as that described for the Br_3^--oxidation except that the molar ratio was 1:1 according to eqn. (2):

$$R_2N\text{–}C_6H_4\text{–}NR_2 + Ag^+ \rightarrow [R_2N\text{–}C_6H_4\text{–}NR_2]^+ + Ag \quad (2)$$

The resulting solutions of the radical cations were filtered through a cotton plug before scanning so as to remove elemental silver. The two most easily oxidizable compounds **1a** and **1h** were oxidized immediately and quantitatively in this manner, and the resulting spectra of $\mathbf{1a}^+$ and $\mathbf{1h}^+$ obtained this way proved to be identical, to within experimental error, with those obtained from oxidation with Br_3^-. As for the remaining substrates, the oxidation with silver ion was slow and incomplete as judged from the observed absorptions in the visible and UV-region as compared with the spectra from oxidation with Br_3^-. All the benzenediamines could be oxidized with Ag^+ in concentrated solution but in 10^{-4} M solutions, **1b** and **1c** did not become colored at all upon addition of stoichiometric amounts of CF_3CO_2Ag. Presumably a competing complex formation is taking place between Ag^+ and the substrates.

Conclusions

A general method for the preparation of *N,N,N',N'*-tetrasubstituted 1,4-benzenediamines has been developed. The oxidation potentials for the compounds prepared are very sensitive to substitution, and thus fine tuning of the oxidation potential becomes possible. This may be of value in order to avoid interference from other redox-active compounds in biosensors based on oxidoreductases such as glucose oxidase.

Experimental

Melting points were recorded with an electrothermal apparatus and are uncorrected. C,H,N analyses were carried out at the Department for General and Organic Chemistry by Preben Hansen and Karin Linthoe, and were within $\pm 0.4\%$ of the theoretical values unless otherwise indicated. ^1H and ^{13}C NMR spectra were determined for degassed solutions in $CDCl_3$ freed from acidic impurities by passage through Al_2O_3 (basic, activity I) prior to use at 250 MHz unless otherwise noted with TMS as an internal standard (*J* values are given in Hz). Mass spectra were recorded with direct inlet and EI-ionization.

Cyclic voltammetry was performed using a standard three-electrode cell configuration, employing a platinum-button working electrode, a platinum counter electrode, and a K901 Calomel reference electrode (Radiometer Copenhagen).

Electronic absorption spectra: stock-solutions of compounds **1a–1i** (10^{-3} M) in acetonitrile were prepared and used within 2 h for recording the spectra of both the neutral (diluted to 10^{-4} M) and the oxidized species. The latter were obtained by dilution, addition of 0.5 mol equiv. Bu_4NBr_3 (from a 10^{-3} M stock-solution in acetonitrile) and adjusting the volume to reach a concentration of 10^{-4} M of the oxidized benzenediamine. Preliminary experiments were carried out similarly on **1a**, **1d** and **1h** using a 10^{-3} M solution of CF_3CO_2Ag in acetonitrile as the oxidant. All spectra were recorded twice with two different stock-solutions of the substrate. The spectra were recorded on a Perkin-Elmer Lambda 9 UV–VIS–NIR spectrometer in the range 250–400 nm for the neutral compounds and in the range 250–800 nm for the oxidized ones. The scan rate was 240 nm min^{-1} for all compounds except $\mathbf{1c}^+$ for which a maximum scan rate 960 nm min^{-1} was chosen because of its very fast decomposition. A preliminary scan on $\mathbf{1a}^+$ in the range 250–1600 nm proved the absence of near-infrared absorptions with $\varepsilon > 100\ M^{-1}\ cm^{-1}$ in this compound. Acetonitrile (HPLC-grade), Bu_4NBr_3 and CF_3CO_2Ag were obtained from Aldrich and used as received.

Representative procedure for preparation of the benzenediamines **1a–1c**. *1,4-Bis(1-pyrrolidinyl)benzene* **1a**. To a degassed, stirred suspension of dry K_2CO_3 (35 g, 0.25 mol) in DMF (100 cm^3) was added 1,4-dibromobutane (43.4 g, 0.20 mol) followed by 1,4-benzenediamine (10.8 g, 0.10 mol). The slurry was heated to +140 °C and stirred there for 8 h. After being cooled to ambient temperature, the mixture was poured

into a solution of $Na_2S_2O_4$ (5 g in 500 cm^3 water. The product was filtered, washed with water and crystallized from EtOH containing a little $NaBH_4$ (approximately 0.5 g/250 cm^3) with the aid of activated carbon. Cream-colored crystals (6.2 g, 29%). An analytical sample was purified by sublimation (0.01 Torr, 100 °C) giving white crystals, m.p. 155–157 °C (lit.[24] 158–159 °C). ^1H NMR (250 MHz; CS_2): δ 6.30 (s, 4 H), 3.12 (m, 4 H), 1.93 (m, 4 H). MS: *m/z* (I%) 216 (M^+, 93), 187 (11), 173 (8), 160 (8).

1,4-Bis(1-piperidinyl)benzene **1b**. Nearly white crystals (70%). The analytical sample was purified by sublimation (0.01 Torr, 90 °C), m.p. 104–106 °C (lit.[22] 108–109 °C). ^1H NMR (250 MHz): δ 6.88 (s, 4 H), 3.02 (t, 8 H, *J* 5.4), 1.68 (m, 8 H), 1.53 (m, 4 H). MS: *m/z* 244 (M^+, 96), 187 (11), 131 (7).

1,4-Bis(1-morpholinyl)benzene **1c**. Off-white crystals (50%). The analytical sample was purified by sublimation (0.01 Torr, 100 °C), m.p. 198–200 °C (lit.[31] 191 °C). ^1H NMR (250 MHz): δ 6.89 (s, 4 H), 3.85 (t, 4 H, *J* 4.6), 3.06 (t, 4 H, *J* 4.6). MS: *m/z* 248 (M^+), 190 (33), 132 (35).

1-[4-(1-pyrrolidinyl)phenyl]morpholine **1d** was prepared from **2**, 1,4-dibromobutane and K_2CO_3 according to the general procedure. White crystals (62%). The analytical sample was purified by sublimation (0.01 Torr, 100 °C), m.p. 142–144 °C. ^1H NMR (250 MHz): δ 6.72 (d, 2 H, *J* 8.9), 6.55 (d, 2 H, *J* 8.9), 3.85 (t, 4 H, *J* 4.6), 3.24 (t, 4 H, *J* 6.1), 3.01 (t, 4 H, *J* 4.6), 1.97 (m, 4 H). MS: *m/z* 232 (M^+, 94), 174 (35), 131 (9), 118 (10).

1-[4-(1-piperidinyl)phenyl]morpholine **1e** was prepared from **2**, 1,5-dibromopentane and K_2CO_3 according to the general procedure. White crystals (76%). The analytical sample was purified by sublimation (0.01 Torr, 100 °C), m.p. 127–129 °C. ^1H NMR (250 MHz): δ 6.91 (d, 2 H, *J* 9.3), 6.85 (d, 2 H, *J* 9.2), 3.83 (t, 4 H, *J* 4.7), 3.03 (m, 8 H), 1.70 (m, 4 H), 1.54 (m, 2 H). MS: *m/z* 246 (M^+, 96), 187 (24), 132 (12).

1-{4-[Ethyl(methyl)amino]phenyl}morpholine **1f**. A solution of **4** (5.0 g, 0.02 mol) in dry ether (200 cm^3) was added dropwise to a stirred suspension of $LiAlH_4$ (1.9 g, 0.05 mol) in dry ether (100 cm^3) at such a rate that the mixture refluxed gently. Reflux was continued for 3 h. The mixture was cooled to room temperature after which the excess of $LiAlH_4$ was hydrolyzed by slow addition of conc. aqueous NaOH-solution (≈33%, ≈15 cm^3). The inorganic salts were removed by filtration through a bed of $MgSO_4$, which was washed with ether. The combined organic phase was concentrated *in vacuo*, and crystallized from EtOH (25 cm^3, cooling to −20 °C). White crystals (1.9 g, 43%), m.p. 58–60 °C. ^1H NMR (250 MHz): δ 6.88 (d, 2 H, *J* 9.1), 6.73 (d, 2 H, *J* 9.1), 3.85 (t, 4 H, *J* 4.7), 3.32 (q, 2 H, *J* 7.1), 3.03 (t, 4 H, *J* 4.7), 2.84 (s, 3 H), 1.09 (t, 3 H, *J* 7.1). MS: *m/z* 220 (M^+, 93), 191 (12), 162 (10), 147 (31), 132 (7).

1-(4-Dimethylaminophenyl)morpholine **1g** was prepared from 4-dimethylaniline dihydrochloride,* bis(2-chlorethyl) ether and K_2CO_3 according to the general procedure with the exceptions that saturated aqueous NaCl was used instead of water, and the crude product was isolated by extraction with ether. White crystals (57%). The analytical sample was purified by sublimation (0.01 Torr, 90 °C), m.p. 122–124 °C. ^1H NMR (250 MHz): δ 6.88 (d, 2 H, *J* 9.1), 6.75 (d, 2 H, *J* 9.1), 3.84 (t, 4 H, *J* 4.7), 3.03 (t, 4 H, *J* 4.8), 2.87 (s, 6 H). MS: *m/z* 206 (M^+, 93), 191 (9), 148 (69), 132 (12).

1-(4-Dimethylaminophenyl)pyrrolidine **1h** was prepared from 4-dimethylaniline dihydrochloride,* 1,4-dibromobutane and K_2CO_3 according to the general procedure. White crystals (21%). The analytical sample was purified by sublimation (0.01 Torr, 60 °C), m.p. 78–80 °C. ^1H NMR (250 MHz): δ 6.82 (d, 2 H, *J* 8.9), 6.56 (d, 2 H, *J* 8.8), 3.22 (m, 4 H), 2.88 (br s, 6 H), 1.96 (m, 4 H). MS: *m/z* 216 (M^+, 10), 190 (95), 175 (32), 146 (14), 134 (9), 118 (7), 104 (7), 83 (14), 73 (10).

1-(4-Dimethylaminophenyl)piperidine **1i** was prepared from 4-dimethylaniline dihydrochloride,* 1,5-dibromopentane and K_2CO_3 according to the general procedure, with the exception that the crude product was isolated by extraction with ether and distillation *in vacuo*. The fraction boiling 137–147 °C/0.03–0.3 Torr was collected, and purified by column chromatography on aluminium oxide (basic, activity I) with ether–petroleum ether (1 : 1) as the eluent. The product was obtained as a colorless oil (52%). ^1H NMR (250 MHz): δ 6.88 (d, 2 H, *J* 8.9), 6.69 (d, 2 H, *J* 8.9), 2.90 (m, 10 H), 1.68 (m, 4 H), 1.51 (m, 2 H). MS: *m/z* 204 (M^+, 71), 189 (19), 148 (15), 118 (10), 85 (95).

1-(4-Aminophenyl)morpholine **2**. *Method A*. Compound **3**[34] (23.0 g, 0.11 mol), 10% Pd–C (0.3 g) and EtOH (500 cm^3) was hydrogenated in a standard low-pressure apparatus. When the hydrogen uptake ceased, the suspension was filtered through a bed of Celite. Removal of the EtOH *in vacuo* left the crude product in almost quantitative yield, which was used without purification for preparation of **1d**, **1e**. ^1H NMR (90 MHz): δ 6.74 (m, 2 H), 6.66 (m, 2 H), 3.82 (m, 4 H), 3.44 (br s, 2 H), 2.99 (m, 2 H).

Method B. This is a modification of Owsley and Bloomfield's procedure for reduction of nitroarenes to amines.[35] A mixture of **3**[34] (20.8 g, 0.10 mol), Fe-powder (hydrogen reduced, ~325 mesh) (23 g, 0.4 mol), AcOH (42 g, 0.70 mol) and EtOH (250 cm^3) were stirred under

* The dihydrochloride (or other salt) was preferred because of superior purity compared with the commercially available free base.

reflux overnight. The grey suspension was poured into water containing sodium citrate (~750 cm^3 + 5 g Na citrate) and extracted with CH_2Cl_2. [We found that addition of citrate prevents the formation of emulsions during the extraction via binding of iron(III)-species formed by air oxidation of the iron(II) present.]

The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude **2** in nearly quantitative yield. (This material contains approximately 5% **6**, which doesn't affect the yield in the cyclisation reactions.)

Ethyl N-*Ethyl,*N-*[4-(1-morpholinyl)phenyl]carbamate* **4**. A mixture of **5** (4.1 g, 0.02 mol), EtOAc (50 cm^3), ClCOOEt (3 cm^3, 0.03 mol), $NaHCO_3$ (3.0 g, 0.04 mol) and water (25 cm^3) was stirred overnight. The organic layer was separated, dried over $MgS0_4$, filtered and concentrated *in vacuo* to give a slightly pink oil, which was purified by column chromatography on Silica gel 60 (0.063–0.200 mm) with ether–petroleum ether (1:1) as the eluent. The colorless oil crystallized on drying *in vacuo*. Colorless crystals (5.5 g, 97%), m.p. 72–74 °C. ^1H NMR (250 MHz): δ 7.07 (d, 2 H, *J* 8.9), 6.87 (d, 2 H, *J* 9.0), 4.12 (q, 2 H, *J* 7.1), 3.85 (m, 4 H), 3.65 (q, 2 H, *J* 7.1), 3.15 (m, 4 H), 1.16 (m, 6 H).

1-(4-Ethylaminophenyl)morpholine **5**. Boron trifluoride–diethyl ether (23 cm^3, 0.19 mol) was added over 20 min to a cooled, well-stirred mixture of **6** (10.0 g, 0.05 mol) and $NaBH_4$ (5.1 g, 0.14 mol) in dry THF (200 cm^3) keeping the internal temperature below 5 °C. After 1 h of additional stirring and cooling, the cooling bath was removed. The mixture was heated to reflux for 5 h. Following cooling to ambient temperature, the excess of boron hydrides was hydrolyzed by dropwise addition of water. The clear solution was diluted with 10% Na_2SO_4 solution (approx. 200 cm^3) and extracted with ether (2 × 200 cm^3). The combined organic phases were dried over $MgS0_4$, filtered, concentrated *in vacuo* and crystallized from EtOH. White crystals (5.3 g, 51%), m.p. 107–109 °C. ^1H NMR: δ 6.83 (d, 2 H, *J* 8.8), 6.59 (d, 2 H, *J* 8.8), 3.84 (t, 4 H, *J* 4.7), 3.06 (m, 7 H). 1.23 (t, 3 H, *J* 7.1).

1-(4-Acetamidophenyl)morpholine **6**. A well-stirred mixture of **3**[34] (50.0 g, 0.24 mol), iron powder (~325 mesh, 60 g, 1.1 mol) and acetic acid (600 cm^3) was refluxed overnight after which time the color of the reaction mixture had changed from yellow to light gray. The suspension was poured onto ice after cooling to room temperature, and the crude product was filtered, washed with water and crystallized from EtOH (activated carbon). White crystals (40.7 g, 77%). m.p. 201–203 °C (in a sealed capillary) (lit.[43] 211.2–212.4 °C). ^1H NMR (400 MHz, DMSO-d_6): δ 2.01 (s, 3 H), 3.02 (t, 4 H, *J* 5), 3.72 (t, 4 H, *J* 5), 6.87 (d, 2 H, *J* 9), 7.47 (d, 2 H, *J* 9), 9.70 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.78, 49.17, 66.24, 115.50, 120.10, 131.92, 147.13, 167.62.

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