Pergamon

Tetrahedron 58 (2002) 3499–3505

TETRAHEDRON

Hydrogen-bonding between benzoic acid and an N,N'-diethyl-substituted benzamidine

Arno Kraft,[a,b,*] Lars Peters[b] and Harold R. Powell[c]

[a]Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, UK
[b]Department of Organic Chemistry and Macromolecular Chemistry, University of Düsseldorf, 40225 Düsseldorf, Germany
[c]MRC Laboratory of Molecular Biology, MRC Centre, Hills Road, Cambridge CB2 2QH, UK

Received 8 January 2002; accepted 14 March 2002

Abstract—The synthesis and crystal structure of 4,N,N'-triethylbenzamidinium benzoate is reported in which the benzoate anion and the (E,E)-configured amidinium group are linked through two hydrogen bonds (with an N···O distance of 2.723 Å). Since an amidine (E,E) isomer was also observed for chloroform solutions of the complex, the binding mode in the crystal and in solution was analogous to that reported for unsubstituted amidines. The strong basicity of the N,N'-diethyl-substituted benzamidine (pK_a 11.99±0.02 in water–dioxane, 1:1) was evident from potentiometric titrations. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Like guanidines, amidines are strong organic bases. The biological activity of many amidines is attributed to a cationic hydrogen-bond donor group that can act as binding site for both carboxylates and phosphates. The amidine pharmacophore is found in a range of pharmaceutical drugs. Benzamidines, in particular, have replaced arginine in various synthetic analogues of natural hormones.[1] Whereas most amidine-based drugs are unsubstituted at the amidine nitrogen site, *N*-substituted amidines have only recently gained interest in drug design. For example, certain *N*-isopropyl and *N*-cycloalkyl amidines tend to bind to the minor groove of oligonucleotides with an affinity larger than their parent analogues.[3,4] However, few crystal structures of *N*-alkyl- and *N*-aryl-substituted amidines have been reported so far: *p*-(dimethylamino)-N,N'-dimethylbenzamidine,[2] various N,N'-diarylbenzamidines[5–8] and semicyclic amidines, generally in the form of the free base or the hydrochloride,[9,10] and just one example of an amidinium carboxylate.[11]

N-Substituted amidines have a number of advantages: (i) they are more stable towards hydrolysis compared to unsubstituted analogues, allowing the amidine base to be isolated and purified; (ii) aggregation through intermolecular hydrogen bonds is generally suppressed; and (iii) the extra substituents make these amidines more hydrophobic as well as more soluble in nonpolar solvents. It should be noted that the hydrogen-bonding arrangement of a phosphate, and presumably also that of a phosphonate, closely resembles the binding of a carboxylate to an amidinium group.[12] Complexes of a polymerisable amidine, N,N'-diethyl-4-vinylbenzamidine (**1**), and a phosphonate template were recently used by Wulff and co-workers in the preparation of molecularly imprinted polymers that, by mimicking catalytic antibodies, were able to hydrolyse esters.[13,14]

An N,N'-diethyl-substituted amidine can exist in two configurations\scale100% with either an (E,E) or an (E,Z) stereochemistry at the partial C–N double bond (Fig. 1), whereas the (Z,Z) isomer is not possible for steric reasons.[11,15–17] Although this seems to be a complication at a first glance, the two isomers can be easily differentiated by NMR. The *N*-ethyl substituents serve as an NMR marker and, thus, provide important information about the binding mode in solution. Previous solution NMR studies have shown that a dynamic equilibrium between (E,E) and (E,Z) configurational isomers is frequently observed for protonated N,N'-disubstituted benzamidines.[11,16,17] The isomer ratio depends

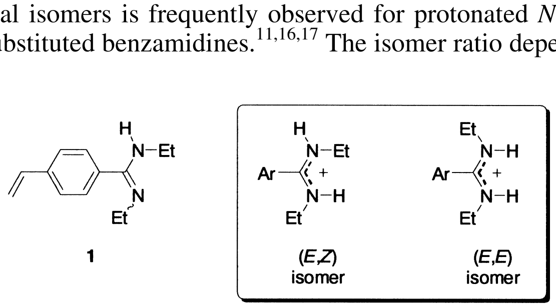


Figure 1. Polymerisable amidine **1** and the two isomers observed for a protonated N,N'-diethyl-substituted benzamidine.

Keywords: amidine; supramolecular; complexation; binding; crystal structure.

[*] Corresponding author. Address: Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, UK; e-mail: a.kraft@hw.ac.uk

PII: S0040-4020(02)00301-0

crucially on solvent, concentration, and counteranion. Wulff and Schönfeld found that association constants between protonated **1** and 4-methylbenzoate were large in chloroform ($>10^6\,M^{-1}$ at 25°C) and involved an exclusively (*E*,*E*)-configured amidine.[15,16] We report in this paper the crystal structure of a benzoic acid complex of 4,*N*,*N′*-triethylbenzamidine (**4**) that provides further insight into the amidinium-carboxylate binding arrangement.

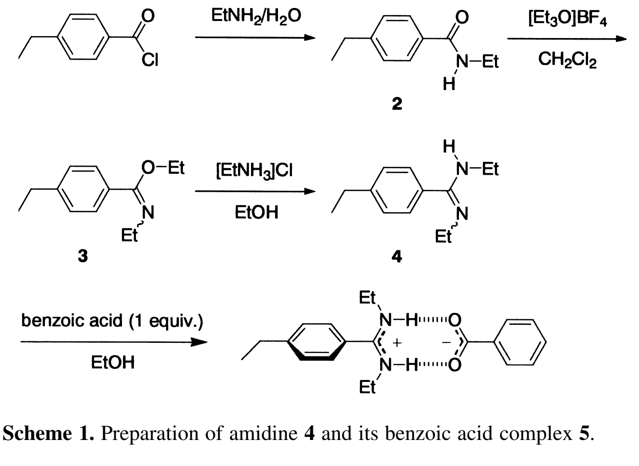
2. Results and discussion

2.1. Synthesis

Benzamidine **4** was obtained in three steps from 4-ethylbenzoyl chloride (Scheme 1). Reaction of the acid chloride with aqueous ethylamine gave **2**. The amide was then converted to benzimidate **3** by treatment with triethyloxonium tetrafluoroborate. Stirring with ethylamine hydrochloride produced the *N*,*N′*-diethyl-substituted benzamidine **4** in good yield. Prior to complexation the crude amidine was purified by gradient sublimation, a method that has been known to furnish photoconducting and charge-transporting organic compounds in the high purity required for device applications.[18] This was necessary since amidine **4** had a tendency to slowly hydrolyse in the presence of moisture.

Amidinium groups typically have pK_a values >11, whereas the pK_a of a protonated primary amine tends to be much lower (between 9 and 10). Potentiometric titrations of amidine **4** in 0.1 M aqueous KCl at 25°C indicated no detectable ionisations at pH$<$11. Under these conditions, the pK_a of *N*,*N′*-diethyl-substituted benzamidine **4** could only be estimated roughly from the experimental data as 12.2±0.5. We therefore repeated the titration in a dioxane–water (1:1) mixture in which the ion product of water is much smaller than in aqueous KCl and contributes little to the hydroxide ion concentration at pH$<$13. Analysis of the titration data by a difference plot[19] then yielded a pK_a of 11.99±0.02, confirming the strong basicity of amidine **4** (Fig. 2).

A 1:1 mixture of amidine **4** and benzoic acid dissolved easily in hot ethanol, and complex **5** was isolated in analytical purity after one recrystallization from hexane. Crystals of complex **5** were grown from a saturated solution in hexane. According to differential scanning calorimetry (DSC) measurements, the complex had a melting point of 141°C. A crystal–crystal phase transition was observed at 39°C, indicating the possibility of polymorphism. Although crystals could also be obtained from heptane, these were of lower quality and seemed to consist of a different polymorph.



Scheme 1. Preparation of amidine **4** and its benzoic acid complex **5**.

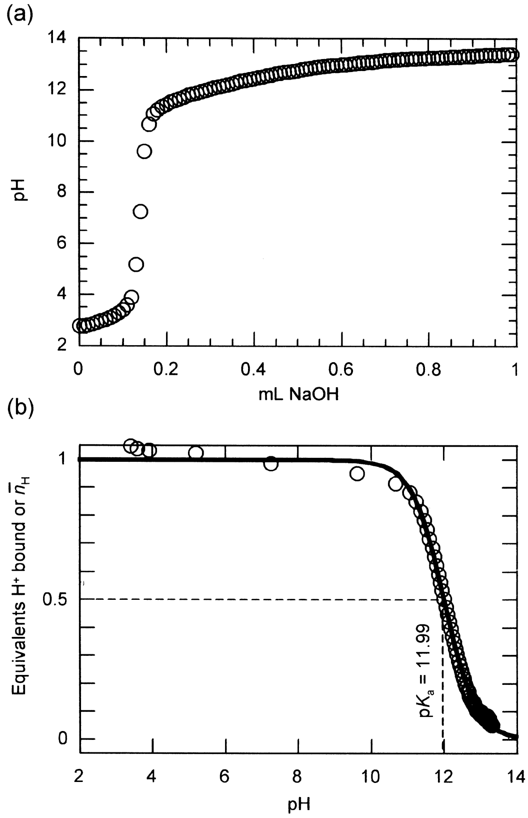


Figure 2. (a) Titration curve and (b) difference plot[19] for *N*,*N′*-diethyl-substituted benzamidine **4** in dioxane–water (1:1) to which KCl was added to maintain a constant ionic strength I=0.1. Titrations were carried out at 25.0°C with 0.4905 M NaOH in 0.01 mL steps. The solid line is the fitted Bjerrum function. The pK_a can be read from the difference plot at n_H=0.5 (50% protonation).

2.2. Crystal structure of amidine–benzoic acid complex

The crystal structure of complex **5** (crystallized from hexane) is shown in Fig. 3. In the space group *C*2/*c* the

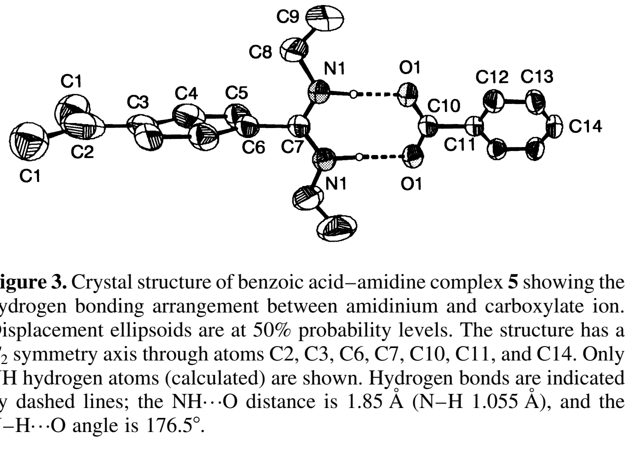


Figure 3. Crystal structure of benzoic acid–amidine complex **5** showing the hydrogen bonding arrangement between amidinium and carboxylate ion. Displacement ellipsoids are at 50% probability levels. The structure has a C_2 symmetry axis through atoms C2, C3, C6, C7, C10, C11, and C14. Only NH hydrogen atoms (calculated) are shown. Hydrogen bonds are indicated by dashed lines; the NH···O distance is 1.85 Å (N–H 1.055 Å), and the N–H···O angle is 176.5°.

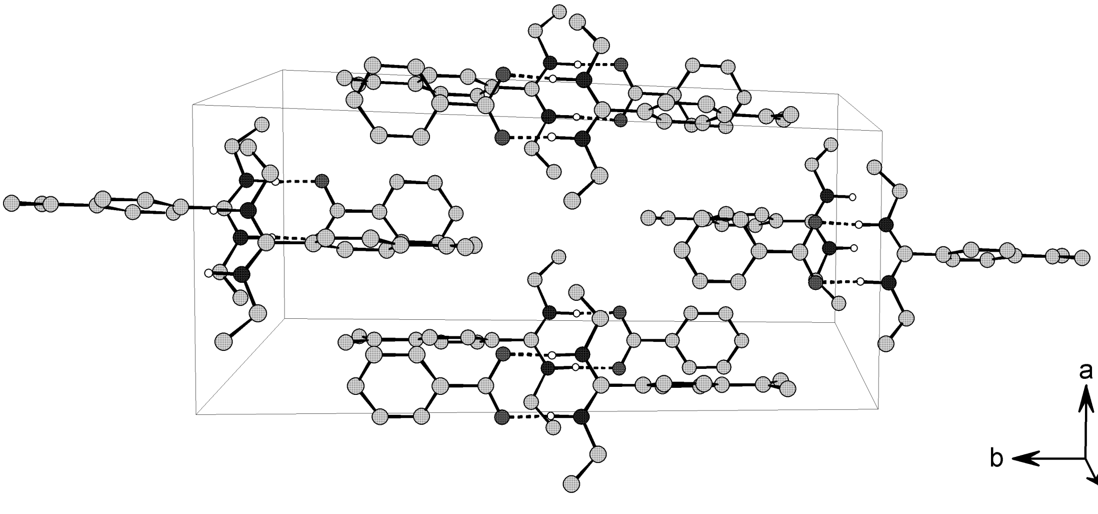


Figure 4. Molecular arrangement of benzoic acid–amidine complex **5** in the unit cell.

complex lies on a crystallographic 2-fold axis. This is a much higher symmetry than previously found for 4-bromo-*N*,*N*′-diethylbenzamidinium benzoate.[11] The *C*-ethyl group is disordered around this diad, the two sites having an occupancy of 0.5 each. We note that the C1–C2 distance of 1.266(7) Å is unusually short for a C–C single bond; furthermore, the C1–C2–C3 angle of 127.6° would also have fitted more a vinylbenzene derivative. However, both synthesis and NMR data left no doubt about the identity of the 4-ethylbenzamidine structure. We suspected therefore that this peculiarity in the structural data could be attributed to the presence of disorder and a high anisotropic thermal motion. A search through the Cambridge Structural Database (CSD) revealed indeed a number of ethylbenzene derivatives with equally short C–C distances, which in most cases proved to be associated with disordered terminal carbons.[20]

As a result of the symmetry of the crystal structure, the two C–N bond lengths of the amidine are identical at 1.306(7) Å, the length being consistent with an amidinium salt configuration. The benzoate forms a salt bridge to the amidinium group. Hydrogen atoms in the H-bonds are calculated and are bound to the nitrogen. They make up a symmetry-related pair, and N–H bond lengths are identical (as are the hydrogen-bonding distances and angles). The N···O distance of 2.723(1) Å is indicative of a strong hydrogen bond; slightly larger values have been reported in the literature for 3-amidinium benzoate (2.766 and 2.791 Å),[21] benzamidinium pyruvate (2.837 and 2.824 Å),[22] and benzamidinium bromoacetate (2.804 and 2.846 Å).[23] The (*E*,*E*) configuration of the *N*,*N*′-diethyl-substituted amidinium group in complex **5** ensures that binding interactions closely resemble those of unsubstituted amidines. The *N*,*N*′-diethylamidinium ion as a whole displays an approximate zig-zag conformation, while the CH_3 groups point above and below the NCN plane. With a C5–C6–C7–N1 torsion angle of 80.8°, the amidinium group and adjacent aromatic ring are almost perpendicular to each other, whereas the rotation of the amidine relative to the plane of the aromatic ring in unsubstituted amidinium carboxylates (30.0–35.2°),[21–23] in an *N*,*N*′-dimethylbenzamidine base (62°),[2] in an (*E*,*Z*)-configured 4-bromo-*N*,*N*′-diethylbenzamidinium tetrazolate (66°),[11] or even in the (*E*,*E*)-configured *N*,*N*′-diphenylbenzamidinium nitrate (61.4°)[7] is much smaller. A packing diagram confirms that the large dihedral angle is not a consequence of crystal packing constraints and long-range interactions between adjacent molecules (Fig. 4). The substantial increase in torsion angle hence reflects the steric bulk of the *N*,*N*′-diethyl-substituted amidine group. In comparison, the planes of the carboxylate and the phenyl group of the benzoate are oriented at an angle of 26.9° with respect to each other. The dihedral angle between the planes defined by the amidinium and carboxylate atoms is 15.3° in the salt bridge, which is again larger than for carboxylate complexes of unsubstituted amidines (3.8–8.4°).[21–23]

2.3. Comparison of crystal and solution structure

The NH chemical shift of $\delta_H \approx 12.9$ in the ^1H NMR spectrum of **5** in chloroform is characteristic of a strongly hydrogen-bonded complex in solution (Fig. 5). Both *N*-ethyl substituents give rise to a triplet and a quartet (in addition to another triplet and quartet from the *C*-ethyl group) indicative of an exclusively (*E*,*E*)-configured amidine. No significant line-broadening or frequency dependence of the NMR signals was noted as one would expect if the substituted amidine isomerised at the NMR timescale. A dynamic process, which has been reported for other *N*-substituted amidinium salts with chloride or tetrazolate counter-anions,[11,16,17] can therefore be excluded. This is clearly a consequence of strong binding interactions between amidine and benzoate. A carboxylate ligand is obviously able to force the *N*,*N*′-diethyl-substituted amidine into an (*E*,*E*) configuration that is perfect for binding. In contrast, benzamidinium salt **7** (prepared from the corresponding hydrochloride **6** by ion exchange (Scheme 2)) with its non-coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate[24] counteranion prefers the (*E*,*Z*) isomer in $CDCl_3$—most likely for steric reasons.

The binding constant for a related complex between **1** and 4-methylbenzoic acid has been previously reported to exceed $10^6\ M^{-1}$ in $CDCl_3$ at 25°C.[15] While complex **5**

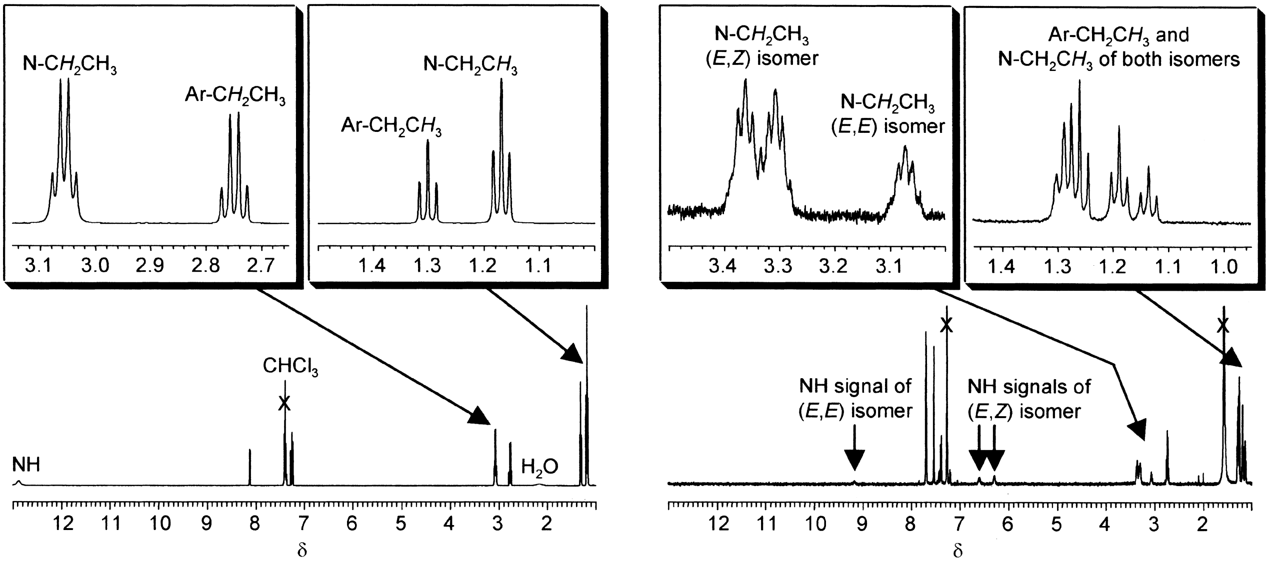
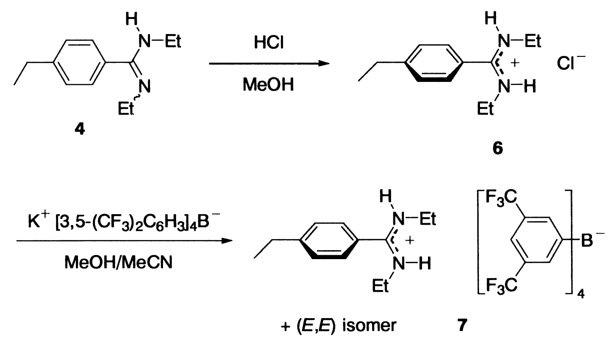


Figure 5. ^{1}H NMR spectra (500 MHz, 25°C, CDCl$_3$) of complex **5** (left) and of a benzamidinium salt **7** with the non-coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate counteranion (right). The quintet multiplicity of the N–CH$_2$CH$_3$ signals of **7** is due to coupling with the vicinal NH as well as CH$_3$ protons. Solvent signals are marked by X.

shows a single set of amidine NMR signals in chloroform, this is no longer the case if the salt is dissolved in a more polar solvent such as DMSO-d$_6$ in which the ^{1}H and ^{13}C NMR signals for the *N*-ethyl group as well as the aromatic protons are broadened owing to isomerisation of the amidine on the NMR timescale. Amidine–tetrazole complexes show such a dynamic behaviour already in chloroform, and binding constants were found to be considerably lower than for typical carboxylic acid complexes.[11] Although the (*E*,*Z*) isomer of the amidine can, in principle, bind through a single hydrogen bond to a suitable counteranion, such a binding mode is unfavorable. Benzamidinium chloride **6** exists therefore as a concentration- and temperature-dependent mixture of (*E*,*E*) and (*E*,*Z*) amidine even in chloroform. No complexation is observed in protic solvents in any of the above-mentioned cases so that the thermodynamically more stable (*E*,*Z*)-configured amidine prevails under these conditions. We note that there seems to be a distinct correlation between the strength of complexation and the preferred configuration of the *N*-substituted amidine. Mixtures of (*E*,*E*) and (*E*,*Z*) isomer are therefore always dominant in the presence of weakly binding ligands (chloride, tetrazolate) that cannot bind to the amidine through two linear (i.e. strong) hydrogen bonds.[11,15–17]



Scheme 2.

3. Conclusions

N,*N*′-Diethylsubstituted amidines are known to form strong noncovalent complexes with carboxylic acids in nonpolar solvents such as chloroform. The crystal structure of model complex **5** confirms that this is due to two almost linear hydrogen bonds between benzoate and the (*E*,*E*)-configured protonated amidine. Such a binding arrangement is also noted for the solution structure of the complex in chloroform. Comparison with previous studies led us to conclude that only strongly binding ligands are able to force the amidine into the sterically more hindered (*E*,*Z*) configuration.

4. Experimental

4.1. General methods

All solvents were distilled prior to use. Mp (DSC): Mettler TC 11 (melting enthalpies are given in brackets). NMR: Bruker AC 200, DRX 500. TMS was used as standard in the NMR measurements. The multiplicities of ^{13}C signals were determined by DEPT experiments. IR: Bruker Vector 22 FT-IR. CI-MS: Finnigan INCOS 50. ESI-MS: Thermoquest Automass benchtop LC/GC MS. Elemental analyses: Pharmazeutisches Institut der Heinrich–Heine-Universität Düsseldorf.

4.1.1. 4,*N*-Diethylbenzamide (2). 4,*N*-Diethylbenzamide (**2**) was prepared by the addition of aqueous ethyl amine (70%, 20 mL, 0.31 mol) to an ice-cold solution of 4-ethylbenzoyl chloride (5.06 g, 30.0 mmol) in ether (20 mL), followed by stirring at room temperature for 24 h. Water (100 mL) was added, and the mixture stirred for another 2 h. The resulting precipitate was collected by suction filtration and recrystallized from acetone. Yield: 5.50 g (97%). Mp 102°C (143 J g^{-1}). ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.25 (~t, J=7.5 Hz, 6H), 2.69 (q, J=7.5 Hz, 2H), 3.50 (quin,

J=6.8 Hz, 2H), 6.05 (br s, 1H), 7.25, 7.68 (AA′XX′, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 15.3 (CH_3), 28.8, 34.9 (CH_2), 126.9, 128.0 (CH), 132.2, 147.9, 167.4 (*ipso*-C, C═O). MS (CI, NH_3): *m/z* 195 ($M+NH_4^+$, 100%), 178 ($M+H^+$, 100). IR (KBr, cm^{-1}): ν 3326, 2968, 1634, 1548, 1505, 1309, 1144, 854, 675. Anal. Calcd for $C_{11}H_{15}NO$ (177.24): C, 74.54; H, 8.53; N, 7.90. Found: C, 74.38; H, 8.41; N, 7.93.

4.1.2. 4,*N*,*O*-Triethylbenzimidate (3). Amide **2** (4.43 g, 25.0 mmol) was dissolved in a 1.0 M solution of triethyloxonium tetrafluoroborate in CH_2Cl_2 (30 mL). After stirring at room temperature under Ar for 24 h, the solvent was removed in vacuum. The residue was treated with ice-cold aqueous NaOH (3 M, 20 mL) and extracted with ice-cold ether (100 mL). The organic extract was dried over Na_2SO_4 and concentrated. Crude benzimidate **3** was distilled once (Kugelrohr, 160°C/0.02 mbar) and used without further purification. Yield: 4.25 g (83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (t, J=6.9 Hz, 3H), 1.24 (t, J=7.6 Hz, 3H), 1.32 (q, J=6.9 Hz, 2H), 2.66 (q, J=7.6 Hz, 2H), 3.29 (q, J=6.9 Hz, 2H), 4.21 (q, J=6.9 Hz, 2H), 7.22, 7.26 (AA′BB′, 4H).

4.1.3. 4,*N*,*N*′-Triethylbenzamidine (4). A solution of **3** (2.67 g, 13.0 mmol) and ethylamine hydrochloride (1.30 g, 16.0 mmol) in dry ethanol (30 mL) was stirred for 5 days at room temperature under Ar. The solvent was removed in vacuum, and the residue suspended in ice-cold ethyl acetate (100 mL). The mixture was then washed with ice-cold aqueous NaOH (6 M, 20 mL). The organic phase was collected, dried over Na_2SO_4, and concentrated. Gradient sublimation (90°C/10^{-4} mbar) gave 4.10 g (98%) of amidine **4**. Mp 69°C (93 J g^{-1}). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (br s, 6H), 1.25 (t, J=7.6 Hz, 3H), 2.67 (q, J=7.6 Hz, 2H), 3.20 (br s, 4H), 7.17–7.23 (br m, 4H). ^{1}H NMR (200 MHz, CD_3OD): δ 1.10 (t, J=7.2 Hz, 6H), 1.24 (t, J=7.6 Hz, 3H), 2.68 (q, J=7.6 Hz, 2H), 3.14 (q, J=7.2 Hz, 4H), 7.20, 7.28 (AA′BB′, 4H). ^{13}C NMR (50 MHz, CD_3OD): δ 16.2, 16.3 (br) (CH_3), 29.7, 41.2 (br) (CH_2), 128.88, 128.94 (CH), 134.4, 146.7, 162.8 (*ipso*-C, C═N). MS (CI, NH_3): *m/z* 205 ($M+H^+$, 100%). IR (KBr, cm^{-1}): ν 3210, 2966, 2929, 2862, 1622, 1539, 1312, 833. Anal. Calcd for $C_{13}H_{20}N_2$ (204.31): C, 76.42; H, 9.87; N, 13.71. Found: C, 76.57; H, 10.06; N, 13.93.

4.1.4. 4,*N*,*N*′-Triethylbenzamidinium benzoate (5). Benzoic acid (122 mg, 0.982 mmol) and **4** (200 mg, 0.982 mmol) were dissolved in hot ethanol (10 mL). The solution was then concentrated in vacuum, and the residue was recrystallized from hot hexane to give colourless needles of complex **5** (121 mg, 92%). DSC: 39°C (9 J g^{-1}), 141°C (82 J g^{-1}). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 (t, J=7.2 Hz, 6H), 1.30 (t, J=7.6 Hz, 3H), 2.75 (q, J=7.6 Hz, 2H), 3.05 (br q, J=7.2 Hz, 4H), 7.24, 7.39 (AA′XX′, ArH amidine), 7.36–7.41, 8.09–8.12 (m, ArH benzoate), 12.93 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1, 15.5 (CH_3), 28.8, 39.6 (CH_2), 127.0, 127.6, 129.0, 129.4, 130.0 (CH), 124.6, 137.9, 147.9, 166.8, 175.0 (*ipso*-C, C═N, C═O). IR (KBr, cm^{-1}): ν 2972, 1646, 1596, 1552, 1377, 718. ESI-MS (CH_3CN): *m/z* 531 (**4**$_2$+benzoic acid+H^+, 100%), 409 (**4**$_2$+H^+, 10), 205 (**4**+H^+, 10). Anal. Calcd for $C_{20}H_{26}N_2O_2$ (326.43): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.37; H, 8.15; N, 8.58.

4.1.5. 4,*N*,*N*′-Triethylbenzamidinium chloride (6). Hydrochloride **6** was obtained as a colourless solid by freeze-drying a solution of **4** in methanolic HCl. Mp 114°C (82 J g^{-1}). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.09 (br t, J=7.3 Hz, 3H), 1.21 (t, J=7.6 Hz, 3H), 1.22 (br t, J=7.3 Hz, 3H), 2.70 (q, J=7.6 Hz, 2H), 3.15 (br q, J=7.3 Hz, 2H), 3.49 (br q, J=7.3 Hz, 2H), 7.45, 7.50 (AA′BB′, 4H), 9.65 (br s, 2H). ^{13}C NMR (50 MHz, CD_3OD): δ 12.9, 15.1, 15.2 (CH_3), 27.9, 37.7, 39.9 (CH_2), 128.0, 128.3 (CH), 125.8, 148.0, 162.8 (*ipso*-C, C═N). IR (KBr, cm^{-1}): ν 3156, 3032, 2977, 2932, 1639, 1568, 1385, 752. Anal. calcd for $C_{13}H_{21}ClN_2$ (240.77): C, 64.85; H, 8.79; N, 11.63. Found: C, 64.81; H, 8.67; N, 11.62.

4.1.6. 4,*N*,*N*′-Triethylbenzamidinium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (7). A mixture of **6** (120 mg, 0.500 mmol) and potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate[24] (451 mg, 0.500 mmol) were dissolved in methanol (25 mL) and concentrated in a vacuum. The residue was then suspended in a 1:1 mixture of $CHCl_3$–MeCN (20 mL) and passed through a membrane filter. The filtrate was concentrated in a vacuum to furnish **7** as a colourless amorphous solid. Yield: 250 mg (71%). ^{1}H NMR (500 MHz, $CDCl_3$) major (*E*,*Z*) isomer: δ 1.19 (t, J=6.9 Hz, 3H), 1.26 (t, J=7.6 Hz, 3H), 1.29 (t, J=6.9 Hz, 3H), 2.74 (q, J=7.6 Hz, 2H), 3.31 (~quin, J=6.9 Hz, 2H), 3.36 (~quin, J=6.9 Hz, 2H), 6.29 (br s, 1H), 6.60 (br s, 1H), 7.25, 7.39 (AA′XX′, 4H), 7.53 (br s, 4H), 7.69 (br s, 8H); an additional set of smaller signals could be assigned to the (*E*,*E*)-configured amidine isomer: δ 1.13 (t, J=6.9 Hz, 6H), 1.26 (t, J=7.6 Hz, 3H), 2.74 (q, J=7.6 Hz, 2H), 3.07 (~quin, J=6.9 Hz, 4H), 7.20, 7.43 (AA′XX′, 4H), 9.18 (br s, 2H). Anal. Calcd for $C_{45}H_{33}BF_{24}N_2$ (1068.53): C, 50.58; H, 3.11; N, 2.62. Found: C, 50.97; H, 3.26; N, 2.73.

4.2. Determination of pK_a

Amidine **4** (20–30 mg, ca. 0.13 mmol) and KCl (221 mg, 3.0 mmol) were dissolved in a mixture of water (15.0 g) and dioxane (15.0 g) to which a known amount of 0.5 M hydrochloric acid was added to lower the pH to about 3. Potentiometric studies were conducted with a Metrohm 702 Titrino autotitrator using a Metrohm 6.0222.100 combined pH glass electrode with a 3 M KCl internal filling. Titrations were carried out at 25°C with 0.4905 M NaOH, and about 100 data points were collected for each titration. The ion product of water (pK_w 15.4) in the mixed solvent was determined by a Gran plot.[25] The equivalents of H^+ bound (Eq. (1)) were calculated from the activity-corrected pH,[19b] the amount of amidine base (L) used in the titration, added strong acid (A), the concentration (C_b) and added volume (v) of NaOH titrant, and the starting volume (V_0).[19] The pK_a was obtained after fitting the experimentally determined values (Eq. (1)) to the theoretical Bjerrum function (Eq. (2)) by an unweighted nonlinear least-squares regression method using Microsoft Excel.

$$\bar{n}_{\mathrm{H}} = \frac{L + A - C_{\mathrm{b}}v - (10^{-\mathrm{pH}} - 10^{-\mathrm{p}K_{\mathrm{w}}+\mathrm{pH}})(V_0 + v)}{L} \qquad (1)$$

$$\bar{n}_H = \frac{10^{\mathrm{p}K_\mathrm{a}-\mathrm{pH}}}{1 + 10^{\mathrm{p}K_\mathrm{a}-\mathrm{pH}}} \qquad (2)$$

4.3. X-Ray crystallographic study of 5

Crystals suitable for X-ray crystallography were grown from a solution of **5** (5–7 mg) in hexane (2 mL) that was kept in a sample vial (sealed with a polypropylene lid) and left to stand at room temperature for several days. Crystal data: $C_{20}H_{26}N_2O_2$, colourless needle $0.23\times0.12\times0.09$ mm^3, monoclinic, space group $C2/c$ (No. 15), a=9.717(2), b=22.074(4), c=9.258(2) Å, β=106.76(3)°, V=1901.4(7) Å^3, Z=4, ρ_{calcd}=1.140 g cm^{-3}, T=230 K. Data collection: 2416 reflections ($\pm h$, $\pm k$, $\pm l$) were collected on a NoniusKappa diffractometer, λ=0.71073 Å (Mo K_α radiation), 1637 independent and 895 observed reflections [$I\geq2\sigma(I)$]. The structure was refined against F^2 (program SHELXL-97, G. M. Sheldrick, University of Göttingen) to give R=0.065 and wR^2=0.170 for 114 parameters, max. residual electron density 0.23 (−0.22) e Å^{-3}. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-176872. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank Dr John E. Davies and the X-ray laboratory of Cambridge University Chemical Laboratory for carrying out the crystal structure determination, Ms S. Johann for assistance in preparing the starting materials, and Professor Dr G. Wulff for support. Financial support by the Deutsche Forschungsgemeinschaft, Heriot–Watt University and the Royal Society is gratefully acknowledged.

References

1. Guilford, W. J.; Shaw, K. J.; Dallas, J. L.; Koovakkat, S.; Lee, W.; Liang, A.; Light, D. R.; McCarrick, M. A.; Whitlow, M.; Ye, B.; Morrissey, M. M. *J. Med. Chem.* **1999**, *42*, 5415–5425.
2. Tinant, B.; Dupont-Fenfau, J.; Declercq, J.-P.; Podlaha, J.; Exner, O. *Collect. Czech. Chem. Commun.* **1989**, *54*, 3245–3251.
3. Trent, J. O.; Clark, G. R.; Kumar, A.; Wilson, W. D.; Boykin, D. W.; Hall, J. E.; Tidwell, R. R.; Blagburn, B. L.; Neidle, S. *J. Med. Chem.* **1996**, *39*, 4554–4562.
4. Simpson, I. J.; Lee, M.; Kumar, A.; Boykin, D. W.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2593–2597.
5. Alcock, N. W.; Blacker, N. C.; Errington, W.; Wallbridge, M. G. H.; Barker, J. *Acta Crystallogr., Sect. C* **1994**, *50*, 456–458.
6. Boeré, R. T.; Klassen, V.; Wolmershäuser, G. *J. Chem. Soc., Dalton Trans.* **1998**, 4147–4154.
7. Barker, J.; Errington, W.; Wallbridge, M. G. H. *Acta Crystallogr., Sect. C* **1999**, *55*, 1583–1585.
8. Ondráček, J.; Pakhomova, S.; Kratochvíl, B.; Smrckova, S. *Collect. Czech. Chem. Commun.* **1995**, *60*, 576–582.
9. Hartmann, S.; Weckert, E.; Frahm, A. W. *Acta Crystallogr., Sect. C* **1999**, *55*, 806–808.
10. McNally, J. J.; Youngman, M. A.; Lovenberg, T. W.; Nepomuceno, D. H.; Wilson, S. J.; Dax, S. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 213–216.
11. Peters, L.; Fröhlich, R.; Boyd, A. S. F.; Kraft, A. *J. Org. Chem.* **2001**, *66*, 3291–3298.
12. Göbel, M. W.; Bats, J. W.; Dürner, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 207–209.
13. Wulff, G.; Groß, T.; Schönfeld, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1962–1964.
14. Strikovsky, A. G.; Kasper, D.; Grün, M.; Green, B. S.; Hradil, J.; Wulff, G. *J. Am. Chem. Soc.* **2000**, *122*, 6295–6296.
15. (a) Wulff, G.; Schönfeld, R. *Adv. Mater.* **1998**, *10*, 957–959. (b) Baumstark, R.; Wildburg, G.; Häußling, L.; Wulff, G.; Schönfeld, R.; Grün, M. German Patent DE 19720345, 1997.
16. Schönfeld, R. PhD Dissertation, University of Düsseldorf, 1998.
17. Hammond, G. S.; Neuman, R. C. *J. Phys. Chem.* **1963**, *67*, 1655–1659.
18. (a) Yeretzian, C.; Wiley, J. B.; Holczer, K.; Su, T.; Nguyen, S.; Kaner, R. B.; Whetten, R. L. *J. Phys. Chem.* **1993**, *97*, 10097–10101. (b) Dimitrakopoulos, C. D.; Brown, A. R.; Pomp, A. *J. Appl. Phys.* **1996**, *80*, 2501–2508.
19. (a) Avdeef, A.; Kearney, D. L.; Brown, J. A.; Chemotti, A. R. *Anal. Chem.* **1982**, *54*, 2322–2326. (b) Billo, E. J. *Excel for Chemists: A Comprehensive Guide*; 2nd ed; Wiley-VCH: New York, 2001; Chapter 22.
20. The following examples are a selection of ethylbenzenes with C–C bond lengths <1.32 Å, excluding poor structures and organometallics (C–C distance, C_{Ar}–C–C angle, and CSD reference code given in brackets): (a) *N*,*N′*-Bis(4-ethylbenzenesulfuryl)-*p*-phenylenediamine (1.093 Å, 126.5°, disordered, GOWSIU): Bock, H.; Nagel, N.; Eller, P. Z. *Naturforsch* **1999**, *B54*, 491–500. (b) A 1,3,5-triethylbenzene derivative (1.231 Å, 131.4°, disordered, NAWXEO): Bisson, A. P.; Lynch, V. M.; Monahan, M.-K. C.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2340–2342. (c) Ethylbenzene solvent included in a metalloporphyrin crystal (1.231 Å, 110.1°, disordered, YEKHIF): Guilard, R.; Brandes, S.; Tabard, A.; Bouhmaida, N.; Lecomte, C.; Richard, P.; Latour, J.-M. *J. Am. Chem. Soc.* **1994**, *116*, 10202–10211. (d) An ethylindole derivative (1.239 Å, 119.6°, disordered, SABKAH): Mobilio, D.; Humber, L. G.; Katz, A. H.; Demerson, C. A.; Hughes, P.; Brigance, R.; Conway, K.; Shah, U.; Williams, G.; Labbadia, F.; De Lange, B.; Asselin, A.; Schmid, J.; Newburger, J.; Jensen, N. P.; Weichman, B. M.; Chau, T.; Neuman, G.; Wood, D. D.; Van Engen, D.; Taylor, N. *J. Med. Chem.* **1988**, *31*, 2211–2217. (e) A 1-ethylnaphthalene charge-transfer complex (1.296 Å, 120.3°, disordered, LAVFOD): Baldwin, S. L.; Baughman, R. G. *Acta Crystallogr., Sect. C* **1993**, *49*, 1840–1844. (f) An ethylbenzene–porphyrin clathrate (1.300 Å, 117.6°, SEMMAY): Byrn, M. P.; Curtis, C. J.; Khan, S. I.; Sawin, P. A.; Tsurumi, R.; Strouse, C. E. *J. Am. Chem. Soc.* **1990**, *112*, 1865–1874. (g) 4-Cyano-4-ethylbiphenyl (1.307 Å, 113.8°, KUSVID01): Haase, W.; Loub, J.; Paulus, H. *Z. Kristallogr.* **1992**, *202*, 7–16. (h) An ethylanthraquinone (1.311 Å, 126.3°, WINWAR): Cotterill, A. S.; Gable, R. W.; Gill, M. *Acta Crystallogr., Sect. C* **1995**, *51*, 500–502. (i) An ethylfluorene macrocycle (1.313 Å, 124.0°, disordered, VATBAT): Ipaktschi, J.; Hosseinzadeh, R.; Schlaf, P.; Dreiseidler, E.; Goddard, R. *Helv. Chim. Acta* **1998**, *81*, 1821–1834.

21. Papoutsakis, D.; Kirby, J. P.; Jackson, J. E.; Nocera, D. G. *Chem. Eur. J.* **1999**, *5*, 1474–1480.
22. Kratochvíl, B.; Ondráček, J.; Krechl, J.; Hašek, J. *Acta Crystallogr., Sect. C* **1987**, *43*, 2182–2184.
23. Kratochvíl, B.; Ondráček, J.; Malú, K.; Csordás, L. *Collect. Czech. Chem. Commun.* **1988**, *53*, 294–300.
24. Nishida, H.; Takada, N.; Yoshimura, M. *Bull. Chem. Soc. Jpn* **1984**, *57*, 2600–2604.
25. Gran, G. *Analyst* **1952**, *77*, 661–671.