Synthesis and Self Association of 4,7-Diamino-2,9-dimethyl-5,6,11a-triaza-6,11,11a,12-tetrahydronaphthacene Derivatives as Dibenzoguanidine Receptors for Oxoanion Recognition

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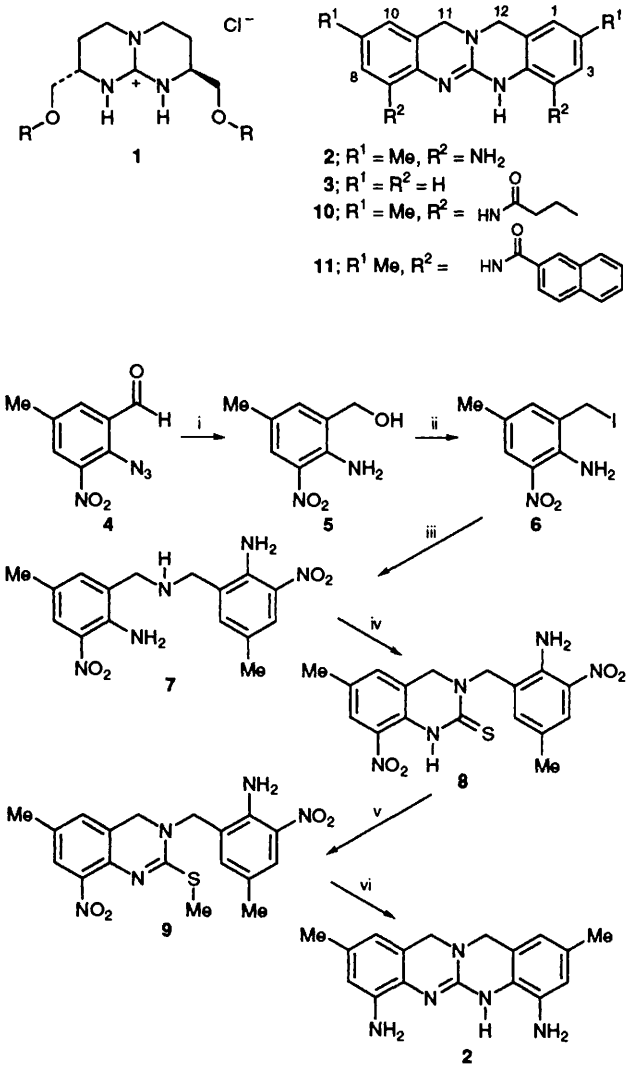
Syntheses of 4,7-diamino-2,9-dimethyl-5,6,11a-triaza-6,11,11a,12-tetrahydronaphthacene and of their 2-naphthoyl and butyroyl amide derivatives are described; the U-shaped 2-naphthoyl derivative stabilizes as an interlocked dimer in $CDCl_3$ solution.

Derivatives of bicyclic guanidinium compounds of general formula **1** have recently been employed successfully for the selective recognition of carboxylates (aminoacid derivatives)[1] and phosphates (nucleotides)[2] in organic media. Although the chirality of **1** (both optically pure enantiomers can be readily prepared in gram amounts)[3] allows the enantioselective recognition of chiral substrates,[4] delivery of the chiral information is hampered by the long distance from the chiral centres of the flexible receptors to those of the bound substrates. We report herein the synthesis of non chiral dibenzoguanidine **2**, a more rigid system for oxoanion binding whose guanidinium diamide derivatives feature four hydrogen atoms that may converge to complement the oxygen lone pairs of the ion-paired anion, as in the carboxylate binding pockets of vancomycin and related antibiotics.[5] Since a variety of optically pure diamide derivatives may be formed, a systematic survey of chiral recognition can thus be achieved.

The parent dibenzoguanidine **3** was easily prepared in only three steps from anthranylonitrile: rhodium–Al_2O_3 catalysed hydrogenation to the corresponding secondary amine,[6] followed by a two-step guanidine formation through a thiourea intermediate [thiocarbonyldiimidazole (TCDI) and iodomethane] in an 31% overall yield. Other aromatic guanidines substituted at 2,3,8,9, and/or 12 positions have been reported from bis(iminophosphoranes).[7] However, none of these systems are endowed with the required amines outflanking the guanidinium function at positions 4 and 7.

The synthesis of **2** is summarized in Scheme 1. Thiourea **8** was obtained in four steps by conventional chemistry from 2-azido-5-methyl-3-nitrobenzaldehyde **4**.[8] The low reactivity of the aromatic amine prevented the direct cyclization (dichloro-



Scheme 1 *Reagents and conditions*: i, $NaBH_4$, THF, room temp., 100%; ii, 2.5 equiv. CITMS, 2.5 equiv. NaI, CH_3CN, room temp., 82%; iii, THF, 30% aq. NH_4OH, room temp., 75%; iv, 1.4 equiv. TCDI, CH_2Cl_2, room temp., 92%; v, 1.4 equiv. MeTfO, 1.4 equiv. Et_2NPr^i, CH_2Cl_2, reflux; vi, 10.0 equiv. $SnCl_2{\cdot}2H_2O$, EtOH, reflux, 77%

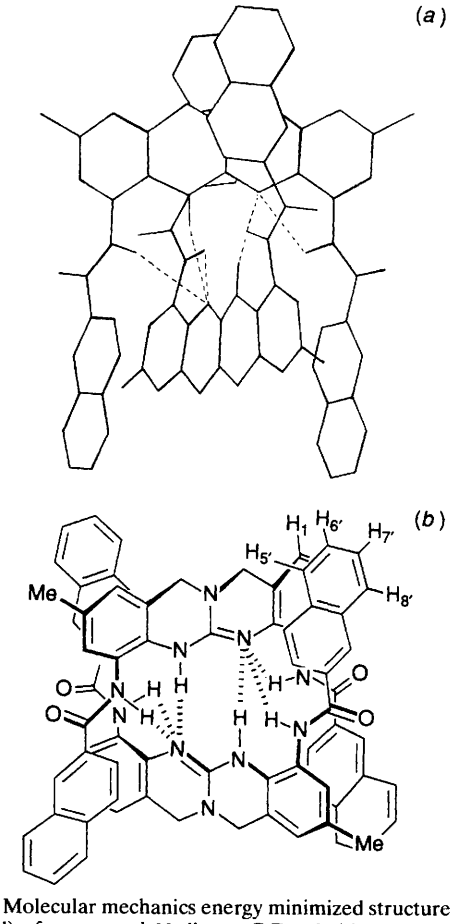


Fig. 1 (*a*) Molecular mechanics energy minimized structure (AMBER force field) of compound **11** dimer. C-Bonded hydrogens have been omitted for clarity. (*b*) Schematic view showing hydrogen atoms involved in NOE contacts.

methane, reflux) of **8** and its activated derivative **9**, but this process occurred spontaneously upon reduction of the nitro groups to the corresponding more reactive triamine intermediate, giving rise to **2** in a 44% overall yield from **4**.† Amides **10** and **11** were prepared from **2** by room temperature acylations with excess butyric anhydride and 2-naphthoyl chloride (Et_3N, CH_2Cl_2), respectively.

Benzylic protons (H-11 and H-12) of **11** appeared at δ 2.29 in the ^1H NMR spectrum ($CDCl_3$).‡ Protonation or addition of methanol resulted in signals at their standard chemical shifts (*ca.* 3.5–4.0). This anomalous strong upfield shift can be explained by self-assembly of the rigid, U-shaped dibenzoguanidine into a well structured, interlocked dimer, stabilized by hydrogen bonding and by stacking interactions. An energy minimized computer generated model [Fig. 1(*a*)][9] clearly showed the naphthoyl rings lying over the methylene groups, accounting for the anisotropic effect observed. Further evidence for this structure for the dimer was obtained from NOESY experiments. While the spectrum of the monomer ($CDCl_3$: CD_3OD 4 : 1) showed only trivial contacts between the methyl groups and the aromatic protons of benzoguanidine, strong NOE signals were observed in the dimer between the H-1 (or H-10) guanidine proton and H-5′, H-6′, H-7′, and H-8′ naphthoyl protons [Fig. 1(*b*)].

Preliminary experiments revealed that addition of butyric and *p*-nitrobenzoic acids to $CDCl_3$ solutions of amides **10** and **11**, respectively, resulted in the formation of strong guanidinium-carboxylate complexes. Downfield shifts of the amide protons (Δδ 0.38 and 0.48 ppm, respectively) accounted for the hydrogen-bonded pockets of these complexes. Other amides, derived from chiral amino acids, are currently being explored for chiral recognition.

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Footnotes

† *Spectroscopic data* for **2**: ^1H NMR (200 MHz, $CDCl_3$) δ 2.05 (bs, 5H, NH), 2.20 (s, 6H), 4.34 (s, 4H), 6.27 (s, 2H), 6.42 (s, 2H); ^{13}C NMR [50 MHz, $(CD_3)_2SO$] δ 20.6, 49.8, 113.7, 118.2, 129.5, 136.4, 147.9; MS (+FAB) *m/z* 294.2 (M^+) (calc. for $C_{17}H_{19}N_5$ 293.2).

‡ *Spectroscopic data* for **11**: Monomer. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD 4 : 1) δ 2.28 (s, 6H, CH_3), 4.06 (s, 4H, CH_2), 5.96 (s, 2H), 7.30 (m, 6H), 7.47 (m, 6H), 7.68 (d, 2H, *J* 8.1 Hz), 8.03 (s, 2H). Dimer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 10H, CH_2, CH_3), 5.96 (s, 2H), 7.26 (t, 2H, *J* 7.5 Hz), 7.35 (d, 2H, *J* 8.1 Hz), 7.45 (t, 2H, *J* 6.8 Hz), 7.46 (d, 2H, *J* 7.8 Hz), 7.53 (s, 2H), 7.59 (d, 2H, *J* 8.6 Hz), 7.68 (d, 2H, *J* 8.1 Hz), 8.06 (s, 2H), 8.82 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0, 48.2, 118.6, 122.4, 122.9, 124.0, 126.0, 127.0, 127.6, 129.6, 130.7, 131.4, 132.2, 134.2, 147.6, 165.8; MS (+FAB) *m/z* 602.3 (calc. for $C_{39}H_{31}N_5O_2$ 601.3).

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