(4*S*,8*S*)-4,8-Bis(diphenylmethyl)-1,5,7-triazabicyclo[4,4,0]dec-5-ene; a Hindered, Chiral, Bicyclic Guanidine Base with Effective C_2-Symmetry

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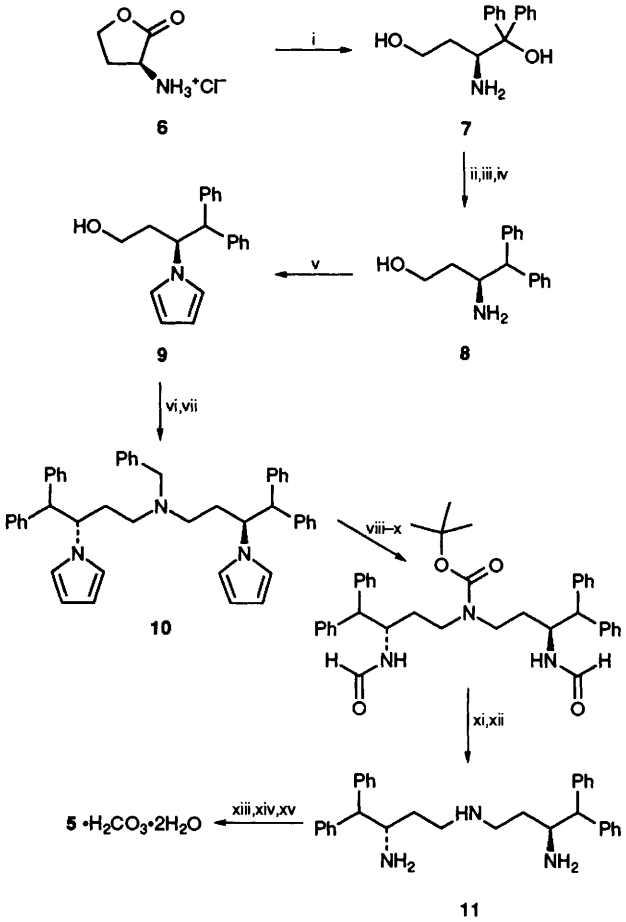
The title compound **5** is prepared from L-methionine and investigated by computational, NMR spectroscopic and other techniques; the results indicate that the N/NH groups of **5** and its conjugate acid occupy hindered, chiral environments due to the disposition of the bulky diphenylmethyl substituents.

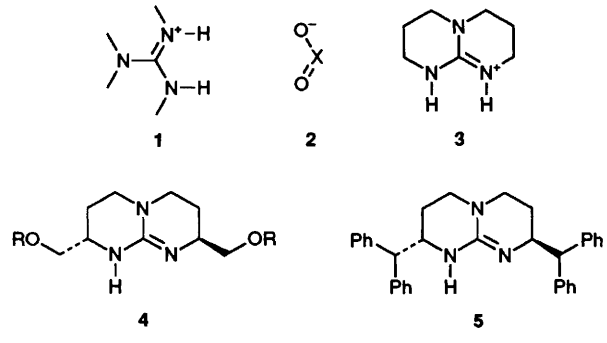
The guanidinium moiety **1** has played an important rôle in the study of anion recognition, being complementary (in terms of charge and H-bonding propensity) to a variety of oxoanion units **2** (X = C, N, P *etc.*).[1] Particular use has been made of the bicyclic system present in **3**, in which the two codirected NH groups may be relied upon to position the oxoanion unambiguously (within certain limitations) with respect to the carbon framework.[1a–i] Recent work has focused on the chiral C_2-symmetric unit **4**/**4H**$^+$, which has been employed independently by two groups in enantiodifferentiating receptors for carboxylate anions.[1b–e] We now report the synthesis of the related system **5**/**5H**$^+$, in which the sterically undemanding CH_2OR side-chains are replaced by bulky $CHPh_2$ groups. Molecular modelling and experimental results imply that these groups can exert steric control over the regions of space around the NH$^{\delta+}$ in **5H**$^+$, and the basic nitrogen in **5**, providing an enforced chiral environment which may in principle be exploited for the development of enantioselective recognition and catalysis.

The synthetic route to **5** is summarised in Scheme 1. The starting material, L-homoserine lactone hydrochloride **6**, was prepared from L-methionine in 68% yield using a procedure based on that of Baldwin *et al.*[2] Hydrogenolysis of the tertiary OH in **7** proved non-trivial, being complicated by loss of stereochemical integrity under some conditions. However, the sequence shown was successful, giving **8** in optically pure form {NMR analysis of bis-MTPA [MTPA = α-methoxy-α-trifluoromethyl)phenylacetyl] derivative}. Protection of the amino group in **8** was achieved by incorporation of the nitrogen in a pyrrole ring.[3] As we have noted previously,[3b] this method is unusual in that it suppresses N-nucleophilicity without introducing vulnerability to strong bases or nucleophiles. Obvious alternatives were tried (Ac, BOC, phthalimido), but all proved unsuccessful. Guanidine formation was accomplished using a procedure due to Gleich and Schmidtchen,[1b] the product **5H**$^+$ being isolated as a hydrated carbonate.† Solutions of **5** itself could be obtained by dissolving the salt in dichloromethane and washing with 3 mol dm^{-3} aqueous sodium hydroxide.

The structure of **5H**$^+$ was assessed using the systematic search-minimisation procedure implemented in the MACROMODEL computer-based molecular modelling program.[4]‡ 59 energy minima were located, including the global minimum shown in Fig. 1. This conformer, in which approach to the NH$^{\delta+}$ is severely constrained by the flanking aryl groups, was found to be 8.9 kJ mol^{-1} below its nearest rival, implying that it should be quite dominant in $CDCl_3$ solution at room temperature. Support for this conjecture was provided by the vicinal $J(Ph_2CH\text{–}CH)$ values of 10.2 and 10.5 Hz for **5**·HI and



Scheme 1 *Reagents and conditions*: i, PhMgBr, THF, 67%; ii, Ac_2O, py; iii, $NH_4^+HCO_2^-$, Pd/C, AcOH; iv, aq. HCl, 58% (from **7**); v, 2,5-dimethoxytetrahydrofuran, AcOH, 70%; vi, $MeSO_2Cl$, py; vii, $PhCH_2NH_2$, $NaHCO_3$, MeCN, 70% (from **9**); viii, $NH_4^+HCO_2^-$, Pd/C, MeOH; ix, $(Bu^tOCO)_2O$, THF; x, O_3, MeOH, then $NaBH_4$; xi, aq. HCl, MeOH; xii, NaOH, 50% (from **10**); xiii, $(MeS)_2C{=}S$, $MeNO_2$, then MeI, AcOH; xiv, NaOH; xv, C_6H_6, atmospheric CO_2 and moisture.



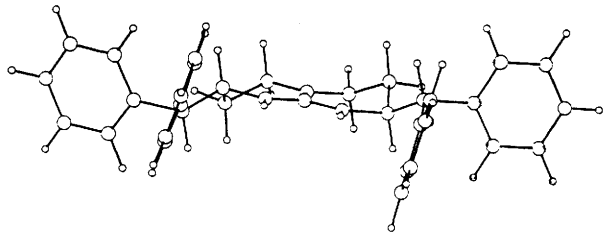
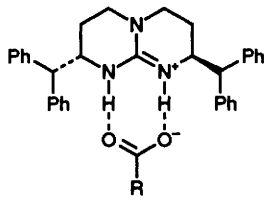


Fig. 1 Lowest-energy conformer **5H**$^+$ as determined by computer-based molecular modelling, oriented such that the N–H bonds are angled towards the viewer



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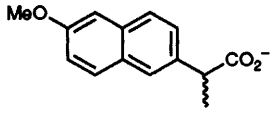

13

$5{\cdot}H_2CO_3$ respectively, consistent with an *anti* relationship (calc.[5] for Fig. 1; 11.2 Hz). Of the next seven energy minima (in a band between 8.9 and 14.6 kJ mol^{-1} above baseline) all bar one had at least one side-chain with *gauche* $Ph_2CH–CH$.

Experimentally, the hindered nature of **5** was revealed by its failure to undergo *N*-alkylation by methyl iodide, even after lengthy exposure to a high concentration of the reagent. In parallel experiments with the unsubstituted analogue (conjugate base of **3**), *N*-methylation was extremely rapid. However, the steric crowding did not prevent the apparent formation of hydrogen-bonded complexes **12** with carboxylic acids in non-polar solvents. Thus, when a $CDCl_3$ solution of **5**·HCl was shaken with excess squeous sodium *p*-nitrobenzoate. ^1H NMR spectroscopy showed that 1 equivalent of the carboxylate was extracted into the organic phase. Formation of NH···O hydrogen-bonds was indicated by a 1.4 ppm downfield displacement of the NH resonance, and intracomplex shielding effects were observed for two of the guanidinium aromatic protons (upfield $\Delta\delta$ of $\geq$0.1 and $\geq$0.33 ppm respectively) and one of the pairs of *p*-nitrobenzoate protons (upfield $\Delta\delta$ of 0.24 ppm, relative to an analogous complex with **3**).§ The influence of the asymmetrically-disposed phenyl groups was seen in a similar experiment involving *R,S*-naproxenate **13**. In addition to a downfield shift of 1.0 ppm for the NH resonance, the spectrum revealed differential upfield shifts for the α-H ($\Delta\delta$ 0.21 and 0.24 ppm) and $CHCH_3$ ($\Delta\delta$ 0.11 and 0.13 ppm) of **13**, presumably corresponding to the two enantiomers.¶ The two sets of peaks were of roughly equal intensity, implying similar interaction energies for the diastereomeric complexes.

Given its basicity, steric hindrance and effective C_2-symmetry, **5** would seem to be well-suited for exploitation as an enantioselective receptor, reagent or catalyst. We hope that such applications will emerge from future research in this and other laboratories.

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Footnotes

† **5**·H_2CO_3·$2H_2O$: δ_H (CD_3CN, 300 MHz) 7.69 (br s, 2H, NH), 7.46–7.16 (m, 20H, Ar), 4.33–4.29 (m, 2H, $CHCHPh_2$), 3.97 (d, *J* 10.5 Hz, $CHCHPh_2$), 3.36–3.20 (m, 4H, NCH_2), 1.95–1.92 (m, 2H, NCH_2CHH), 1.72–1.57 (m, 2H, NCH_2CHH). Satisfactory elemental analysis was obtained. **5**·HI: HR MS (CI), *m/z* 472.2763 ($\mathbf{5H^+}$, $C_{33}H_{34}N_3$, requires 472.2753).

‡ MACROMODEL V3.1X, running on a Silicon Graphics IRIS 4D25TG workstation. Starting from the three possible conformations of the bicyclic system (side chains diequatorial, equatorial–axial and diaxial), the MULTIC submode was used to generate starting conformations by systematic variations of the side chain torsion angles. The resulting structures were minimised (PRCG) using the Amber force field and GB/SA solvation treatment ($CHCl_3$).[6]

§ *cf.* Ref. 1(*d*).

¶ In a control experiment employing *S*-(+)-naproxenate, only one set of peaks was observed.

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