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Synthesis of a New Family of Receptors having Dibenz[*c*,*h*]acridine as Spacers and their Binding Affinity with Urea

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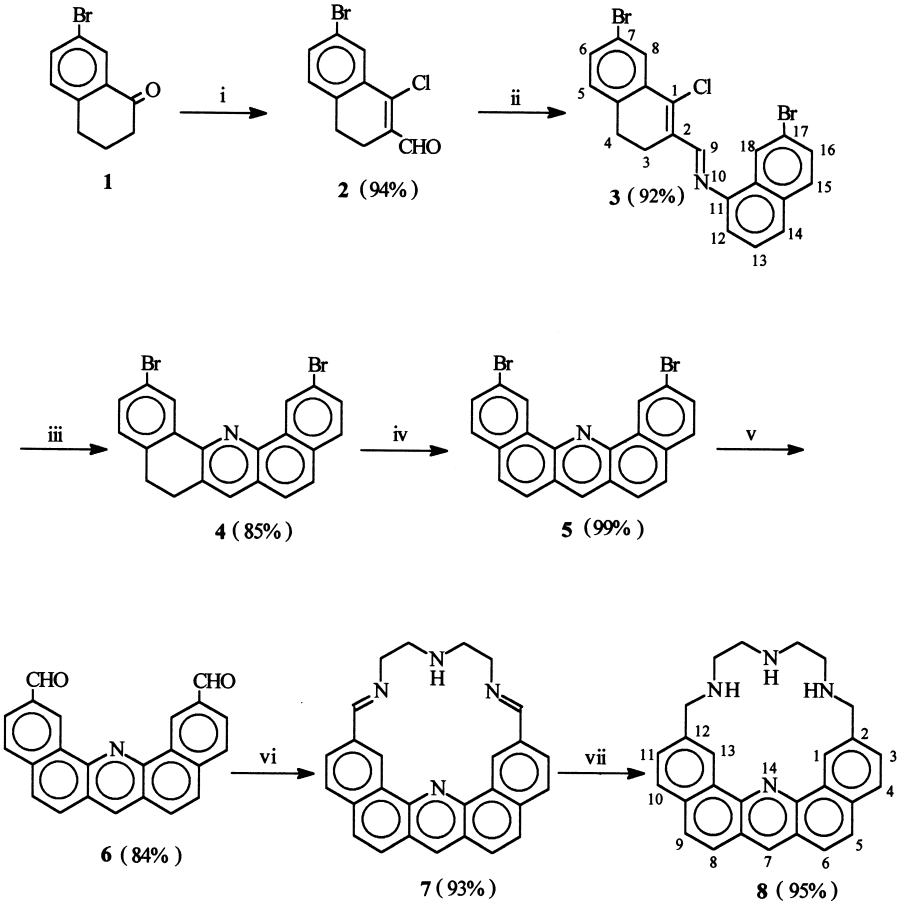
Abstract—New molecular receptors with a dibenz[*c*,*h*]acridine as spacer and having functionality complementary to urea have been developed. © 2000 Elsevier Science Ltd. All rights reserved.



Scheme 1. Reagents and conditions: (i) $POCl_3$, DMF, trichloroethylene, 60–65°C, 6 h; (ii) 7-bromo-1-naphthylamine, benzene, reflux, 20 h; (iii) 250–270°C, 25 min; (iv) DDQ, C_6H_5Cl, reflux, 20 h; (v) *n*-BuLi, TMEDA, THF, −78°C, 35–40 min, then DMF at −78°C, 2 h; (vi) diethylenetriamine, benzene, reflux, 15 h; (vii) $NaBH_4$, EtOH, rt, 12 h.

Keywords: dibenz[*c*,*h*]acridine; spacers; urea.

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Molecular recognition of dibenz[*c*,*h*]acridine derivatives as spacers carrying different functional groups are interesting due to their potential to mimic enzyme-like catalysts and suitability for binding guests by hydrogen bonds.[1] In recent years, many such receptors have been designed and their binding capabilities with dicarboxylic acid derivatives have been studied.[2–4] The incorporation of substituents by functionalising the parent nucleus with three more ligands should have a profound influence on the capabilities of dibenz[*c*,*h*]acridine derivatives to act as good receptors and chelating agents.

Here, we report the synthesis and complexation properties of two novel receptors with a defined geometry suitable for association with urea. Synthesis of the receptors was achieved from 7-bromo-1-tetralone (**1**) (Scheme 1), which was converted to the β-chlorovinylaldehyde derivative (**2**) with $POCl_3$/DMF in 94% yield. The chlorovinylimine (**3**) was obtained from the chloroaldehyde (**2**) on refluxing with 7-bromo-1-naphthylamine in 92% yield. The thermal cyclization (250–270°C) of the chlorovinylimine produced the dihydrodibenz[*c*,*h*]acridine derivative (**4**) in 85% yield as the only isolable regioisomer in agreement with our earlier findings.[5,6] The dehydrogenation of **4** with DDQ generated 2,12-dibromodibenz[*c*,*h*]acridine (**5**) in 94% yield. The dibromo derivative was converted to dialdehyde (**6**) by *n*-BuLi/DMF in 84% yield. This was condensed with diethylenetriamine to generate the macrocyclic compound (**7**) in 93% yield. Compound **7** on reduction with $NaBH_4$ in ethanol afforded **8** in 95% yield, which has the correct functionalities to bind the urea molecule.

As urea is insoluble in chloroform, quantitative binding studies were carried out with **8** at 300 K in $CDCl_3$. Binding was evaluated by NMR titration in $CDCl_3$ at 300 K by adding increasing amounts of the guest. The addition of powdered urea to $CDCl_3$ solution of receptor **8** leads to its dissolution and a downfield shift of the receptor NH protons. The binding constant of urea and receptor **8** was found to be 1.5×10^2 M^{-1} as determined by the gravimetric method of Horman.[7] The effect of addition of urea to receptor **7** led to an association constant <10 M^{-1}.

The binding capability of **7** and **8** with urea was not that strong compared with some reported receptors;[1] however, **7** and **8** are not as rigid or complementary to urea. The 3D structure of the compound **8** is absolutely symmetric (Fig. 1), so the formation of a complex with urea with a greater binding constant might be expected. However, DTMM[8] (Desktop Molecular Modeller) energy minimization for the complex clearly showed that the linker portion is tilted to one side (Fig. 2).

Thus, when urea approaches **8** for complexation, it can only do so from the bottom side because of some steric crowding; we presume the reduction of the association constant is a consequence of this.

In summary, we have achieved the first synthesis of new 18-membered macrocyclic ligands based on dibenz[*c*,*h*]-acridine framework incorporating four nitrogen atoms in

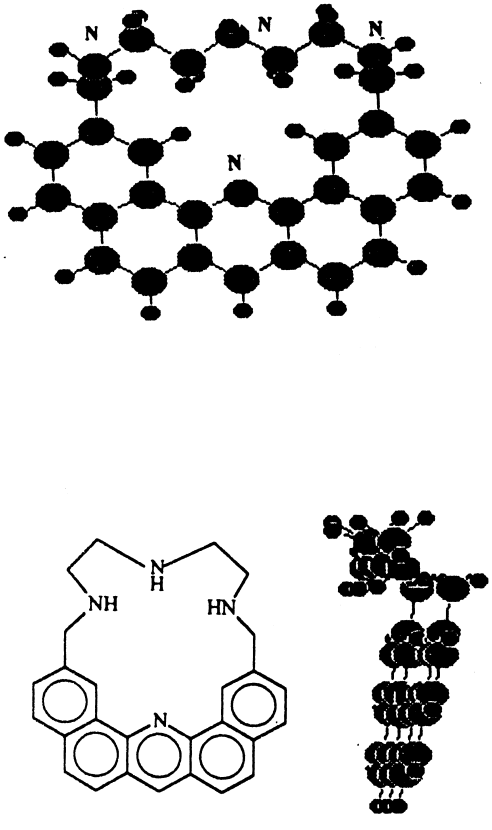

Figure 1.

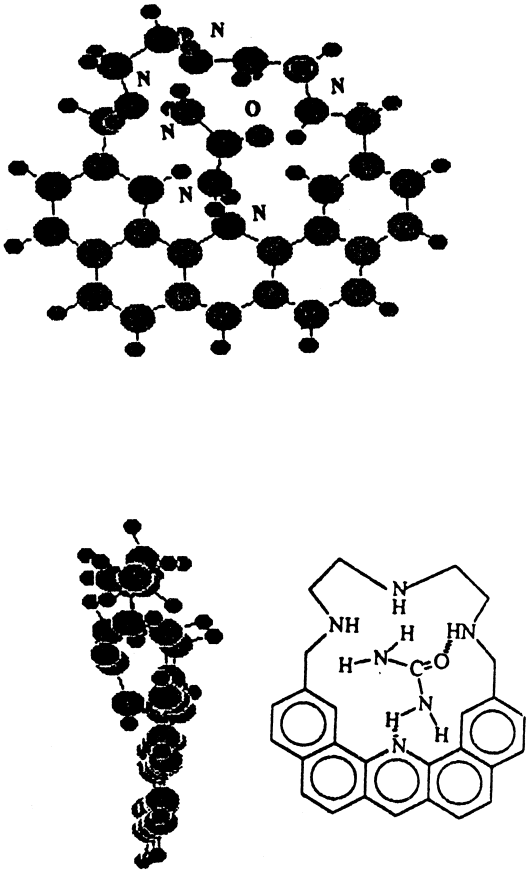

Figure 2.

the macrocyclic cavity, the binding studies show its affinity for urea.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a 200 MHz Bruker machine. Chemical shifts are expressed in ppm using TMS as internal standard. Coupling constant (*J*) values are given in Hz. IR spectra were recorded on a Perkin–Elmer 800 machine. Melting points (uncorrected) were taken in one-side open glass capillaries using a sulphuric acid bath. Elemental analyses have been performed by CDRI, Lucknow (India). Yields of the products are referred to spectroscopically homogeneous substances.

7-Bromo-1-chloro-3,4-dihydronaphthalene-2-aldehyde (2). To an ice cooled solution of DMF (3–4 ml) in trichloroethylene (10 ml), $POCl_3$ (3.5 ml) was added dropwise and stirred at 0–5°C for an additional 10 min. To this solution, a solution of 7-bromo-1-tetralone (6.07 g, 27 mmol) in trichloroethylene (65 ml) was added dropwise, maintaining the temperature at 0–5°C. The mixture was allowed to warm to room temperature gradually over 1 h and then stirred at 60–70°C for 6 h. During this time the colour of the solution changed to deep brown. It was then cooled to room temperature, poured into 100 ml ice cooled 25% NaOAc solution and extracted with dichloromethane. The organic layer was washed successively with brine solution, 5% $NaHCO_3$ solution and finally several times with water. The organic layer was separated, dried (Na_2SO_4) and the solvent removed to afford a yellow coloured residue. It was purified by recrystallization (ether) to afford **2** as a light yellow solid (6.9 g, 94%); mp 93–94°C; ν_{max} (KBr): 1665 cm^{-1}; δ_H ($CDCl_3$) 2.59–2.68 (m, 2H, C*H*$_2$), 2.77–2.85 (m, 2H, C*H*$_2$), 7.09 (d, 1H, *J*=8.0 Hz, H^5), 7.47 (dd, 1H, *J*=1.5 and 8.0 Hz, H^6), 8.0 (brs, 1H, H^8), 10.37 (s, 1H, C*H*O). [Found: C, 48.53; H, 2.79. $C_{11}H_8BrClO$ requires C, 48.62; H, 2.94%].

7-Bromo-1-chloro-2-(7′-bromo-1′-naphthyliminomethyl)-3,4-dihydronaphthalene (3). A mixture of bromochloroaldehyde **2** (800 mg, 2.94 mmol) and 7-bromo-1-naphthylamine (640 mg, 2.88 mmol) was refluxed for 14 h on a water bath in dry benzene (65 ml). The solvent was removed by distillation and 50 ml of fresh dry benzene was added to the reaction mass and refluxing was continued for an additional 6 h. The solvent was evaporated to give a solid mass which was purified by column chromatography (Al_2O_3, pet. ether/benzene 4:1). Crystallization from benzene, pet. ether afforded the pure compound as a bright yellow solid **3** (1.12 gm, 92%), mp 106–107°C; ν_{max} (KBr) 1580, 1637 cm^{-1}; δ_H ($CDCl_3$) 2.87–2.94 (m, 2H, C*H*$_2$), 3.05–3.12 (m, 2H, C*H*$_2$), 7.08–7.14 (m, 2H, H^5,H^{13}), 7.40–7.45 (dd, 1H, *J*=1.9 and 7.4 Hz, H^6), 7.49 (d, 1H, *J*=7.5 Hz, H^{12} or H^{15}), 7.55–7.73 (m, 3H, H^{14}, H^{15} or H^{12}, H^{16}), 7.93 (d, 1H, *J*=1.9 Hz, H^8), 8.50 (d, 1H, *J*=1.6 Hz, H^{18}), 8.96 (s, 1H, N=C*H*); δ_C ($CDCl_3$) 23.74, 26.88, 113.67, 120.05, 120.50, 126.22, 126.27, 126.46, 128.39, 128.95, 129.33, 129.80, 130.15, 132.31, 132.44, 133.80, 134.57, 136.89, 136.92, 147.88, 158.15. [Found: C, 52.85; H, 2.77; N, 2.81. $C_{21}H_{14}NClBr_2$ requires C, 52.99; H, 2.94; N, 2.94%].

2,12-Dibromo-5,6-dihydrodibenz[*c*,*h*]acridine (4). Chlorovinylimine (510 mg, 1.07 mmol) was taken in a 25 ml single neck round bottom flask, fitted with an air condenser and a guard tube. It was then heated at 250–260°C. First the solid melted to an orange oil and at 240–250°C a vigorous exothermic reaction began with liberation of white sublimate. The reaction almost subsided within 5 min. It was kept at 250–260°C for another 15 min, cooled to room temperature, extracted with hot benzene, washed with water, dried (Na_2SO_4) and the solvent evaporated off. The brownish yellow solid thus obtained was purified by column [Al_2O_3, pet. ether/benzene 1:4] to afford a light yellow solid, (400 mg, 85%); mp 211–212°C; δ_H ($CDCl_3$): 2.92–2.96 (m, 2H, C*H*$_2$), 3.07–3.14 (m, 2H, C*H*$_2$), 7.11(d, 1H, *J*=8.0 Hz, H^4), 7.45 (dd, 1H, *J*=2.1 and 8.0 Hz, H^3), 7.56 (d, 1H, *J*=8.8 Hz, H^9), 7.66 (d, 1H, *J*=8.8 Hz, H^8), 7.66–7.80 (m, 2H, H^{10}, H^{11}), 7.85 (s, 1H, H^7), 8.71(d, 1H, *J*=2.1 Hz, H^1), 9.44 (d, 1H, *J*=1.2 Hz, H^{13}). [Found: C, 57.31; H, 2.79; N, 3.07. $C_{21}H_{13}NBr_2$ requires C, 57.40; H, 2.96; N, 3.19%].

2,12-Dibromodibenz[*c*,*h*]acridine (5). To a solution of dihydrodibromo compound **4** (540 mg, 1.23 mmol) in chlorobenzene (70 ml), DDQ (307 mg, 1.35 mmol) was added and refluxed for 20 h. After the usual work up, treatment with charcoal and passing through small column (neutral Al_2O_3/$CHCl_3$) led to a light cream coloured solid. Yield 99%; mp 257–258°C; δ_H ($CDCl_3$) 7.70–7.85 (m, 6H, H^{4-6}, H^{8-10}), 7.83 (dd, 2H, *J*=1.8 and 8.6 Hz, H^3, H^{11}), 8.56 (s, 1H, H^7), 9.68 (d, 2H, *J*=1.8 Hz, H^1, H^{13}). [Found: C, 57.59; H, 2.41; N, 3.09. $C_{21}H_{11}NBr_2$ requires C, 57.67; H, 2.52; N, 3.20%].

2,12-bisformyldibenz[*c*,*h*]acridine (6). To a cooled solution (−78°C) of the fully aromatic dibromide **5** (100 mg, 0.23 mmol) in THF (7 ml) and TMEDA (120 l, 0.8 mmol) under an argon atmosphere was added *n*-BuLi (600 l, 0.8 mmol) over a period of 5 min. The solution first became light red and on continued addition of BuLi turned blood red. The solution was stirred at this temperature for an additional 30 min to ensure the completion of the formation of the anion. Now, DMF (200 l) was added dropwise to the reaction mixture maintaining the same temperature (−78°C). No change in colour was observed. Stirring was continued for 1 h and monitoring by TLC showed the completion of the reaction. After additional stirring for 1 h at this temperature, water (20 ml) was added to the reaction flask. The aqueous layer was extracted with chloroform (2×15 ml) and the combined organic extract was washed well with water, dried (Na_2SO_4) and removal of solvent afforded a sticky dirty yellow solid. This was purified by preparative TLC (benzene/EtAc 4:1) to afford the title compound **6** as an yellow solid (73 mg. 95%); mp 249–250°C; ν_{max} (KBr) 1688, 2851 cm^{-1}; δ_H ($CDCl_3$): 7.85 (d, 2H, *J*=9.0 Hz, H^5, H^9), 7.97 (d, 2H, *J*=9.0 Hz, H^6, H^8), 8.02 (d, 2H, *J*=8.8 Hz, H^4, H^{10}), 8.26 (dd, 2H, *J*=1.4 and 8.8 Hz, H^3, H^{11}), 8.66 (s, 1H, H^7), 10.03 (d, 2H, *J*=1.4 Hz, H^1, H^{13}), 10.44 (s, 2H, C*H*O). [Found: C, 82.32; H, 3.73; N, 4.01. $C_{23}H_{13}O_2N$ requires C, 82.39; H, 3.88; N, 4.18%].

Macrocyclic bisimine derivative (7). The dialdehyde **6** (58 mg, 0.17 mmol) and diethylene triamine (18 mg, 0.17 mmol) were taken together in dry benzene (15 ml) and refluxed for 15 h. The solvent was evaporated to give

compound **7** as a yellow solid (65 mg, 93%); mp >300°C; ν_{max} (KBr) 1610, 1632, 3411–3811 (br) cm^{-1}; δ_H ($CDCl_3$) 2.21–2.26 (brs, 1H, N*H*), 3.11 (t, 4H, *J*=4.8 Hz, CH_2–NH), 4.02 (t, 4H, *J*=4.8 Hz, CH_2–N=), 7.72–7.83 (m, 6H, H^{4-6}, H^{8-10}), 7.90 (d, 2H, *J*=8.0 Hz, H^3, H^{11}), 8.52 (s, 1H, H^7), 8.63 (s, 2H, H^1, H^{13}), 10.59 (s, 2H, C*H*=N); δ_C ($CDCl_3$) 50.30, 57.91, 78.34, 112.30, 124.85, 126.13, 126.65, 127.36, 129.27, 130.72, 133.82, 134.4, 144.88, 160.03. [Found: C, 80.66; H, 5.17; N, 13.88. $C_{27}H_{21}N_4$ requires C, 80.79; H, 5.24; N, 13.97%].

Macrocycle (8). To a stirred suspension of compound **7** (76 mg, 0.2 mmol) in 10 ml of ethanol, $NaBH_4$ (30 mg, 0.8 mmol) was added portionwise. After the addition was over the reaction was stirred at room temperature for 12 h. Ethanol was removed under reduced pressure, the residue was diluted with water and extracted with chloroform. The organic layer was washed thoroughly with water, dried (Na_2SO_4) and removal of solvent under reduced pressure afforded the title compound **8** (73 mg, 95%); mp 181–182°C; δ_H ($CDCl_3$) 1.70–2.15 (br, 3H, N*H*), 2.93 (t, 4H, *J*=5.2 Hz, CH_2), 3.07 (t, 4H, *J*=5.2 Hz, CH_2), 4.22 (brs, 4H, ArCH_2), 7.55 (dd, 2H), 7.75–7.85 (m, 4H), 7.86 (d, 2H, *J*=8.1 Hz), 8.60 (s, 1H, H^7), 9.99 (brs, 2H, H^1, H^{13}). [Found: C, 80.33; H, 5.66; N, 13.76. $C_{27}H_{23}N_4$ requires C, 80.40; H, 5.70; N, 13.90%].

Acknowledgements

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