Supplementary Material for Organic & Biomolecular Chemistry

Steric and electronic factors influencing recognition by a simple, charge neutral norbornene based anion receptors

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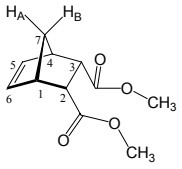
Supplementary Information

Syntheses

endo-Dimethyl noborna-5-ene-2,3-dicarboxylate (3)

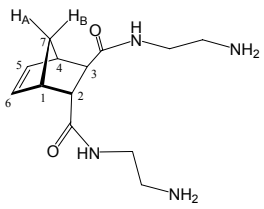


Freshly cracked cyclopentadiene (1.837 g, 27.79 mmol) was added drop-wise with stirring to dimethyl maleate (4.006 g, 27.79 mmol). This reaction mixture was stirred under nitrogen for 8 h, a water bath was used to maintain room temperature throughout the exothermic reaction. TLC indicated complete consumption of the starting materials and the formation of a single pure product (R_f = 0.41, 35 % ethyl acetate/40-60 °C petroleum spirits) as a clear oil in a quantitative yield (5.842 g, 100.0 %). No further purification was required for subsequent steps.

^{1}H ($CDCl_3$, 270 MHz) δ (ppm): 1.33 (1H, d, *J* = 6.9 Hz, H 7_A); 1.44 (1H, d, *J* = 6.9 Hz, H 7_B); 3.12 (2H, t, *J* = 1.6 Hz, H 2, 3); 3.26 (2H, t, *J* = 1.6 Hz, H 1, 4); 3.58 (6H, s, CH_3); 6.23 (2H, t, *J* = 1.0 Hz, H 5, 6)
^{13}C ($CDCl_3$ 270 MHz) δ (ppm): 46.3, 48.1, 51.6, 135.0, 138.0, 172.9.

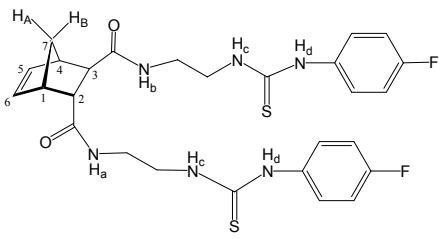
LRMS: calc for $C_{11}H_{14}O_4 + H^+$ = 211.1, found 211.2

Bicyclo[2.2.1]hept-5-ene-*endo*-2,*exo*-3 bis-[(2-amino-ethyl)-amide] (4)



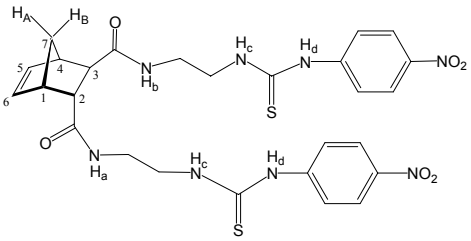
A solution of *endo*-dimethyl norborna-5-ene-2,3-dicarboxylate **3** (550 mg, 2.62 mmol) in neat ethylenediamine (3.0 ml, 45 mmol) was prepared in a 25 ml round-bottomed flask equipped with a reflux condenser. Following stirring at 100 °C for 18 h, excess ethylenediamine was removed under reduced pressure to yield 682 mg (97.9 %) of an extremely viscous orange/brown oil. This material was not purified further and was used directly in the following steps.

Bicyclo[2.2.1]hept-5-ene-*endo*-2,*exo*-3 bis-({2-[3-(4-fluoro-phenyl)-thioureido]-ethyl}-amide (1)



To a solution of bicyclo[2.2.1]hept-5-ene-*endo*-2,*exo*-3 bis-[(2-amino-ethyl)-amide] **4** (500 mg, 1.88 mmol) in dry $CHCl_3$ (3.0 ml), 4-fluorophenyl isothiocyanate (719 mg, 4.69 mmol) was added in a single portion. This reaction mixture was stirred under nitrogen, at room temperature for 24 h before removal of excess solvent under reduced pressure resulted in a crude yellow solid. The crude product was purified by chromatography (10 % iso-propanol/ethyl acetate, R_f = 0.61) to yield 665 mg (68.7 %) of a white powdery solid.
MP: 93.2-95.3 °C
^{1}H (DMSO, 400 MHz) δ (ppm): 1.21 (1H, d, *J* = 4.7 Hz, H 7_A); 1.68 (1H, d, *J* = 5.3 Hz, H 7_B); 2.54 (1H, s, H 3); 2.84 (1H, s, H 4); 3.16 (2H, s, H 1, 2); 3.22 (2H, m, CH_2); 3.34 (2H, m, CH_2); 3.51 (4H, m (b), CH_2); 5.95 (1H, t, *J* = 2.2 Hz, H 6); 6.18 (1H, t, *J* = 2.1 Hz, H 5); 7.15 (4H, m, ArH); 7.36 (4H, m, ArH); 7.68 (2H, b, Hc); 7.87 (1H, t, *J* = 3.3 Hz, Ha); 8.07 (1H, t, *J* = 3.4 Hz, Hb); 9.58 (2H, b, Hd)
^{13}C (DMSO 400 MHz) δ (ppm): 44.3, 46.2, 47.0, 47.4, 48.1, 49.6, 115.7, 116.0, 126.5, 135.2, 135.8, 137.8, 157.9, 161.4, 173.1, 174.5, 181.4
LRMS: calc for $C_{27}H_{30}O_2N_6S_2F_2 + H^+$ = 573.2, found 573.5
HRMS: calc for $C_{27}H_{30}O_2N_6S_2F_2 + H^+$ = 573.1919, found 573.1918

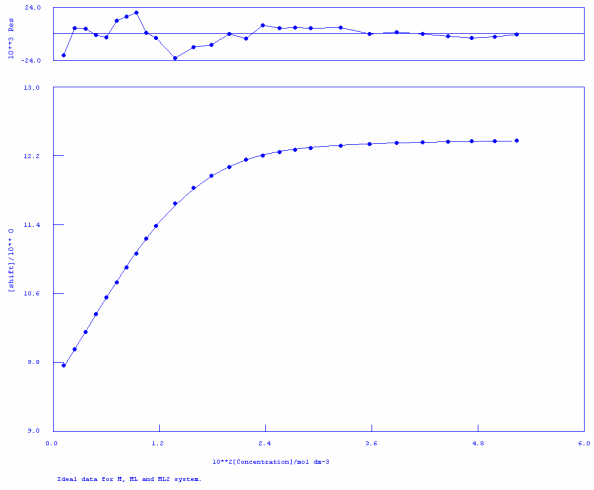
Bicyclo[2.2.1]hept-5-ene-*endo*-2,*exo*-3 bis-({2-[3-(4-nitro-phenyl)-thioureido]-ethyl}-amide) (2)



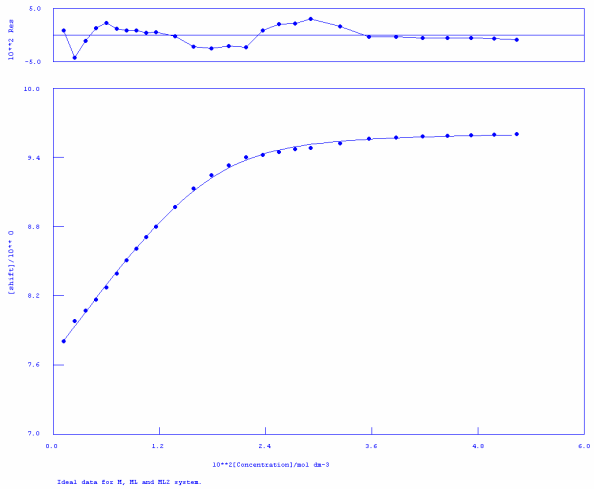
To a solution of bicyclo[2.2.1]hept-5-ene-*endo*-2,*exo*-3 bis-[(2-amino-ethyl)-amide] **4** (701 mg, 2.63 mmol) in dry $CHCl_3$ (5.0 ml), 4-nitrophenyl isothiocyanate (1.008 g, 5.59 mmol) was added in a single portion. This reaction mixture was stirred under nitrogen, at room temperature for 24 h before removal of excess solvent under reduced pressure resulted in the crude orange product. The crude product was purified by chromatography (10 % methanol/ethyl acetate, $R_f = 0.35$) to yield 786 mg (47.7 %) of a yellow powdery solid.
MP: 127.6-129.4 °C
^{1}H (DMSO, 400 MHz) δ (ppm): 1.21 (1H, d, $J = 5.2$ Hz, H 7_A); 1.69 (1H, d, $J = 5.1$ Hz, H 7_B); 2.53 (1H, s, H 3); 2.87 (1H, s, H 4); 3.19 (2H, s, H 1, 2); 3.28 (2H, m, CH_2); 3.32 (2H, m, CH_2); 3.57 (4H, m (b), CH_2); 5.97 (1H, t, $J = 1.7$ Hz, H 6); 6.19 (1H, t, $J = 1.5$ Hz, H 5); 7.79 (4H, d, $J = 5.4$ Hz, ArH); 7.94 (1H, s, Ha); 8.13 (1H, s, Hb); 8.17 (4H, d, $J = 5.6$ ArH); 8.28 (2H, b, Hc) 10.24 (2H, b, Hd)
^{13}C (DMSO 400 MHz) δ (ppm): 14.7, 21.4, 44.5, 46.4, 47.1, 48.5, 49.1, 60.6, 121.8, 125.8, 135.9, 138.6, 143.2, 147.5, 174.1, 175.5, 181.8
LRMS: calc for $C_{27}H_{30}O_6N_8S_2 + H^+ = 627.2$, found 627.4
HRMS: calc for $C_{27}H_{30}O_6N_8S_2 + H^+ = 627.1803$, found 627.1809

Binding Studies

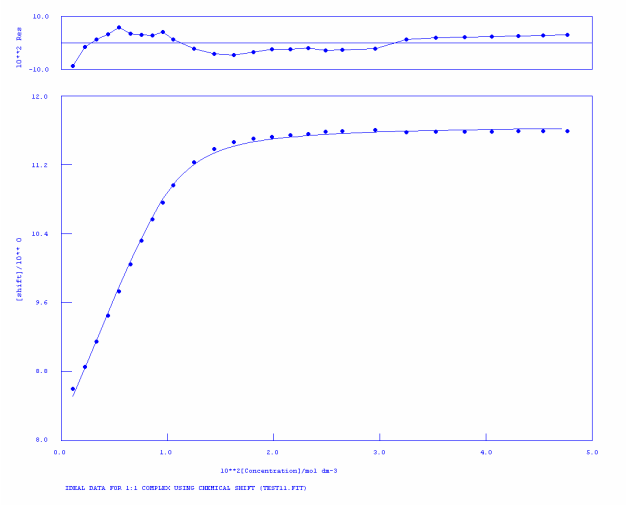
Fit Plots



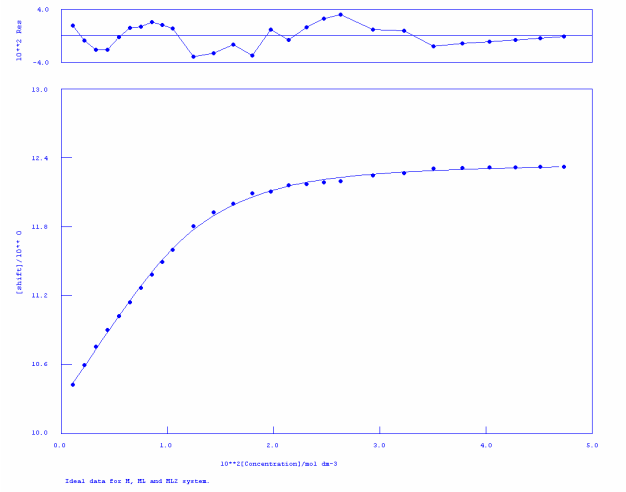
Receptor 1-AcO^- (Hc) 1:2 model
K1 = 5990.89 Error = 378.0 (6.31 %)
Log K1 = 3.78
B2 = 3322600 Error = 27780 (0.84 %)
K2 = 554.609
Log K2 = 2.74



Receptor 1-$H_2PO_4^-$ (Hc) 1:2 model
K1 = 4258.82 Error = 553.2 (12.99 %)
Log K1 = 3.63
B2 = 1958170 Error = 31390 (1.60 %)
K2 = 459.79
Log K2 = 2.66



Receptor 2-AcO^- (Hc) 1:1 model
K1 = 1880.38 Error = 148.8 (7.91 %)
Log K1 = 3.27



Receptor 2-$H_2PO_4^-$ (Hc) 1:2 model
K1 = 1387.73 Error = 154.1 (11.10 %)
Log K1 = 3.14
B2 = 609591Error = 19620 (3.22 %)
K2 = 439.27
Log K2 = 2.64

Job Plots

Note: for all job plots the [Total] = ([H]+[G]) was kept constant at 12.5 mM.