Thermochimica Acta 503–504 (2010) 28–32

Contents lists available at ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Calorimeteric and NMR binding studies of hydrogen-bonding receptors for carboxylates

Mohammad H. Al-Sayah [a,*], Neil R. Branda [b]

[a] Department of Biology and Chemistry, American University of Sharjah, PO Box 26666, Sharjah, United Arab Emirates
[b] Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia, V5A 1S6 Canada

ARTICLE INFO

Article history:
Received 2 February 2010
Received in revised form 25 February 2010
Accepted 1 March 2010
Available online 6 March 2010

Keywords:
Anion binding
Synthetic receptors
NMR titrations
ITC titrations
Squaramide

ABSTRACT

Two receptors (**1** and **2**) were designed and prepared to bind carboxylate anions through donor–donor hydrogen-bonding motifs provided by thiourea (**1**) and squaramide (**2**) groups. The binding efficacy of each receptor was studied using NMR and isothermal calorimetric titrations in DMSO and $CH_3CN/CHCl_3$ solvent systems. Binding constants and changes in enthalpy and entropy of the binding process were calculated and evaluated.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Non-covalent interactions play an important role in a wide range of biological recognition processes such as molecular transport, antigen–antibody interactions, enzymatic reactions and cellular recognition [1–3]. One of the most versatile of these non-covalent interactions is the hydrogen bond, which provides the recognition basis of a substrate by its receptor and ensures high level of selectivity of the active site. Although an individual hydrogen bond is accompanied by small changes in energy, they are vital for the binding process. For example, bacteria can resist powerful antibiotics, such as vancomycin, by replacing an amide group in the peptide with an ester [4]. This elimination of a single hydrogen bond is enough to render the binding of vancomycin to the bacteria too weak to be an efficient drug. Besides, the strength of a hydrogen bond is greatly affected by the solvent. The stability of a hydrogen-bonded complex is usually highest in non-polar organic solvents and lower in solvents that can act either as a hydrogen bond donor or acceptor, such as water [5,6]. In general, in order for the receptor and the substrate to form a stable intermolecular complex, solvation of the receptor–substrate complex should be favored over that of the associating species.

One approach to understanding the bimolecular hydrogen-bonding association of biological systems pivots on the design and synthesis of small-molecule receptors, which can recognize and bind a substrate using hydrogen bonding. Non-covalent interactions, including hydrogen bonding, between organic molecules have been the focus of several studies during the last years [7–20]. Previously, we have reported the design, synthesis and binding investigations of several hydrogen-bonding receptors for barbiturates [21], uracils [22,23] and carboxylates [22,24]. In this report, we present two receptors designed to bind carboxylates through donor–donor hydrogen bond recognition sites. This binding motif is provided by thiourea [7–16] and squaramide [17–20] scaffolds in receptors **1** and **2**, respectively (Fig. 1). The receptors were prepared in good yields in one step from 6-aminomethyl-6′-methyl-2,2′-bipyridine (**3**) [22,23,25] (Scheme 1) using adapted procedures. Thiourea receptor **1** was obtained in 78% yield by the addition of 0.5 equivalents of thiophosgene to amine **3** in CH_2Cl_2. Meanwhile, squaramide receptor **2** was prepared in 82% yield by the reaction of amine **3** with diethyl squarate in ethanol.

2. Experimental

2.1. General information

All solvents (Caledonia) for synthesis and purification were used as received including solvents used for NMR analysis (Cambridge Isotope Laboratories). All reagents and starting materials were purchased from Aldrich Organics. ^{1}H NMR characterizations were performed on a Varian Inova-300 instrument, working at 299.96 MHz. Chemical shifts (δ) are reported in parts per million

* Corresponding author. Tel.: +97165152426; fax: +97165152450.
E-mail address: malsayah@aus.edu (M.H. Al-Sayah).

0040-6031/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.tca.2010.03.003

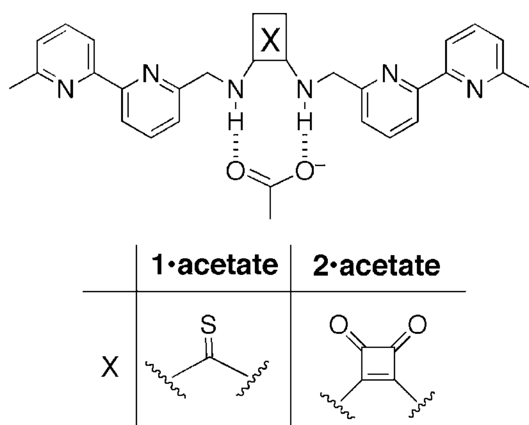


Fig. 1. Representation of hydrogen-bonding complexation of the receptors with the acetate ion.

relative to tetramethylsilane using the residual solvent peak as a reference standard. Coupling constants (*J*) are reported in hertz. ^{13}C NMR characterizations were performed on a Bruker-300 instrument, working at 74.99 MHz or a Varian Inova-500 instrument, working at 125.29 MHz. FT-IR measurements were performed using a Nicolet Magna-IR 750. Mass spectrometry measurements were performed a Kratos MS-50 with an electron impact source or by positive mode electrospray ionization on a Micromass ZabSpec Hybrid Sector-TOF. Data acquisition and processing was achieved by using the OPUS software package on a Digital Alpha station with VMS operating system.

2.2. General procedure of ^{1}H NMR titration experiments

A solution of the receptor (**1** or **2**) at a concentration between 2 and 5 mM was prepared in an appropriate deuterated solvent. A measured amount (500–600 μL) of this solution was immediately transferred into an NMR tube fitted with a rubber septum to minimize the evaporation of the solvent. A solution of the guest (tetrabutylammonium (TBA) acetate) at a concentration of 20–100 mM was prepared in the same solvent. The guest solution was prepared in a vial fitted with a controlled seal or a septum to minimize the evaporation of the solvent. Aliquot amounts of the guest solution were added to the NMR tube through the rubber septum via a syringe. The number of additions varied between 25 and 30 with an increase in the amount of guest solution added until a total of 10 equivalents of the guest was attained. A ^{1}H NMR spectrum was recorded after each addition. The chemical shift of the protons associated with the recognition process was recorded after each ^{1}H NMR spectrum was run. The collected data was analyzed using a non-linear least square regression program (kindly provided by Dr. Christopher A. Hunter Department of Chemistry, University of Sheffield, UK) to fit the data to a theoretical model for the binding process by programs.

2.3. General procedure of isothermal titration calorimeter (ITC) experiments

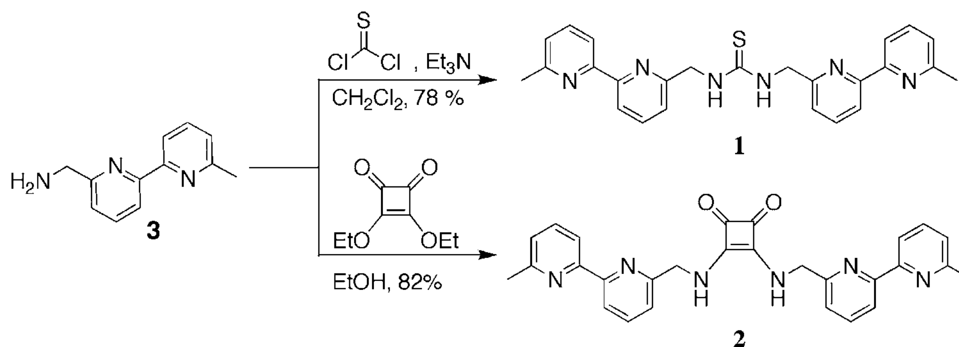
All of the calorimetric binding experiments were performed using an isothermal titration calorimeter (ITC) from MicroCal Inc. In a typical experiment a 5 mM receptor solution was added to the calorimetry cell (1.47 mL). A 100 mM solution of the substrate was introduced in fifty 5 μL injections, for a total of 250 μL added substrate. The solution was continuously stirred to ensure rapid mixing and kept at an operating temperature of 25 °C through the combination of an external cooling bath (at 18 °C) and an internal heater. Dilution effects were determined by a second experiment adding the same guest solution into pure solvent and subtracting this data from the raw titration data to produce the final binding isotherm. Association parameters were calculated by applying a one-site model using the Origin® software. These methods rely on standard non-linear least square regression to fit the titration curves, taking into account the change in observable volume that occurs during the calorimetric titration. In some cases, where the complex formed has weak association, the stoichiometry of the binding was fixed at one equivalent in the binding analysis.

2.4. N,N′-bis(6′-methyl-2,2′-bipyridin-6-yl)thiourea (**1**)

Thiophosgene (59 mg, 0.5 mmol) was added to a solution of 6-aminomethyl-6′-methyl-2,2′-bipyridine (300 mg, 1.5 mmol) and triethylamine (155 mg, 1.5 mmol) in dry CH_2Cl_2 (30 mL) at room temperature. The solution was stirred for 2 h at room temperature under argon. The mixture was then washed with water (3 × 10 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under vacuum to afford a yellow residue. The product was isolated from the residue by flash chromatography (alumina, 1% MeOH in $CHCl_3$) (0.26 g, 78%). M.p. > 128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (t, *J* = 6 Hz, 2H), 8.26 (d, *J* = 8 Hz, 2H), 7.87 (t, *J* = 7 Hz, 2H), 7.78 (t, *J* = 7 Hz, 2H), 7.38 (d, *J* = 7 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 4.89 (br, s, 4H), 2.55 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.3, 158.0, 155.8, 155.1, 154.9, 137.9, 137.0, 123.4, 121.9, 120.1, 118.0, 49.7, 24.6; FT-IR (cast) ν 3247, 3060, 1706, 1572, 1439, 1364, 1263, 1152, 1108, 1082, 991, 956, 783, 753, 663 s, 634 cm^{-1}; HRMS (ES) *m*/*z*: 441.1857 [M+H]$^+$, $C_{25}H_{25}N_6S$; calculated 441.1861 [M+H]$^+$, $C_{25}H_{25}N_6S$.

2.5. 3,4-Bis[(6′-methyl-2,2′-bipyridin-6-yl)amino]cyclobut-3-ene-1,2-dione (**2**)

A mixture of diethyl squarate (0.20 mg, 1.2 mmol) and 6-aminomethyl-6′-methyl-2,2′-bipyridine (0.50 mg, 2.5 mmol) in ethanol (20 mL) was stirred at room temperature for 24 h. The solvent was then evaporated under vacuum to afford a yellow residue.



Scheme 1.

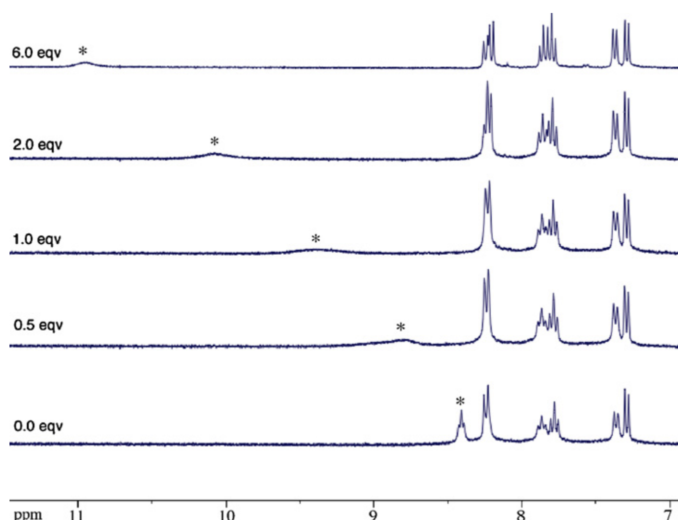


Fig. 2. Partial ^{1}H NMR spectra of receptor **1** (5 mM) upon titrating with TBA acetate (100 mM) in DMSO-d_6. The signal corresponding to thiourea N–H protons is denoted by (*).

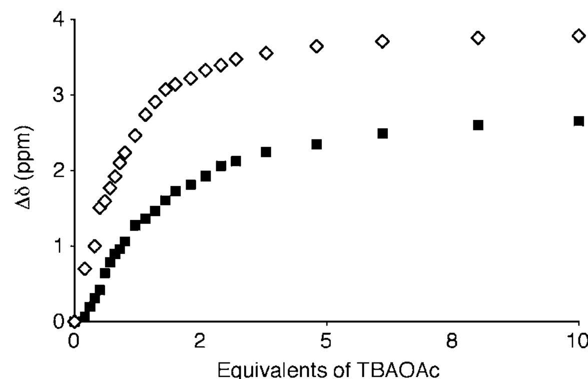


Fig. 3. Titration curves of receptor **1** (5 mM) with TBA acetate (100 mM) in DMSO-d_6 (◊) and in 1:1 $CDCl_3/CD_3CN$ (■).

The product was isolated for the residue by column chromatography (alumina, 1% MeOH in $CHCl_3$) (0.48 g, 82%). M.p. > 160 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 2H), 7.59 (d, J = 8 Hz, 2H), 7.71 (t, J = 8 Hz, 2H), 7.42 (t, J = 8 Hz, 2H), 7.25 (d, J = 7 Hz, 2H), 7.03 (d, J = 7 Hz, 2H), 4.87 (d, J = 7 Hz, 2H), 2.54 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 183.7, 168.9, 158.2, 156.3, 155.0, 138.2, 137.1, 123.6, 122.2, 120.5, 118.2, 49.4, 24.8; FT-IR (microscope) ν 3252, 3002, 1797, 1666, 1580, 1537, 1439, 1388, 1350, 1243, 1151, 1082, 992, 783, 752, 665, 634, 584 cm^{-1}; HRMS (ES) m/z: 477.2033 [M+H]$^+$, $C_{28}H_{25}N_6O_2$; calculated 477.2039 [M+H]$^+$, $C_{28}H_{25}N_6O_2$

3. Results and discussion

The binding efficacy of **1** and **2** as receptors for carboxylate anions was evaluated using NMR and isothermal calorimetric titrations. In the former technique, the change in the chemical shift of the N–H protons upon the formation of a hydrogen-bonding complex was monitored as the substrate was added to the receptor. Proton NMR spectrum of **1** in DMSO-d_6 (5 mM) showed well-resolved signals for the aromatic protons with the signal corresponding to the N–H protons of the thiourea group appearing at 8.42 ppm (Fig. 2). As acetate anion was added (as a solution of tetrabutylammonium (TBA) acetate), the signal of N–H protons shifted significantly downfield ($\Delta\delta$ about 2 ppm) indicating the formation of effective hydrogen bonding between the substrate and the receptor. Besides, the signal became broader as more acetate anions were added due to increased chemical exchange upon hydrogen bonding. After the addition of 4–5 equivalents of the acetate ion, the observable shift of the signal corresponding to the N–H protons of the thiourea receptor was insignificant. This observation implies that the receptor had reached saturation where the signal for the N–H protons reached 11.10 ppm after 10 equivalents of the acetate were added. The obtained titration curve was fitted to 1:1 binding model giving an association constant K_a of 241 ± 35 M^{-1}.

The ^{1}H NMR titration of the thiourea receptor **1** with TBA acetate (100 mM) was also conducted in $CD_3CN/CDCl_3$ (1:1) to determine the extent of the solvent effect on the affinity of the receptor for its substrate. A 5 mM solution of thiourea receptor **1** in $CD_3CN/CDCl_3$ (1:1) was treated with aliquot amounts of TBA acetate (100 mM) in the same solvent. Before the addition of the acetate, the chemical shift corresponding to the N–H protons of the receptor appeared at 6.82 ppm as a very broad signal. As the acetate was added, the signal became sharper and its chemical shift moved significantly downfield ($\Delta\delta$ about 4 ppm) indicating the formation of effective hydrogen bonding between the substrate and the receptor. After the addition of ~1 equivalent of the acetate, the observable shift of the signal corresponding to the N–H protons of the thiourea receptor became insignificant, implying that the receptor had reached saturation. After 10 equivalents of the acetate were added the signal for the N–H protons reached 10.63 ppm. The obtained titration curve (Fig. 3) was fitted to 1:1 binding model giving an association constant K_a of 5790 M^{-1}. This value indicates that the hydrogen-bonded complex **1**·acetate is more stable in a 1:1 mixture of chloroform and acetonitrile than it is in DMSO. This reflects the negative effect this highly polar solvent has on hydrogen-bonding complexation due to the competitive association of the solvent with the receptor.

The binding of receptor **2** was also studied by ^{1}H NMR titration in $CD_3CN/CDCl_3$ (1:1) where the change in the chemical shift of the N–H peaks of the squaramide (5 mM) was monitored as TBA acetate (100 mM) was added in the same solvent. Before the addition of the acetate, the signal for the N–H protons of the receptor appeared at ~6.90 ppm as a broad peak overlapping with two aromatic signals (Fig. 4). As the acetate was added, the signal of the N–H protons shifted significantly downfield ($\Delta\delta$ about 4 ppm) indicating a strong association of the squaramide receptor **2** with the acetate guest. The receptor reached saturation after ~1 equivalent of the substrate was added where there was insignificant change in the chemical shift of the N–H protons signal reaching 10.66 ppm after the addition of a total of 10 equivalents of the acetate ion. It was also observed that at saturation, the signals corresponding

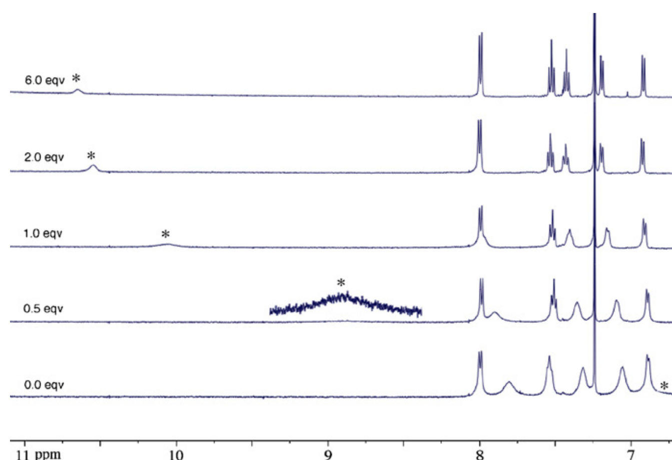


Fig. 4. Partial ^{1}H NMR spectra of receptor **2** (5 mM) upon titrating with TBA acetate (100 mM) in 1:1 $CDCl_3/CD_3CN$. The signal corresponding to the squaramide N–H protons is denoted by (*).

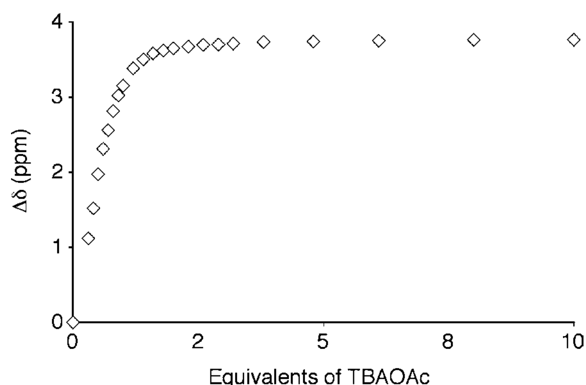


Fig. 5. Titration curve of squaramide receptor **2** (5 mM) with TBA acetate (100 mM) in 1:1 $CDCl_3/CD_3CN$ (◇).

to the bipyridine protons were sharper than before the addition of the acetate ion. This observation was attributed to the limited rotation around the squaramide C–N bonds imposed by the hydrogen bonding of the receptor to the N–H protons. The association constant was calculated to be 7390 M^{-1} when the titration curve (Fig. 5) was fitted to a 1:1 binding model.

The binding activities of receptors **1** and **2** were also studied by calorimetric titration experiments using an isothermal titration calorimeter. In each case, the heat absorbed or released upon the formation of a hydrogen-bonding complex was monitored as the substrate was added to the receptor cell. A 100 mM solution (DMSO) of TBA acetate was injected into a microcalorimetric cell containing a 5 mM solution of receptor **1** at 25 °C. The heat evolved with each injection is displayed versus the time in the top panel of Fig. 6. The first series of injections usually deviate from ideal binding behavior due to the presence of the receptor in large excess compared to the substrate. The heat evolved in the initial injections produced larger signals due to significant complexation of the added substrate with the receptor. As the titration proceeded, the signal diminished due to the decrease in the concentration of unbound receptor. However, even after the addition of significant amount the substrate, the heat evolved was still significant indicating large heat of dilution of the injected TABOAc solution. This is explained by the strong ability of DMSO to solvate organic salts due to its large dielectric constant. Therefore, the binding isotherm for this titration was generated by subtracting the heat of dilution of TBA acetate solution (calculated from separate titration of the injectant into blank solvent) from the generated heat due to the binding process. The resulting curve (depicted in bottom panel of Fig. 6 by (◯)) correlated well with a one-site binding model giving a K_a value of $191 \pm 13\ M^{-1}$, a ΔH value of -505 ± 16 cal mol^{-1} and a ΔS value of 8.7 cal $mol^{-1}\ K^{-1}$.

The observed negative enthalpy suggests that **1**·acetate complex is stabilized by strong hydrogen bonding between the receptor and the substrate. This exothermic nature of the association indicates that the hydrogen bonds that are formed upon receptor–substrate complexation are stronger than those initially formed to the solvent (DMSO), which can engage in hydrogen bonding itself. The association is also driven by positive entropy, suggesting that the energy gained by the release of solvent from the binding sites is more than the energy lost through bimolecular association and the freezing of bond rotations that occur upon formation of the **1**·acetate complex. Therefore, the association of thiourea receptor **1** and the acetate ion is both enthalpy and entropy driven (Table 1).

The squaramide scaffold of receptor **2** provides another donor–donor hydrogen-bonding site suitable for binding of carboxylates and its binding activity was also studied using isothermal calorimetery. A solution of TBA acetate (100 mM) in 1:1 mixture of $CH_3CN/CHCl_3$ was injected into a solution of receptor 2 (5 mM) in

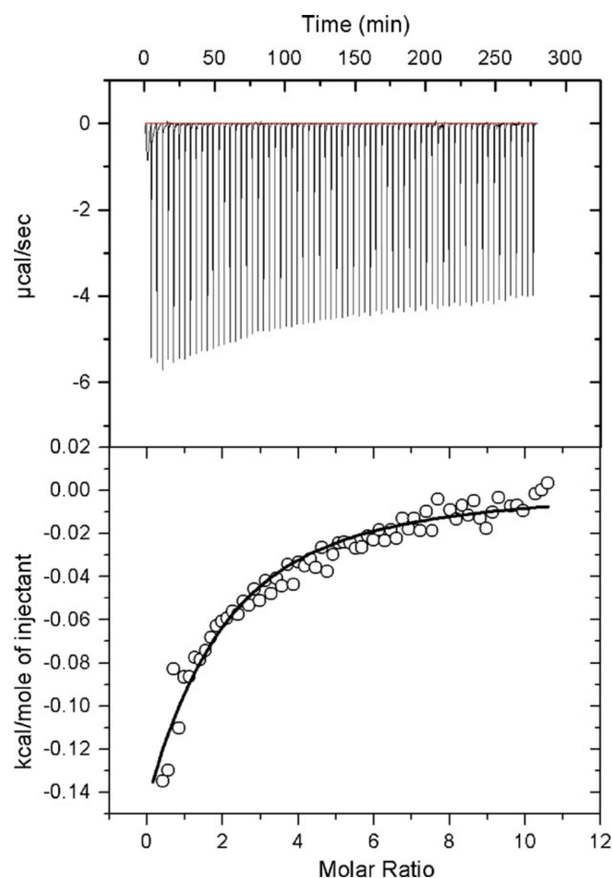


Fig. 6. Calorimetric titration of receptor **1** (5 mM) with TBA acetate (100 mM) in DMSO at 25.0 °C. Top panel: raw data showing heat evolved with each injection of the acetate ion. Bottom panel: integrated curve of the raw titration (◯); the solid line represents a non-linear least squares fit using 1:1 binding model. The heat evolved due to the dilution of the injected substrate was measured by a separate titration where a solution of TBA acetate (100 mM in DMSO) was injected into blank DMSO. The heat evolved from the blank titration was subtracted from the binding isothermal curve for receptor **1** before the fitting analysis. Also, the integrated value of the first few injections were not considered (removed) in the fitting analysis because of the reasons mentioned above.

the same solvent. The heat evolved with each injection is displayed versus the time in the top panel in Fig. 7. Once again, the first series of injections deviated from ideal binding behavior due to the presence of the squaramide receptor **2** in large excess compared to the substrate. The binding isotherm was generated by integrating the area under each peak and plotting the resulting data versus molar ratio of the acetate substrate (Fig. 7, bottom panel (◯)). The heat evolved in the initial injections produced larger signals due to the complete complexation of the added acetate substrate but as titration proceeded, the signal became smaller due to the saturation of receptor **2** by the acetate substrate. The heat produced at saturation is due to the dilution of the acetate substrate. However, the heat of dilution of TBA acetate in $CH_3CN/CHCl_3$ was less than that in DMSO due to the lower association of the non-polar solvent-mixture ($CH_3CN/CHCl_3$) with the organic salt. The fitting of this curve to a one-site binding model receptor (the solid line in the bottom panel, Fig. 7) gave a K_a value of $7336 \pm 416\ M^{-1}$. Similar to **1**, the values (Table 1) of ΔH and ΔS for **2** indicate that the binding is also enthalpically and entropically favored. However, the greater negative enthalpy for the formation **2**·acetate complex in $CH_3CN/CHCl_3$ as compared **1**·acetate complex in DMSO is greatly due to the solvent effect. DMSO is more involved in hydrogen bonding with the receptor as compared to CH_3CN or $CHCl_3$. Thus, the greater exothermic nature of the association is due to stronger hydrogen bonds

Table 1
The results of the isothermal titration calorimetry (T = 25.0 °C).

Receptor	Solvent	n^a	K_a (M^{-1})	ΔH (cal mol^{-1})	ΔS (cal mol^{-1} K^{-1})
1	DMSO	1.00[b]	191 ± 13	−505 ± 16	8.7
2	$CH_3CN/CHCl_3$	1.12	7336 ± 416	−2209 ± 54	10.3

[a] The stoichiometry of the binding; ratio of substrate to receptor.
[b] This was fixed at one equivalent in the binding analysis.

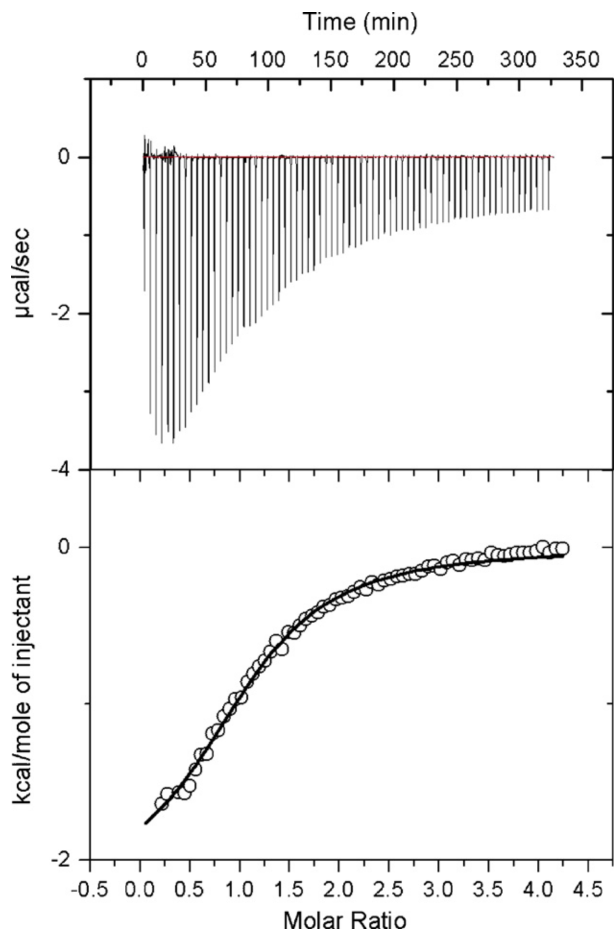


Fig. 7. Calorimetric titration of receptor **2** (5 mM) with TBA acetate (100 mM) in 1:1 mixture of $CH_3CN/CHCl_3$ at 25.0 °C. Top panel: raw data showing heat evolved with each injection of the acetate. Bottom panel: integrated curve of the raw titration; the solid line represents a non-linear least squares fit using 1:1 binding model. The heat evolved due to the dilution of the injected substrate was evaluated by taking the average value of the heat produced in the last 25 injections. This value was then subtracted from the isothermal curve before the fitting analysis. The data points corresponding to the heat produced by the first few injections were removed from the curve.

that are formed upon **2**·acetate complexation than those initially formed to the solvent ($CH_3CN/CHCl_3$). Besides, the association is also driven by positive entropy as energy is gained by the release of low-polarity solvents from the binding sites. This energy is greater for $CH_3CN/CHCl_3$ than DMSO as the latter has a better ability to solvate charged species due to its high dielectric constant.

4. Conclusions

The binding studies of **1** and **2** have shown that both thiourea and squaramide scaffolds provide suitable hydrogen-bonding motifs for binding carboxylates with similar affinities. Thiourea and squaramide receptors were effective receptors for carboxylates with comparable association constants in same solvents. For both receptors, the solvent played crucial role in the receptor–substrate binding process where hydrogen-bonding complexation was favored in non-polar organic solvents. The competition of the substrate with the polar solvent (DMSO) for the binding sites of **1** and **2** made receptor–substrate association more difficult and resulted in lower binding affinities. ITC experiments have shown that the binding of both receptors was enthalpy and entropy driven. Enthalpic effects are the result of energy gained from attraction between the receptor and its guest which overcame the solvation energy of the substrate. Meanwhile, favorable entropy was observed since the receptor-substrate binding is associated with the liberation of solvent from the binding surfaces. This entropically favorable event compensated for the entropy loss associated with the decrease in rotational and translational degrees of freedom and the immobilization of the substrate to the receptor that occur upon molecular assembly.

References

[1] D.E. Metzler, Biochemistry. The Chemical Reactions of Living Cells, vol. 1–2, Academic Press, New York, 1977.
[2] J.C. Paulson, in: P.M. Conn (Ed.), The Receptors, vol. 2, Academic Press, New York, 1985.
[3] A.L. Lehninger, Principles of Biochemistry, vol. 1, Worth Publishers, Inc., 1982.
[4] P.D. Beer, P.A. Gale, D.K. Smith, Supramolecular Chemistry, Oxford University Press Inc., New York, 1999.
[5] J.C. Adrian Jr., C.S. Wilcox, J. Am. Chem. Soc. 113 (1991) 678–680.
[6] B.R. Linton, M.S. Goodman, E. Fan, S.A. van Arman, A.D. Hamilton, J. Org. Chem. 66 (2001) 7313–7319.
[7] A.M. Costero, P. Gavina, G.M.R.-M. Salvador Gil, Tetrahedron 62 (2006) 8571–8577.
[8] L. Fang, W.-H. Chan, Y.-B. He, D.W.J. Kwong, A.W.M. Lee, J. Org. Chem. 70 (2005) 7640–7646.
[9] T. Gunnlaugsson, H.D.P. Ali, M. Glynn, P.E. Kruger, G.M. Hussey, F.M. Pfeffer, C.M.G. Santos, J. Tierney, J. Fluoresc. 15 (2005) 287–299.
[10] D.E. Gomez, L. Fabbrizzi, M. Licchelli, E. Monzani, Org. Biomol. Chem. 3 (2005) 1495–1500.
[11] T. Gunnlaugsson, A.P. Davis, J.E. O'Brien, M. Glynn, Org. Biomol. Chem. 3 (2005) 48–56.
[12] J.-l. Wu, Y.-B. He, Z. Zeng, L. Wei, L. Meng, T. Yang, Tetrahedron 60 (2004) 4309–4314.
[13] S. Rossi, G.M. Kyne, D.L. Turner, N.J. Wells, J.D. Kilburn, Angew. Chem. Int. Ed. 41 (2002) 4233–4236.
[14] J.M. Benito, M. Gomez-Garcia, J.L.J. Blanco, C.O. Mellet, J.M.G. Fernandez, J. Org. Chem. 66 (2001) 1366–1372.
[15] B.R. Linton, M.S. Goodman, A.D. Hamilton, Chem. Eur. J. 6 (2000) 2449–2455.
[16] V. Jullian, E. Shephard, M.B. Hursthouse, J.D. Kilburn, Tetrahedron Lett. 41 (2000) 3963.
[17] A. Frontera, J. Morey, A. Oliver, M.N. Pina, M. Neus, D. Quinonero, A. Costa, P. Ballester, P.M. Deya, E.V. Anslyn, J. Org. Chem. 71 (2006) 7185–7195.
[18] A. Frontera, M. Orell, C. Garau, D. Quinonero, E. Molins, I. Mata, J. Morey, Org. Lett. 7 (2005) 1437–1440.
[19] R. Prohens, M.C. Rotger, M.N. Pina, P.M. Deya, J. Morey, P. Ballester, A. Costa, Tetrahedron Lett. 42 (2001) 4933–4936.
[20] R. Prohens, S. Tomas, J. Morey, P.M. Deya, P. Ballester, A. Costa, Tetrahedron Lett. 39 (1998) 1063–1066.
[21] M.H. Al-Sayah, R. McDonald, N.R. Branda, Eur. J. Org Chem. (2004) 173–182.
[22] M.H. Al-Sayah, N.R. Branda, Angew. Chem., Int. Ed. 39 (2000) 945–947.
[23] M.H. Al-Sayah, N.R. Branda, Chem. Commun. (2002) 178–179.
[24] M.H. Al-Sayah, N.R. Branda, Org. Lett. 4 (2002) 881–884.
[25] M.H. Al-Sayah, A.S. Salameh, Arab. J. Sci. Eng. 25 (2000) 67–72.