Design and synthesis of novel diphenic acid-based molecular tweezers

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The design and synthesis of a new type of molecular tweezers is reported which have a 2,2'-diphenic acid backbone and two side chains that are attached to the backbone. This type of molecular tweezers has been to incorporate multiple hydrogen bonding groups into cleft to provide both orientation and selective complexation of substrate.

Anions play a pivotal role in bioorganic chemistry, clinical diagnosis and in monitoring the environment. Consequently, the recognition of anions is currently attracting great interest in supramolecular chemistry.[1–7] So far, the basic strategies that have been exploited for the construction of anion-binding receptors are electrostatic interaction, hydrogen bonding, hydrophobicity, coordination to a metal ion, or a combination of these interactions.[8,9] Among these non-covalent interactions, we have been interested in developing hydrogen bond-based anion receptors. Although the energy of a single hydrogen-bond is weak, the coordination of multiple hydrogen-bonding will result in high selectivity or combining with the substrates. A number of artificial receptors involving hydrogen bonding have been reported in recent years,[10–12] but arylhydrazide-type molecular tweezers receptors have seldom been reported. In view of these facts and as part of our work on the synthesis and recognition study on molecular tweezers receptors, we report here our results related to the preparation of arylhydrazide-type molecular tweezers receptors based on diphenic acid. To our knowledge, this has not been attempted up to now. Diphenic acid-based molecular tweezers **6a–j**, which contain four NH bonds, were synthesised according to Scheme 1.
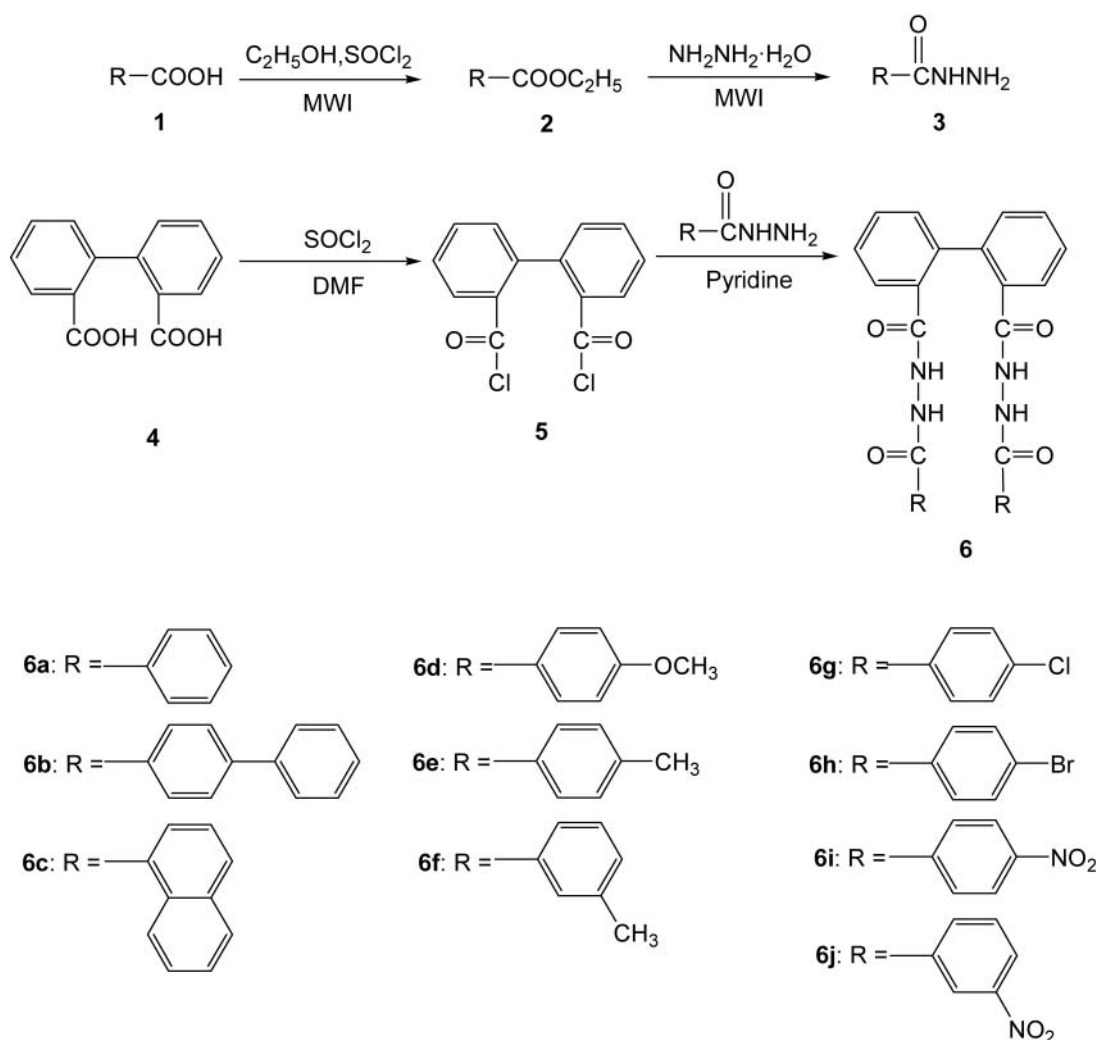
Scheme 1

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Result and discussion

A series of experiments were carried out to optimise the reaction conditions. When we started our work, we used a conventional reflux in CH_2Cl_2 for 4 hours to produce **6a.** However, it gave a low yield of 43%. We then tried microwave irradiation but the yield was also unsatisfactory at 40%. We considered that the low yield and byproducts may be caused by the vigorous conditions, so the reaction was carried out in ice water and a satisfactory result was obtained as shown in Table 1.

CH_2Cl_2, $CHCl_3$ and THF were compared to evaluate the solvent effect on the reaction. Different solvents were employed under the similar reaction conditions, but the results did not differ much as shown in Table 2. Considering that CH_2Cl_2 is less toxic than $CHCl_3$ and THF and is more easily removed

Table 1 The effect of reaction conditions on the yield of compounds **6a–c**

Entry	Reaction Condition	Yield of **6a** /%	Yield of **6b** /%	Yield of **6c** /%
1	Conventional heating	43	40	51
2	Microwave irradiation	40	38	35
3	Ice water	75	85	81

Table 2 The effect of solvent on the yield of compounds **6a–c**

Entry	Solvent	Yield of **6a** /%	Yield of **6b** /%	Yield of **6c** /%
1	THF	80	72	75
2	CH_2Cl_2	75	85	81
3	$CHCl_3$	73	81	71

than the other two solvents, we concluded that CH_2Cl_2 is the best solvent to use in this reaction.

This provided a good methodology for the preparation of arylhydrazide-type molecular anion receptors in ice water. It possesses the advantages of a good yield, easy manipulation and easy purification of the products.

The recognition of molecular tweezers **6a**, **6b** for halogen anions has been investigated by UV-vis spectra titration in $CHCl_3$ at 25 °C. Using the nonlinear least squares curve-fitting method, we obtained the association constants for the complex. The preliminary results showed that these molecular tweezers possessed the ability to form a complex with guest anions examined. The supramolecular complexes consisted of 1:1 host and guest molecules. The association constants of molecular tweezer **6a**, for example, is 124.65, 326.31, 5771.27 mol L^{-1} for Cl$^-$, Br$^-$, I$^-$ anions respectively. The main driving force is the multiple hydrogen bonds in molecular recognition. The UV-vis plot of **6a** for I$^-$ is shown in Fig. 1.

The main reason is that when the host **6a** at the minimum energy, its conformation is a cleft, which has the ability to form complex with guest molecules. The minimum energy conformation of **6a** is shown in Fig.2. The details of molecular recognition of **6a–j** are being further studied.

Experimental

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. 1H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were determined on Finnigan LCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 autoanalyser. Microwave irradiation was carried out with a MCL-3 microwave oven at full power (700 W). This was a modified domestic microwave oven and tested to conform to the performance index before use. All solvents were purified before use.
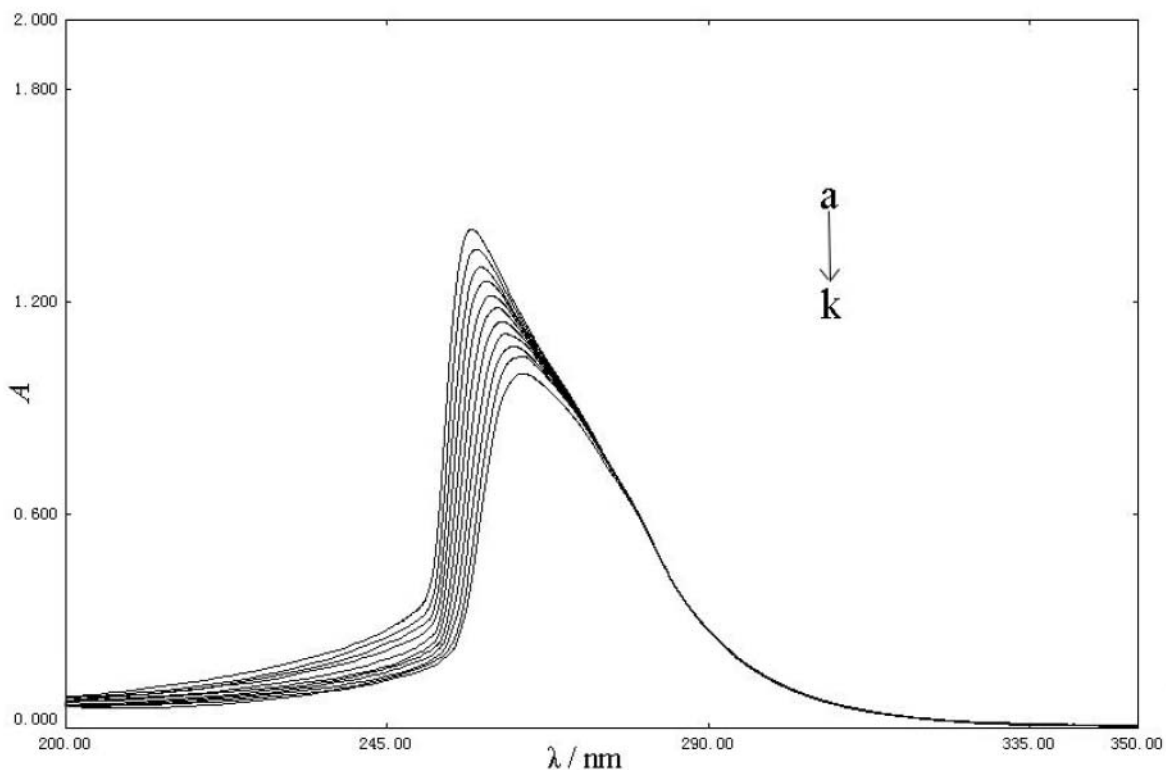
Fig. 1 UV-vis spectra of molecular tweezers **6a** (1.6 × 10^{-5} mol L^{-1}) in the presence of I$^-$: (a) 0 mol L^{-1}; (b) 0.24 × 10^{-3} mol L^{-1}; (c) 0.48 × 10^{-3} mol L^{-1}; (d) 0.48 × 10^{-3} mol L^{-1}; (e) 0.72 × 10^{-3} mol L^{-1}; (f) 0.96 × 10^{-3} mol L^{-1}; (g) 1.20 × 10^{-3} mol L^{-1}; (h) 1.44 × 10^{-3} mol L^{-1}; (i) 1.68 × 10^{-3} mol L^{-1}; (j) 1.92 × 10^{-3} mol L^{-1}; (k) 2.16 × 10^{-3} mol L^{-1} with λ_{max} at 256.9 nm.
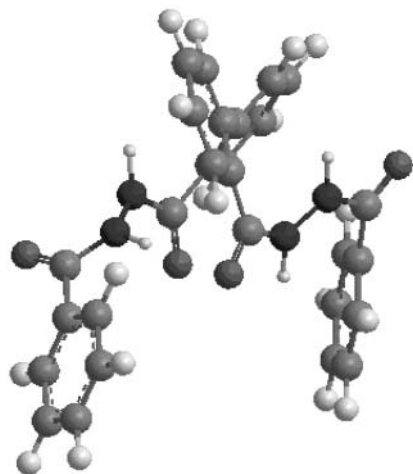
Fig. 2 Minimum energy conformation of molecular tweezer **6a**.

General procedure for preparation of **3a–j**

The aromatic acid (5 mmol), ethanol (15 mL) and thionyl chloride (0.2 mL) were placed in a dried round-bottomed flask and the mixture was irradiated by microwave (75 W) for 4 min. On completion of the reaction, the mixture was cooled to room temperature. The excess thionyl chloride was removed. Then the reaction mixture was added to 85% hydrazine hydrate (2 mL) and subjected to microwave irradiation (75 W) for 3 min. The mixture was evaporated to give the crude product. The crude product was recrystallised from ethanol to give a pure sample.

General procedure for preparation of **6a–j**

Compound **3** (3 mmol), dichloromethane (10 mL) and pyridine (0.2 mL) were placed in a dried round-bottomed flask and the mixture was put in a beaker which was filled with ice water. The solution of **5** (1 mmol) in dichloromethane (5 mL) was added slowly to the mixture and a solid was obtained. After addition was completed, the reaction for 2 hours. The solid was collected by suction filtration and washed with cold ethanol. The crude product was recrystallised from ethanol to give a pure sample. The progress of the reaction was monitored by TLC. The physical and spectra data of the compounds **6a–j** are as follows.

6a: White solid, yield 75%, m.p. 261–263 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.48 (s, 2H, PhCONH), 10.41 (s, 2H, PhCONH), 7.24–7.85 (m, 18H, ArH); IR (KBr, cm^{-1}): 3236, 3049, 1693, 1636, 1602, 1579, 1519, 1125, 914, 773; ESI–MS *m/z* (%): 477.40 [(M-1)$^-$, 100]. Anal. Calcd for $C_{28}H_{22}N_4O_4$: C 70.28, H 4.63, N 11.71. Found: C 70.21, H 4.56, N 11.76%.

6b: White solid, yield 85%, m.p. 254–256 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.55 (s, 2H, PhCONH), 10.45 (s, 2H, PhCONH), 7.26–7.96 (m, 26H, ArH); IR (KBr, cm^{-1}): 3237, 3026, 1678, 1626, 1562, 1484, 1466, 1192, 856, 746, ESI–MS *m/z* (%): 629.41 [(M-1)$^-$, 100]. Anal. Calcd for $C_{40}H_{30}N_4O_4$: C 76.17, H 4.79, N 8.88. Found: C 76.08, H 4.82, N 8.83%.

6c: White solid, yield 81%, m.p. 258–260 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.46 (s, 2H, PhCONH), 10.45 (s, 2H, PhCONH), 7.33–8.30 (m, 22H, ArH); IR (KBr, cm^{-1}): 3245, 3020, 1673, 1621, 1496, 1135, 870, 771; ESI–MS *m/z* (%): 577.67 [(M-1)$^-$, 100]. Anal.

Table 3 The physical data of hydrazides prepared

Entry	Product	Yield/%	M.p. /°C	Lit M.p. /°C
1	**3a**	86	112–114	112.5[13]
2	**3b**	77	221–223	225–227[13]
3	**3c**	83	161–163	160–162.5[13]
4	**3d**	81	134–136	137–139[13]
5	**3e**	79	116–118	115[13]
6	**3f**	82	96–98	101–103[13]
7	**3g**	83	116–118	118–120[13]
8	**3h**	82	249–251	251–253[13]
9	**3i**	77	210–212	210[13]
10	**3j**	79	150–153	153–154[13]

Calcd for $C_{36}H_{26}N_4O_4$: C 74.73, H 4.53, N 9.68. Found: C 74.78, H 4.56, N 9.70%.

6d: White solid, yield 76%, m.p. 242–244 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.39 (s, 2H, PhCONH), 10.34 (s, 2H, PhCONH), 6.98–7.84 (m, 16H, ArH), 3.81 (s, 6H,CH$_3$); IR (KBr, cm^{-1}): 3230, 3019, 1641, 1620, 1494, 1178, 852, 760; ESI–MS *m/z* (%): 539.33 [(M+1)$^+$, 100]. Anal. Calcd for $C_{30}H_{26}N_4O_6$: C 66.91, H 4.87, N 10.40. Found: C 66.82, H 4.89, N 10.34%.

6e: White solid, yield 80%, m.p. 264–266 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.40 (s, 4H, PhCONH), 7.23–7.76 (m, 16H, ArH), 2.34 (s, 6H,CH$_3$); IR (KBr, cm^{-1}): 3237, 3021, 1679, 1630, 1565, 1518, 1494, 1185, 770; ESI–MS *m/z* (%): 505.33 [(M-1)$^-$, 100]. Anal. Calcd for $C_{30}H_{26}N_4O_4$: C 71.13, H 5.17, N 11.06. Found: C 71.25, H 5.19, N 11.08%.

6f: White solid, yield 77%, m.p. 253–255 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.41 (s, 4H, PhCONH), 7.23–7.66 (m, 16H, ArH), 2.33 (s, 6H,CH$_3$); IR (KBr, cm^{-1}): 3256, 1690, 1641, 1586, 1519, 1333, 1292, 943, 773; ESI–MS *m/z* (%): 505.40 [(M-1)$^-$, 100]. Anal. Calcd for $C_{30}H_{26}N_4O_4$: C 71.13, H 5.17, N 11.06. Found: C 71.26, H 5.20, N 10.99%.

6g: Pale yellow solid, yield 63%, m.p. 277–279 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.57 (s, 2H, PhCONH), 10.43 (s, 2H, PhCONH), 7.23–7.87 (m, 16H, ArH); IR (KBr, cm^{-1}): 3235, 3021, 1629, 1499, 1290, 1176, 854, 759; ESI–MS *m/z* (%): 545.60 [(M-1)$^-$, 100]. Anal. Calcd for $C_{28}H_{20}Cl_2N_4O_4$: C 61.44, H 3.68, N 10.24, Cl 12.95. Found: C 61.33, H 3.70, N 10.29%.

6h: Pale yellow solid, yield 68%, m.p. 269–271 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.57 (s, 2H, PhCONH), 10.43 (s, 2H, PhCONH), 7.23–7.79 (m, 16H, ArH); IR (KBr, cm^{-1}): 3231, 3021, 1624, 1592, 1565, 1503, 1481, 1299, 843, 748; ESI–MS *m/z* (%): 635.36 [(M+1)$^+$, 100]. Anal. Calcd for $C_{28}H_{20}Br_2N_4O_4$: C 52.85, H 3.17, N 8.81, Br 25.12. Found: C 52.78, H 3.20, N 8.84%.

6i: Pale yellow solid, yield 65%, m.p. 292–294 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.85 (s, 2H, PhCONH), 10.53 (s, 2H, PhCONH), 7.25–8.33 (m, 16H, ArH); IR (KBr, cm^{-1}): 3203, 2992, 1687, 1644, 1602, 1527, 1348, 1109, 847, 769; ESI–MS *m/z* (%): 567.31 [(M-1)$^-$, 100]. Anal. Calcd for $C_{28}H_{20}N_6O_8$: C 59.16, H 3.55, N 14.78. Found: C 59.27, H 3.53, N 14.85%.

6j: Pale yellow solid, yield 67%, m.p. 234–236 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.91 (s, 2H, PhCONH), 10.55 (s, 2H, PhCONH), 7.25–8.67 (m, 16H, ArH); IR (KBr, cm^{-1}): 3250, 3090, 1629, 1526, 1351, 1076, 769; ESI–MS *m/z* (%): 567.47 [(M-1)$^-$, 100]. Anal. Calcd for $C_{28}H_{20}N_6O_8$: C 59.16, H 3.55, N 14.78. Found: C 59.19, H 3.58, N 14.73%.

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