Electronic Supplementary Information (ESI)

Complexes within Complexes: Hydrogen Bonding in Capsules

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1. Experimental Section

General Methods. All reagents and solvents involved in this research were commercially available unless otherwise noted and used without further purification. Cavitand **1**,[1] **3**,[2] and compound **2**[3] and **4**[4] were synthesized according to the published procedures. ^{1}H NMR spectra were recorded on a Bruker DRX-600 spectrometer. All chemical shifts are reported in *ppm* with residual solvents as the internal standards. Energy minimized structures and electrostatic potential surfaces were calculated on the program of Spartan 04 (Wavefunction, Inc.).

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1 D. Ajami, T. Iwasawa, J. Rebek, Jr. *Proc. Natl. Acad. Sci. U.S.A.* 2006, **103**, 8934.

2 M. H. K. Ebbing, M. J. Villa, J. M. Valpuesta, P. Prados, J. de Mendoza, *Proc. Natl. Acad. Sci. U.S.A.* 2002, **99**, 4962; H.-J. Choi, Y. S. Park, C. S. Cho, K. Koh, S.-H. Kim, K. Paek, *Org. Lett.* 2004, **6**, 4431.

3 D. Ajami,; J. Rebek, Jr. *J. Org. Chem.* 2009, **74**, 6584-6591.

4 K. Tiefenbacher, J. Rebek, Jr. *J. Am. Chem. Soc.* 2012, **134**, 2914–2917.

2. Disproportionation Reactions in Capsules

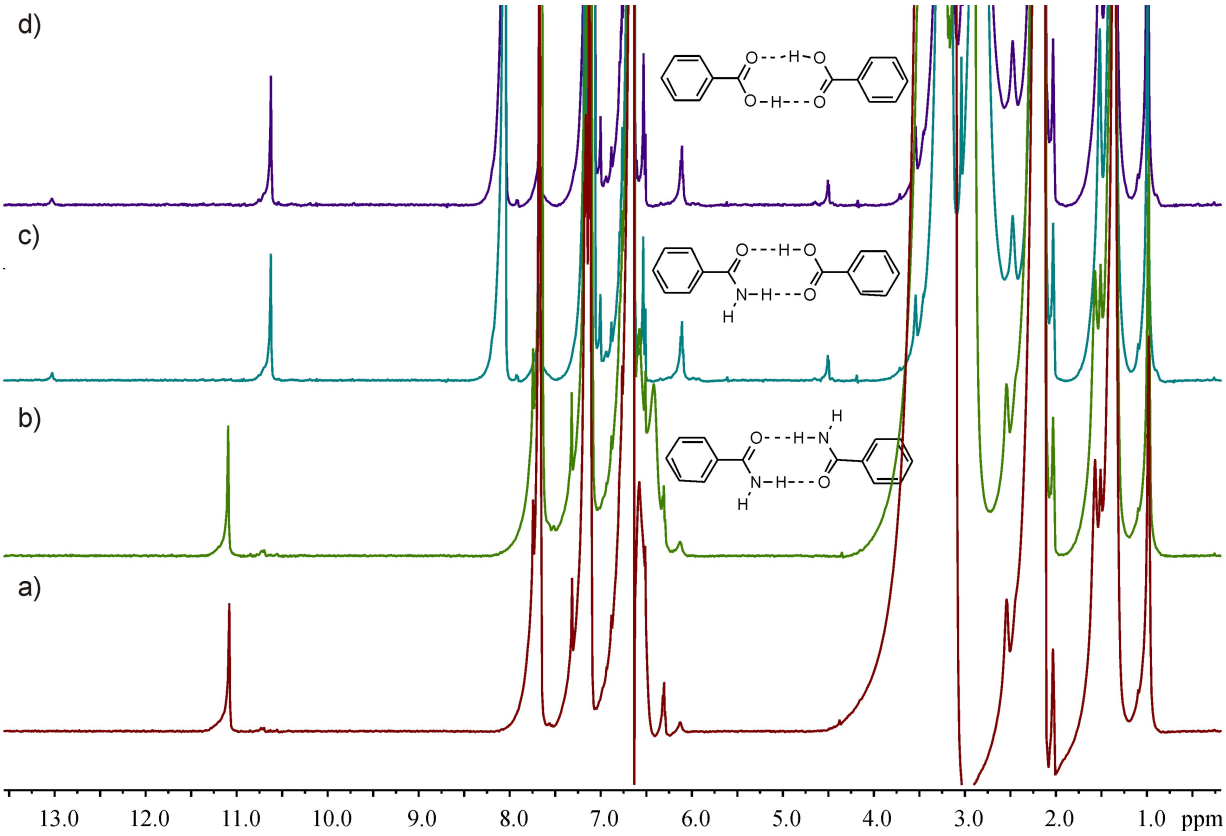

Fig. S1 ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 5%(vol/vol) MeOH, 300 K) of the capsule **3.3** ([A]:[C]:[**1**] = 1.5:1.5:1; [**3.3**]=1.0 mM) in the presence of no guest (a), benzamide (b), benzoic acid (d), and the mixture of benzoic acid and benzamide (c). 5%(vol/vol) MeOH was used to de-aggregate the capsule **3.3**. When there is no other guest, three MeOH molecules were believed to be encapsulated in the capsule **3.3**.[5] Thus, the encapsulated benzamide homodimer and benzoic acid and benzamide heterodimer are not detected. Benzoic acid homodimer is the only guest occupying the capsule **3.3** in the mixture benzamide, benzoic acid, and the capsule **3.3**.

(5) Tiefenbacher, K. Rebek, J., Jr. *Unpublished Results*.

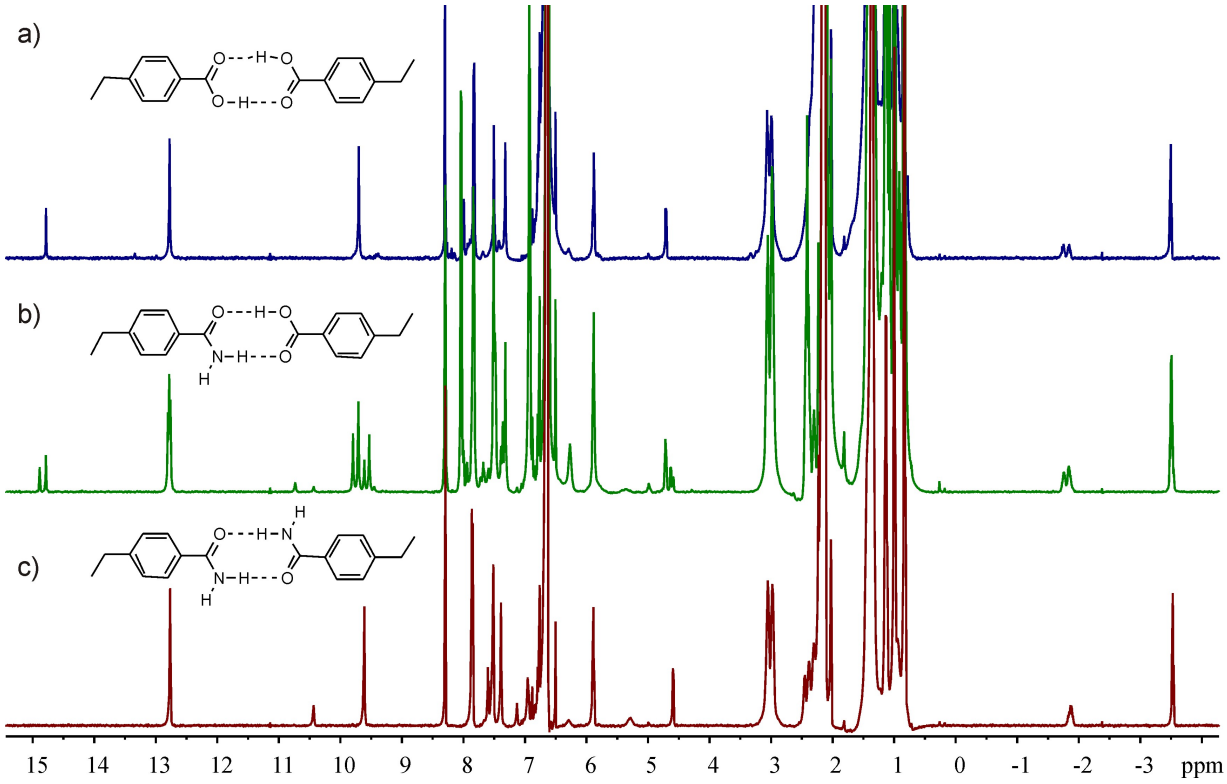

Fig. S2 ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of (a) *p*-ethylbenzoic acid homodimer, (c) *p*-ethylbenzamide homodimer, and (b) acid-amide heterodimer in the capsule **1.2$_4$.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.2$_4$.1**]=1.0 mM). The ratios of homodimers and heterodimer in the capsules were calculated according to the integration on the capsule peaks at ca. 9.6 ppm.

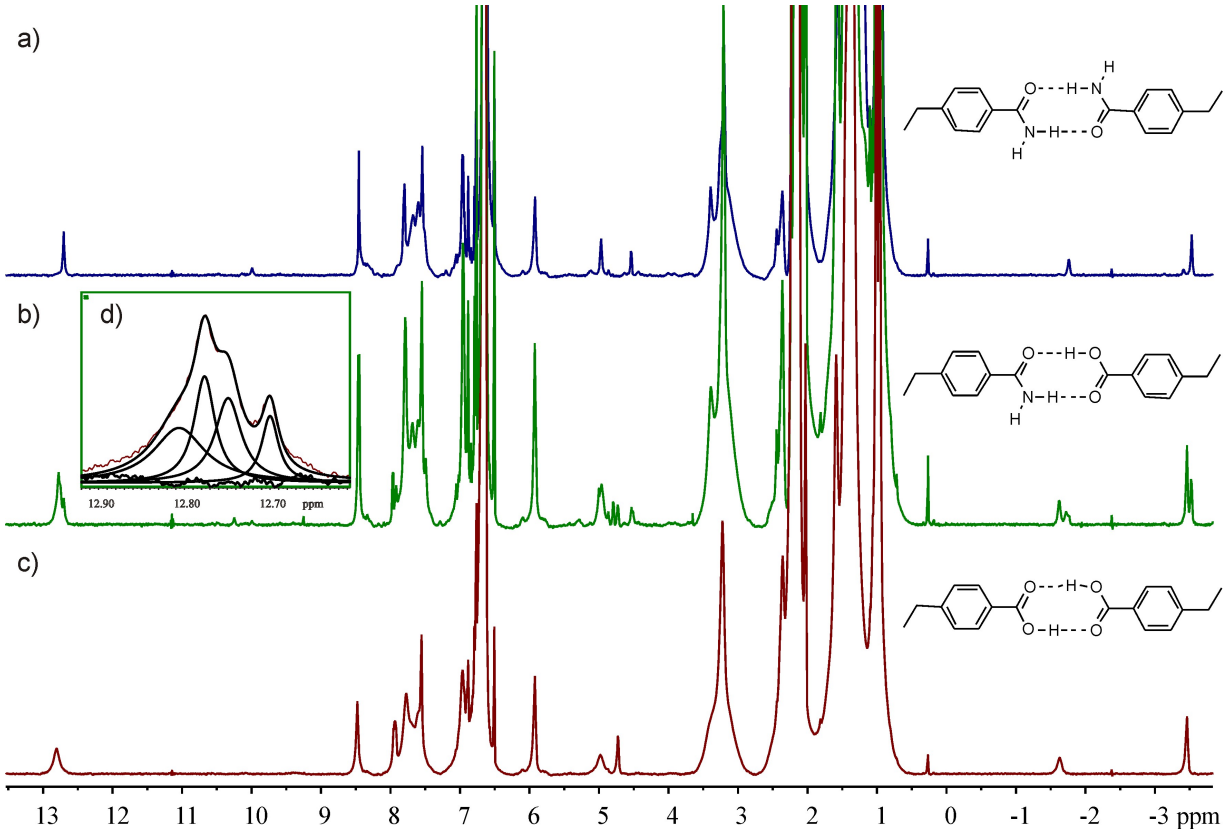

Fig. S3 ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of (a) *p*-ethylbenzamide homodimer, (c) *p*-ethylbenzoic acid homodimer, and (b) acid-amide heterodimer in the capsule **1.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.4$_4$.1**]=1.0 mM); and (d) the deconvolution of the capsule peaks at 12.8 ppm by line fitting program of MestRenova 7 (Mestrelab Research) and considering the chemical shift of homodimer-containing capsules' peaks from spectra (a) and (c). The integrations on the deconvoluted peaks are used to calculate the relative ratio of homodimers and heterdimer in the capsule. The four propanediurea **4** in the capsule **1.4$_4$.1** have a similar chiral arrangement as the glycourils in **1.2$_4$.1**.[4]

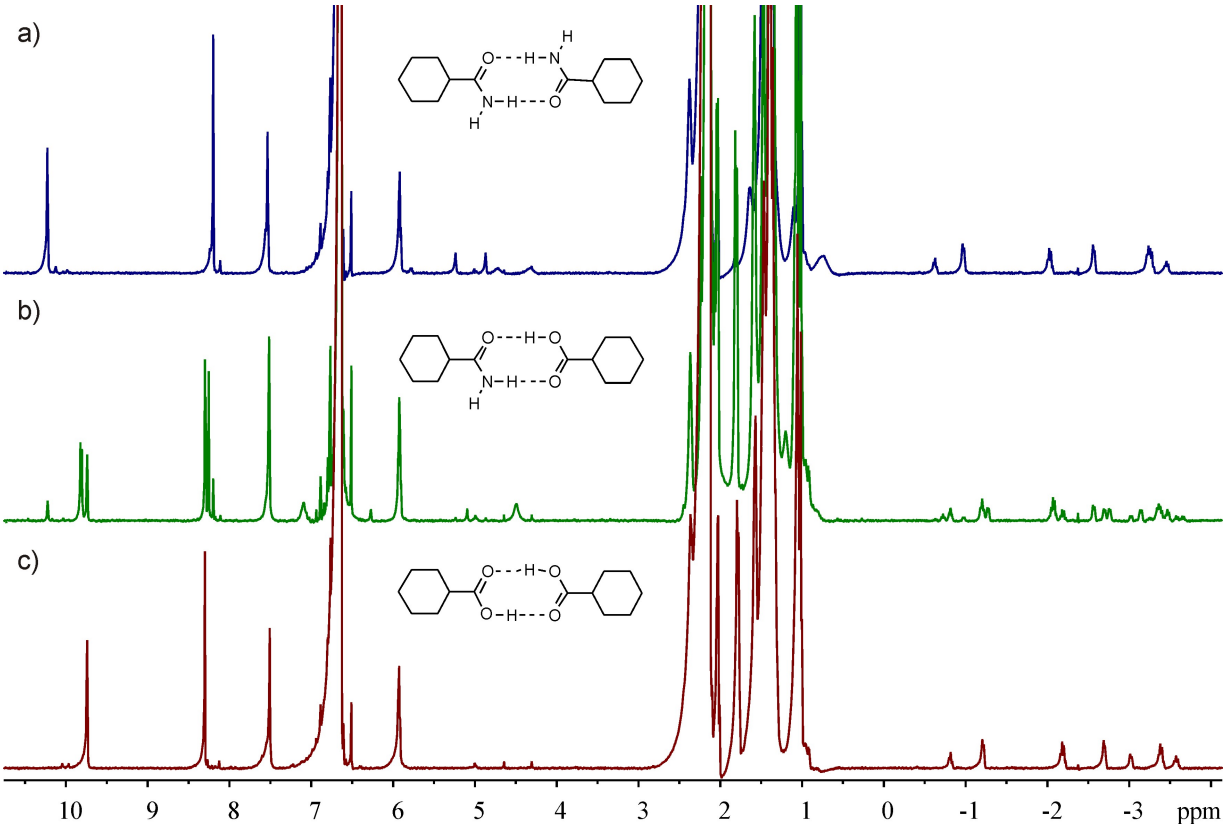

Fig. S4 ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of cyclohexane carboxamide homodimer (a), cyclohexane carboxylic acid homodimer (c), and acid-amide heterodimer (b) in the capsule **1.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.1**]=1.0 mM). The ratios of homodimers and heterodimer in the capsules were calculated according to the integrations on the capsule N-H peaks at ca. 10.0 ppm.

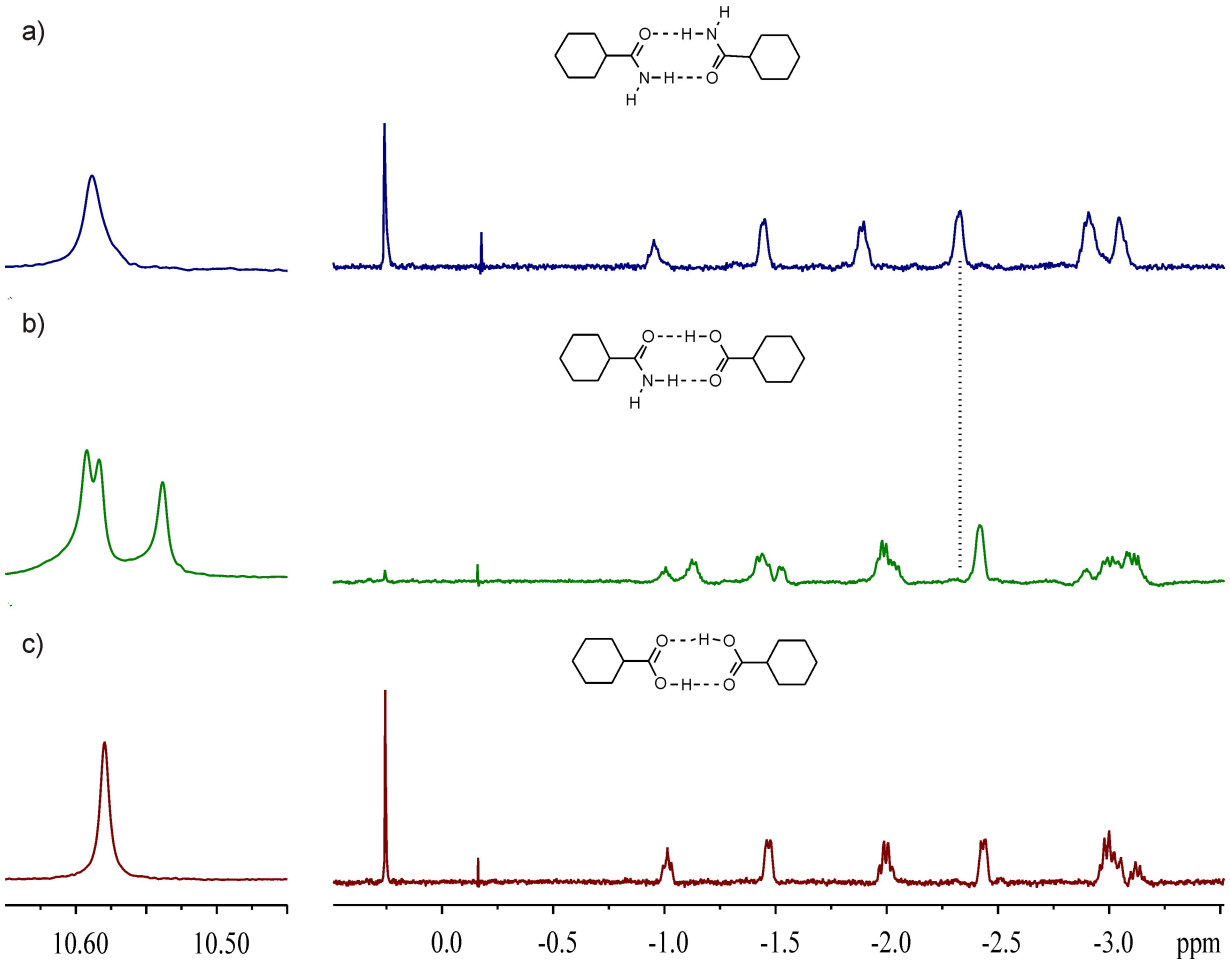

Fig. S5 ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of cyclohexane carboxamide homodimer (a), cyclohexane carboxylic acid homodimer (c), and acid-amide heterodimer (b) in the capsule **3.3** ([A]:[C]:[**3**] = 1.5:1.5:1; [**3.3**]=1.0 mM). 5% (vol/vol, versus Mesitylene-d_{12}) MeOH is used to de-aggregate the capsule **3.3**. The ratios of carboxylic acid homodimer and acid-amide heterodimer in the capsules were calculated according to the integrations on the capsule N-H peaks at ca. 10.6 ppm, and the ratio of amide homodimer is calculated according to the integration on the peaks at ca. -2.4 ppm.

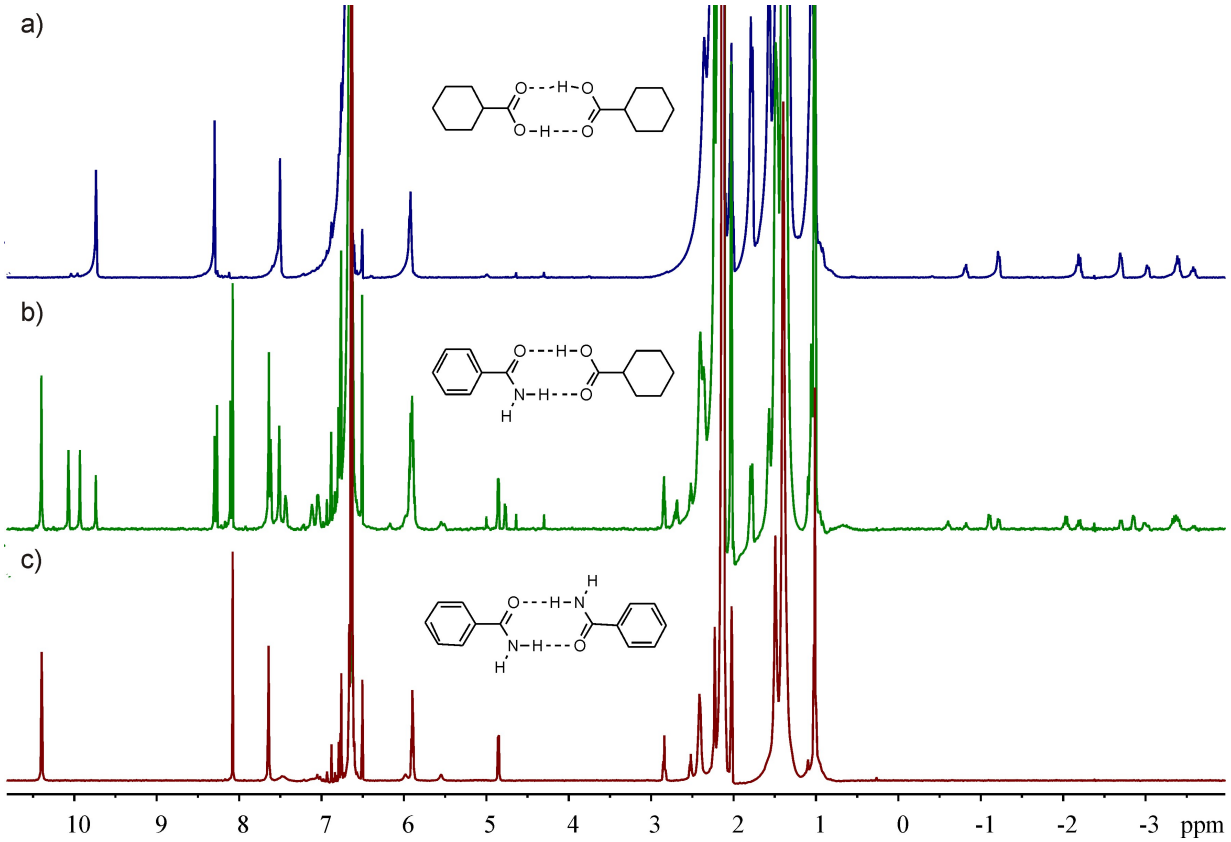

Fig. S6 ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of cyclohexane carboxylic acid homodimer (a), benzamide homodimer (c), and acid-amide heterodimer (b) in the capsule **1.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.1**]=1.0 mM). The ratios of homodimers and heterodimer in the capsules were calculated according to the integrations on the capsule N-H peaks at ca. 10.0 ppm.

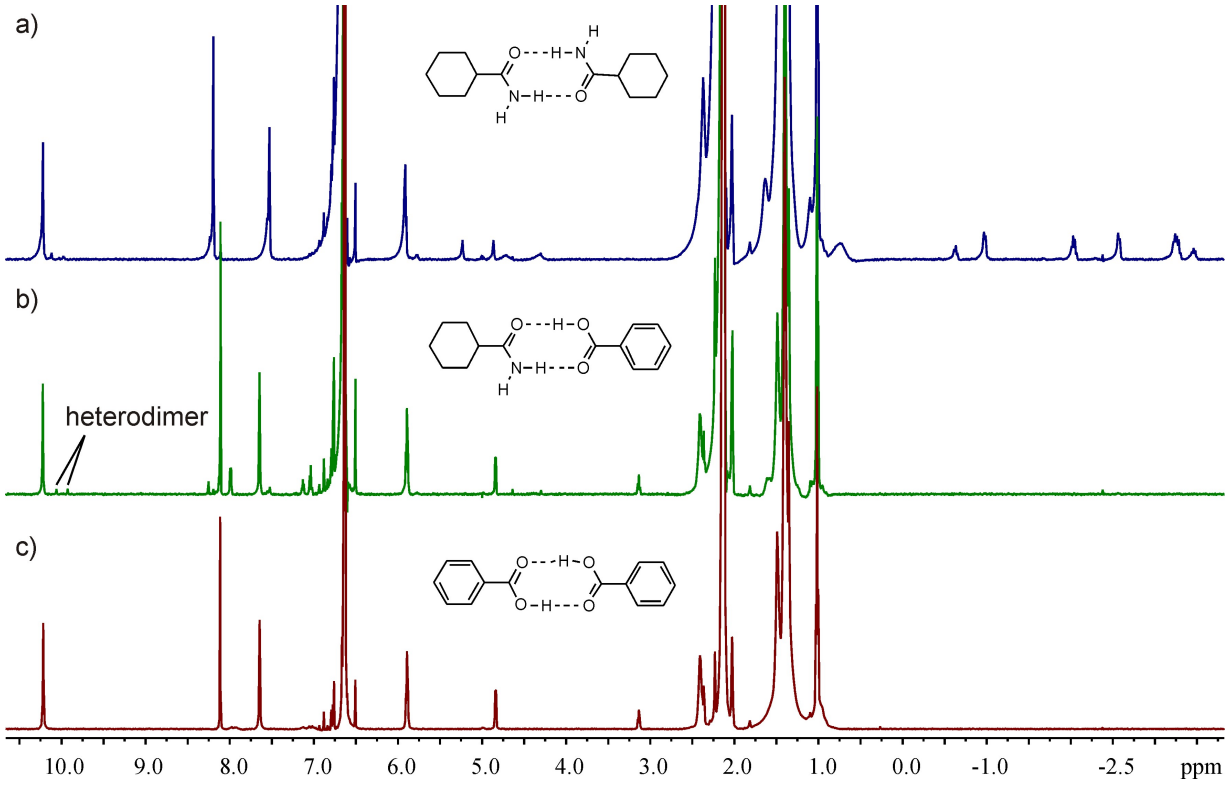

Fig. S7 ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of cyclohexane carboxamide homodimer (a), benzoic acid homodimer (c), and acid-amide heterodimer (b) in the capsule **1.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.1**]=1.0 mM). The heterodimer is observable from the peaks at ca. 10.0 ppm, and the integrations on the peaks at ca. 10.0 ppm indicates that heterdimer occupy 6% of all the capsules. However, the diagnostic N-H peak for cyclohexane carboxamide dimer occupied capsule is overlapped with the one of benzoic acid dimer occupied capsule. We could not detect any NMR peaks at upfield region (b), indicating that very small portion of the capsules is occupied by cyclohexane carboxamide homodimer. Thus, the disproportionation constant cannot be calculated in this case.

Table S1 Chemical shifts (ppm) of the N-H protons of the capsule **1.1** when different guests are accommodated in the cavity. The chemical shifts of the N-H protons can be used as the indicators of the hydrogen-bonding stability of the capsule.

	N-H (I)	N-H (II)
A_{ben}•A_{ben}	10.40	
C_{ben}•C_{ben}	10.22	
A_{ben}•C_{ben}	10.19	10.01
A_{hex}•A_{hex}	10.22	
C_{hex}•C_{hex}	9.74	
A_{hex}•C_{hex}	9.82	9.80
A_{ben}•C_{hex}	10.17	9.98
A_{hex}•C_{ben}	10.06	9.93

3. Calculation of Amide and Carboxylic Acid Dimers

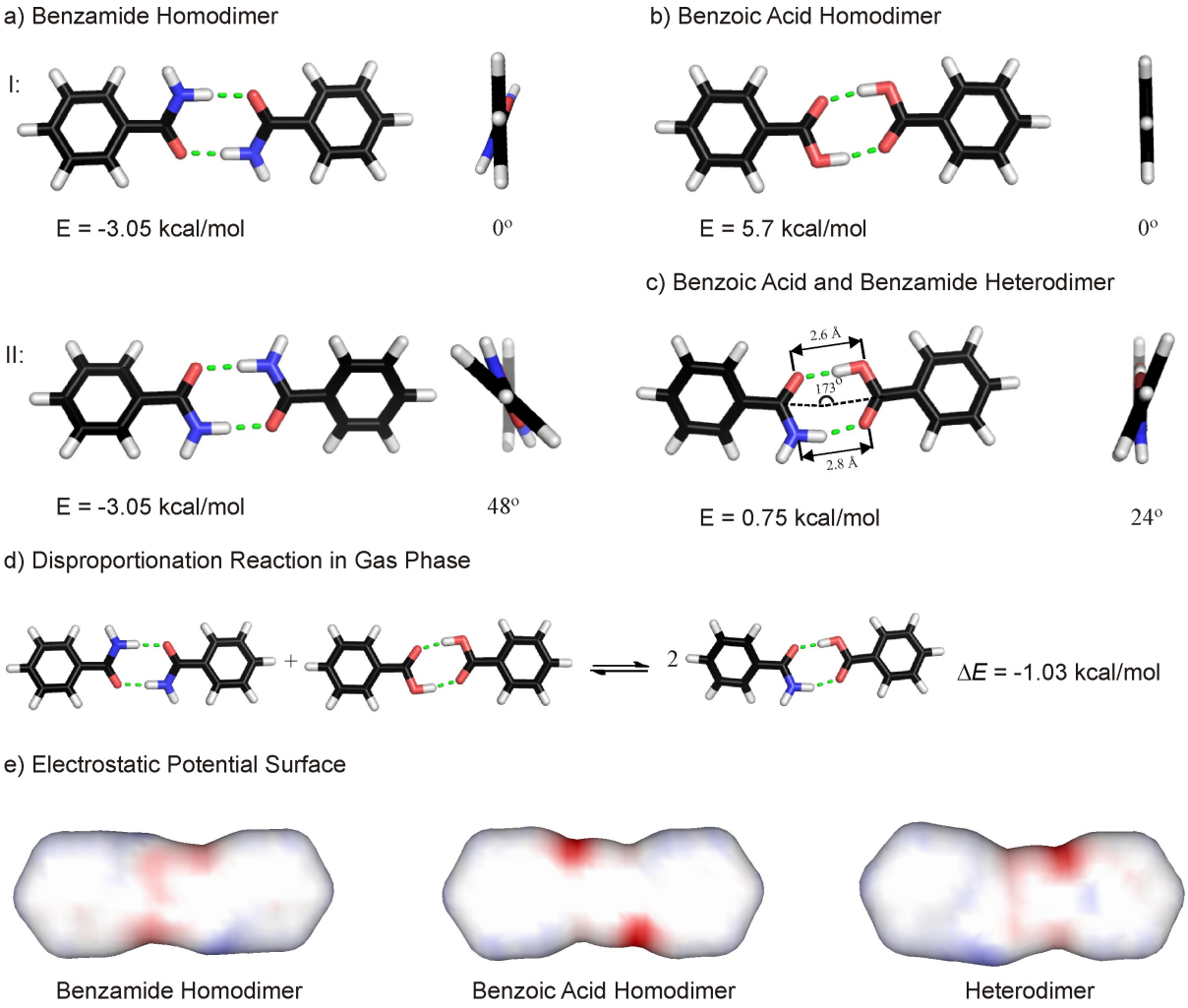

Fig. S8 Energy minimized structures, calculated energies, dihedral angles between two aromatic panels, electrostatic potential surface, and stable conformers of benzamide and benzoic acid homodimers and heterodimers.

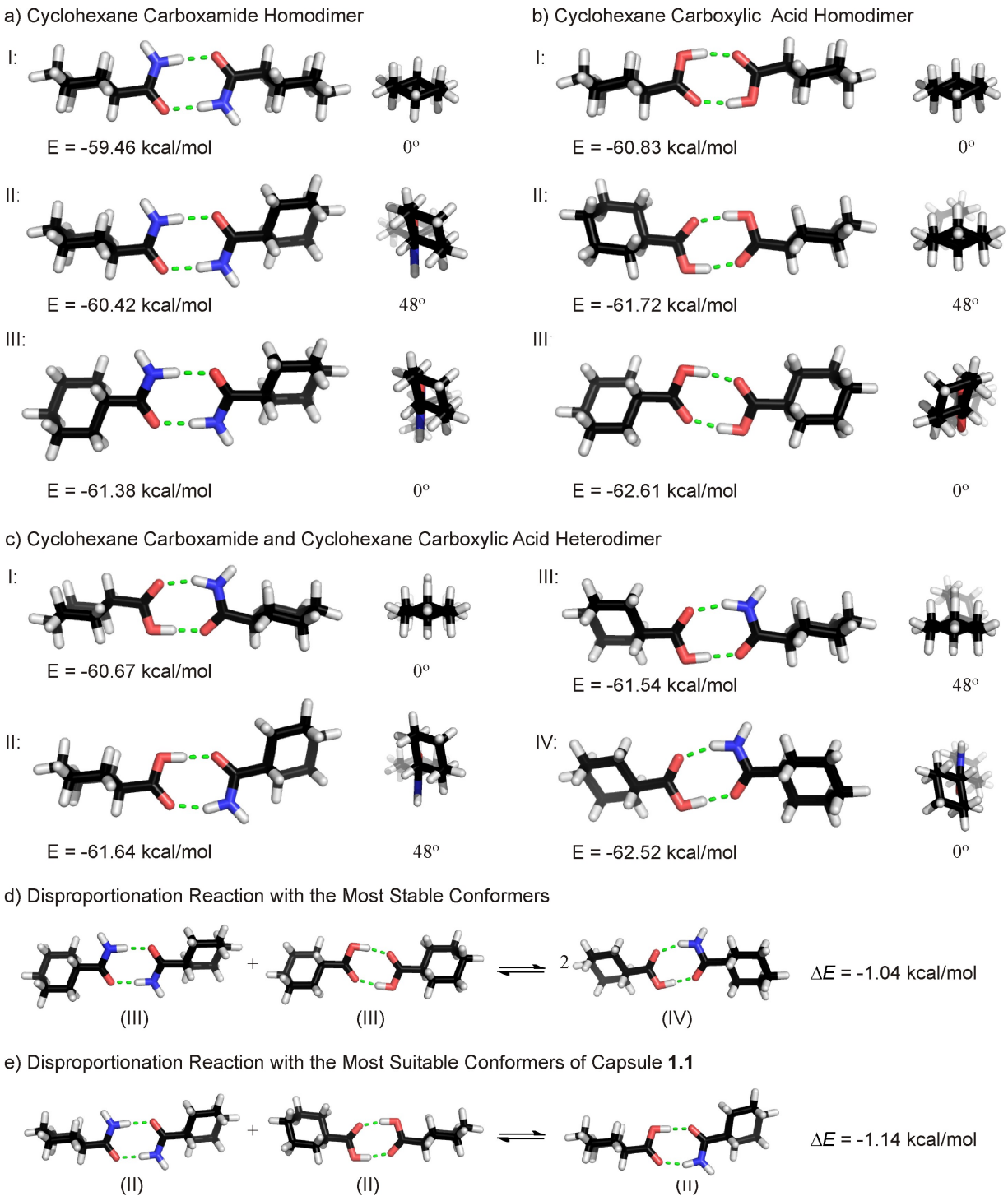

Fig. S9 Energy minimized structures, calculated energies, dihedral angles between two cyclohexane planes, and stable conformers of cyclohexane carboxamide and cyclohexane carboxylic acid homodimers and heterodimers.

4. Variable-Temperature NMR Experiments

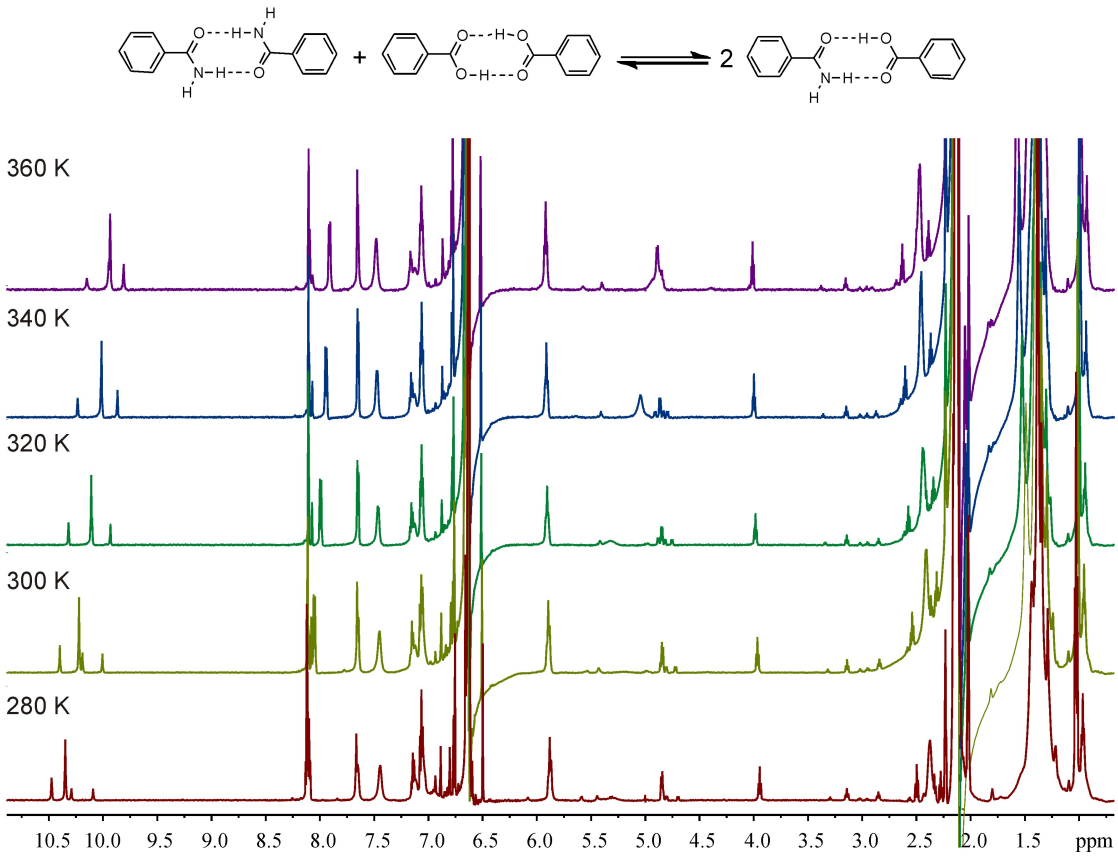

Fig. S10 Variable-Temperature ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of benzoic acid and benzamide mixture in the capsule **1.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.1**]=1.0 mM). The ratios of homodimers and heterodimer in the capsules were calculated according to the integration on the capsule peaks at ca. 10.3 ppm.

Table S2 The relative ratios of benzoic acid and benzamide homodimers and heterodimer in the capsule **1.1** at different temperatures calculated using ^{1}H NMR spectra in Figure S10 and the resulting disproportionation constants (K_d).

	A.A	C.C	A.C	K_d
280 K	21%	64%	16%	0.2
300 K	19%	59%	22%	0.4
320 K	15%	59%	26%	0.8
340 K	14%	54%	32%	1.4
360 K	8%	58%	34%	2.5

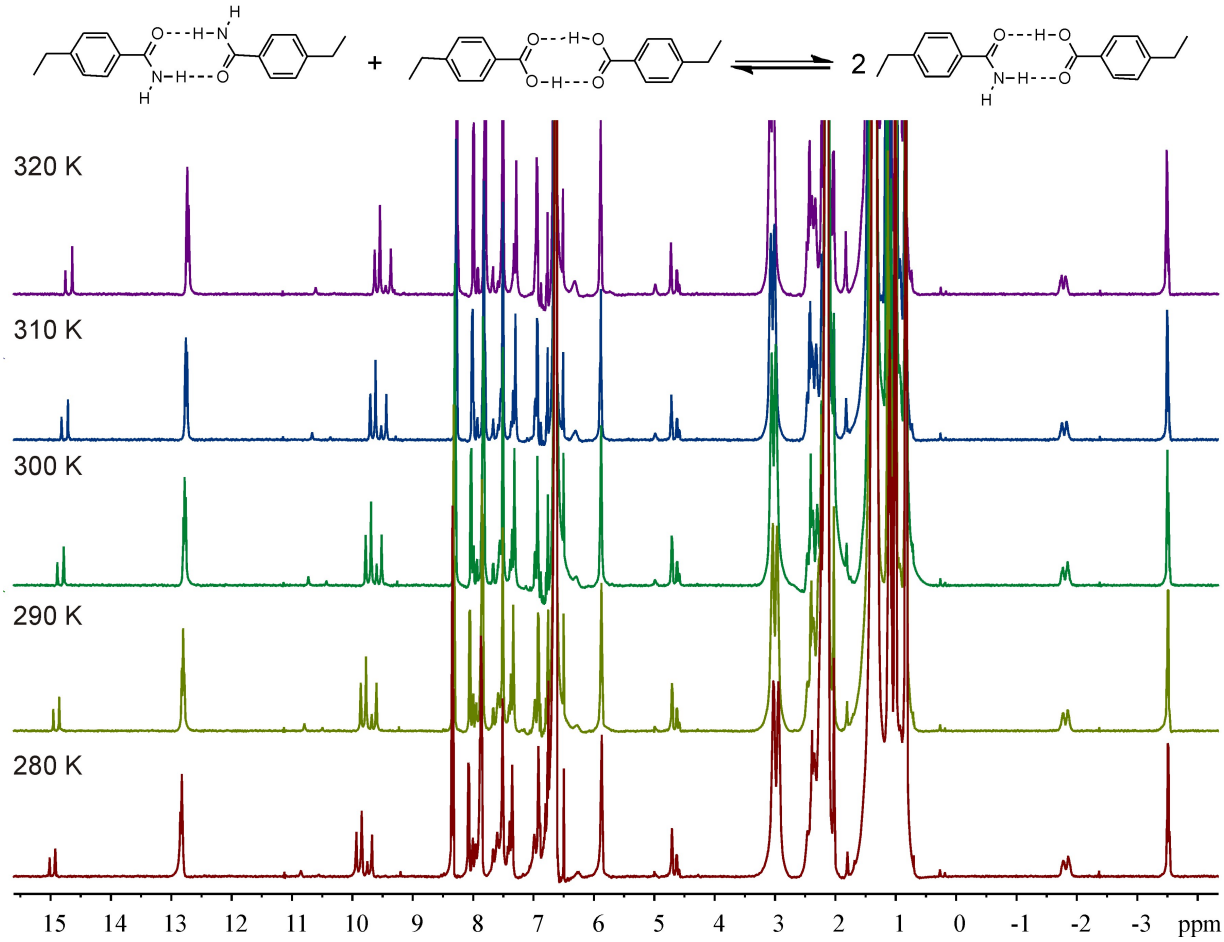

Fig. S11 Variable-Temperature ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of *p*-ethylbenzoic acid and *p*-ethylbenzamide mixture in the capsule **1.2$_4$.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.2$_4$.1**]=1.0 mM). The ratios of homodimers and heterodimer in the capsules were calculated according to the integration on the capsule peaks at ca. 9.6 ppm.

Table S3 The relative ratios of *p*-ethylbenzoic acid and *p*-ethylbenzamide homodimers and heterodimer in the capsule **1.2$_4$.1** at different temperatures calculated using ^{1}H NMR spectra in Figure S11 and the resulting disproportionation constants (K_d).

	A.A	C.C	A.C	K_d
280 K	9%	43%	49%	6.2
290 K	9%	42%	50%	6.6
300 K	10%	38%	52%	7.1
310 K	9%	39%	52%	7.7
320 K	7%	43%	50%	8.3

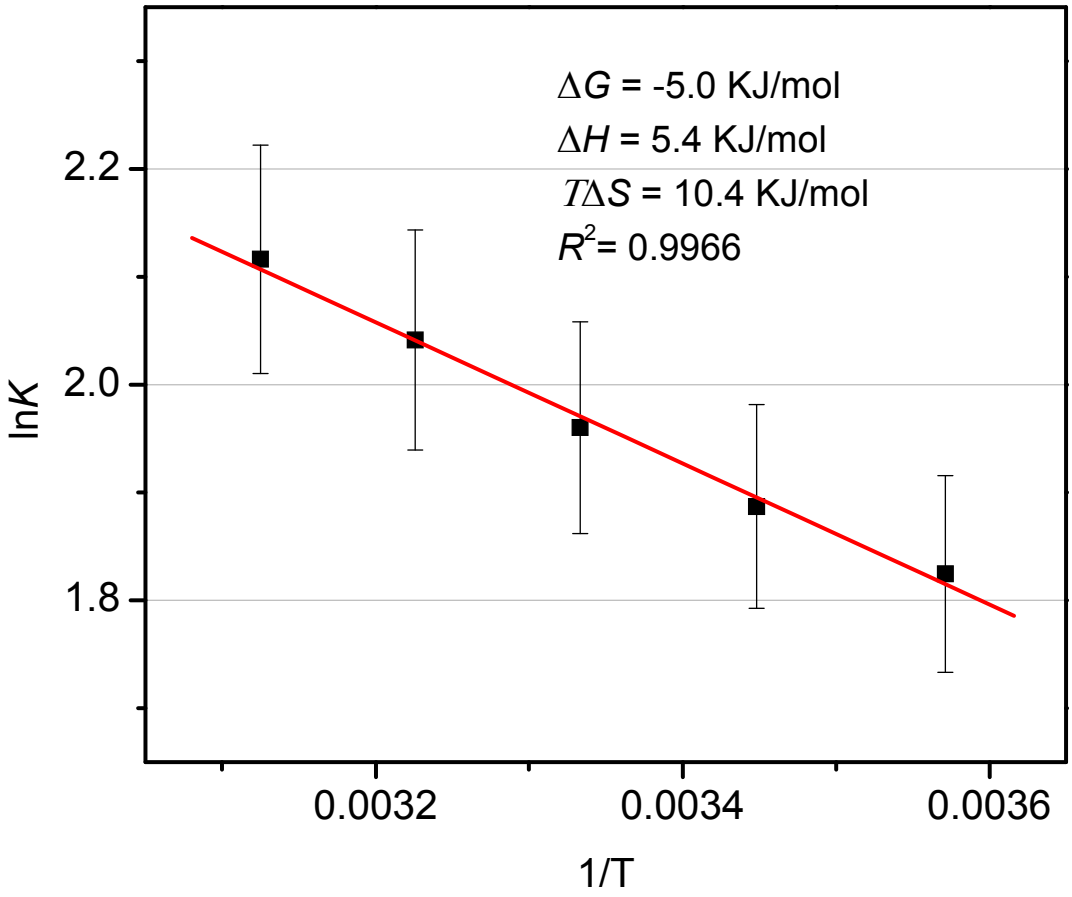

Fig. S12 van't Hoff plot of the disproportionation reaction of *p*-ethylbenzoic acid and *p*-ethylbenzamide homodimers and heterodimer in the capsule **1.2$_4$.1** to calculate the thermodynamic parameters. Error bar was estimated as ±5%.

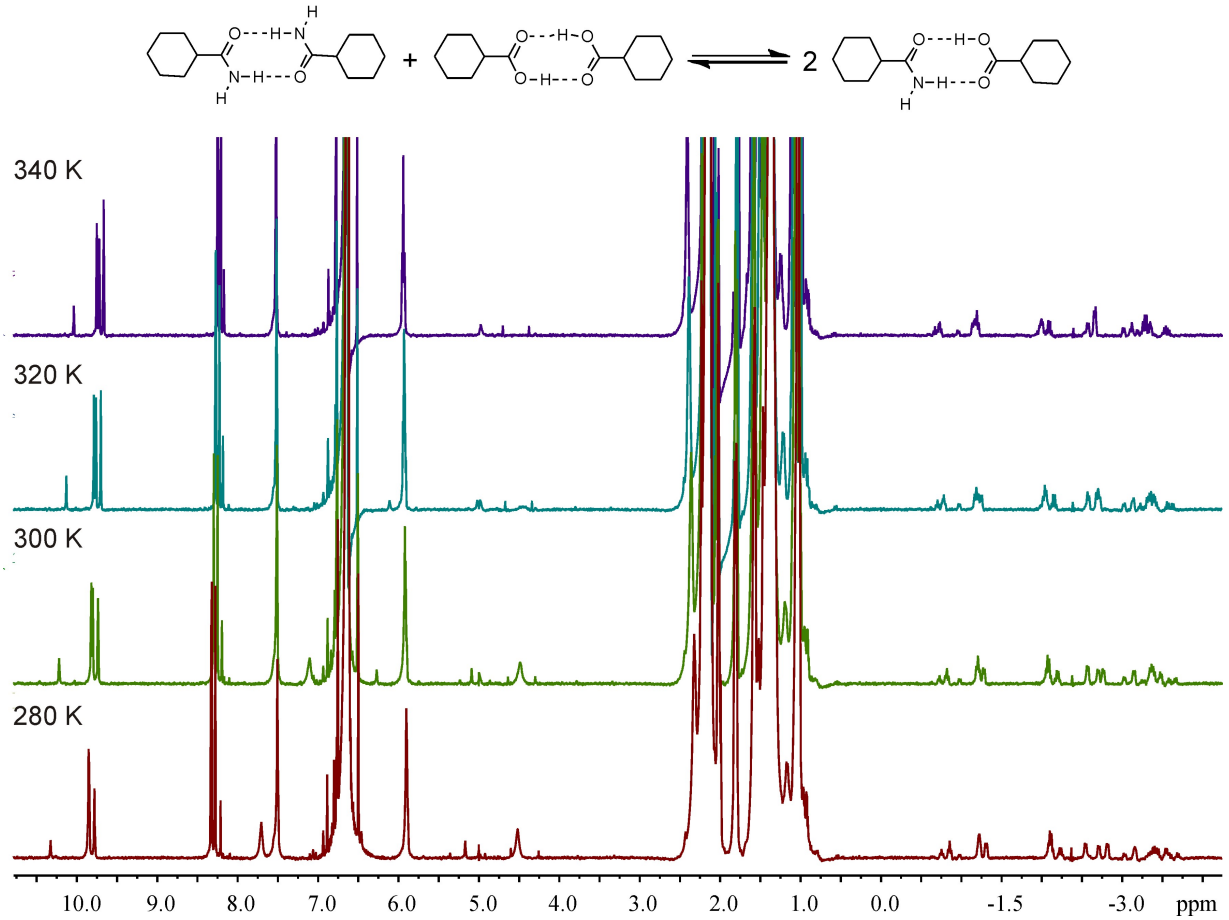

Fig. S13 Variable-Temperature ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of cyclohexane carboxylic acid and cyclohexane carboxamide mixture in the capsule **1.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.1**]=1.0 mM). The ratios of homodimers and heterodimer in the capsules were calculated according to the integration on the capsule peaks at ca. 10.0 ppm.

Table S4 The relative ratios of cyclohexane carboxylic acid and cyclohexane carboxamide homodimers and heterodimer in the capsule **1.1** at different temperatures calculated using ^{1}H NMR spectra in Figure S13 and the resulting disproportionation constants (K_d).

	A.A	C.C	A.C	K_d
280 K	6%	26%	68%	30
300 K	8%	28%	64%	18
320 K	9%	30%	61%	14
340 K	9%	33%	58%	11

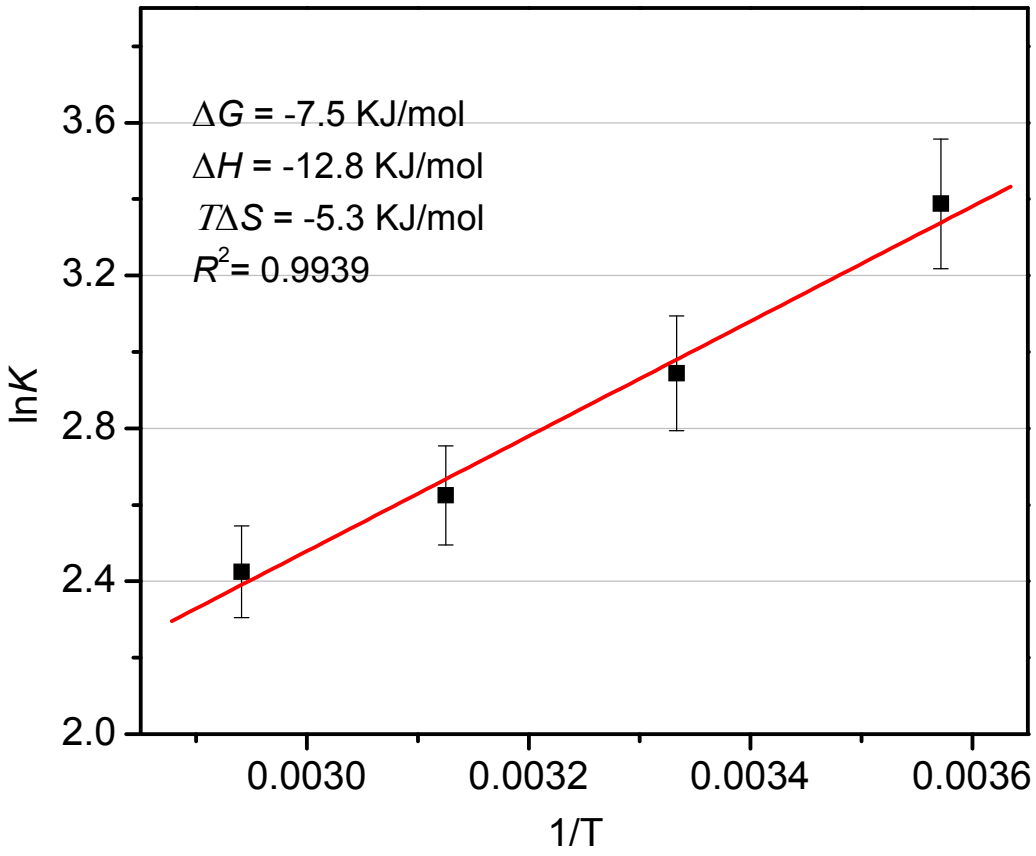

Fig. S14 van't Hoff plot of the disproportionation reaction of cyclohexane carboxylic acid and cyclohexane carboxamide homodimers and heterodimer in the capsule **1.1** to calculate the thermodynamic parameters. Error bar was estimated as ±5%.

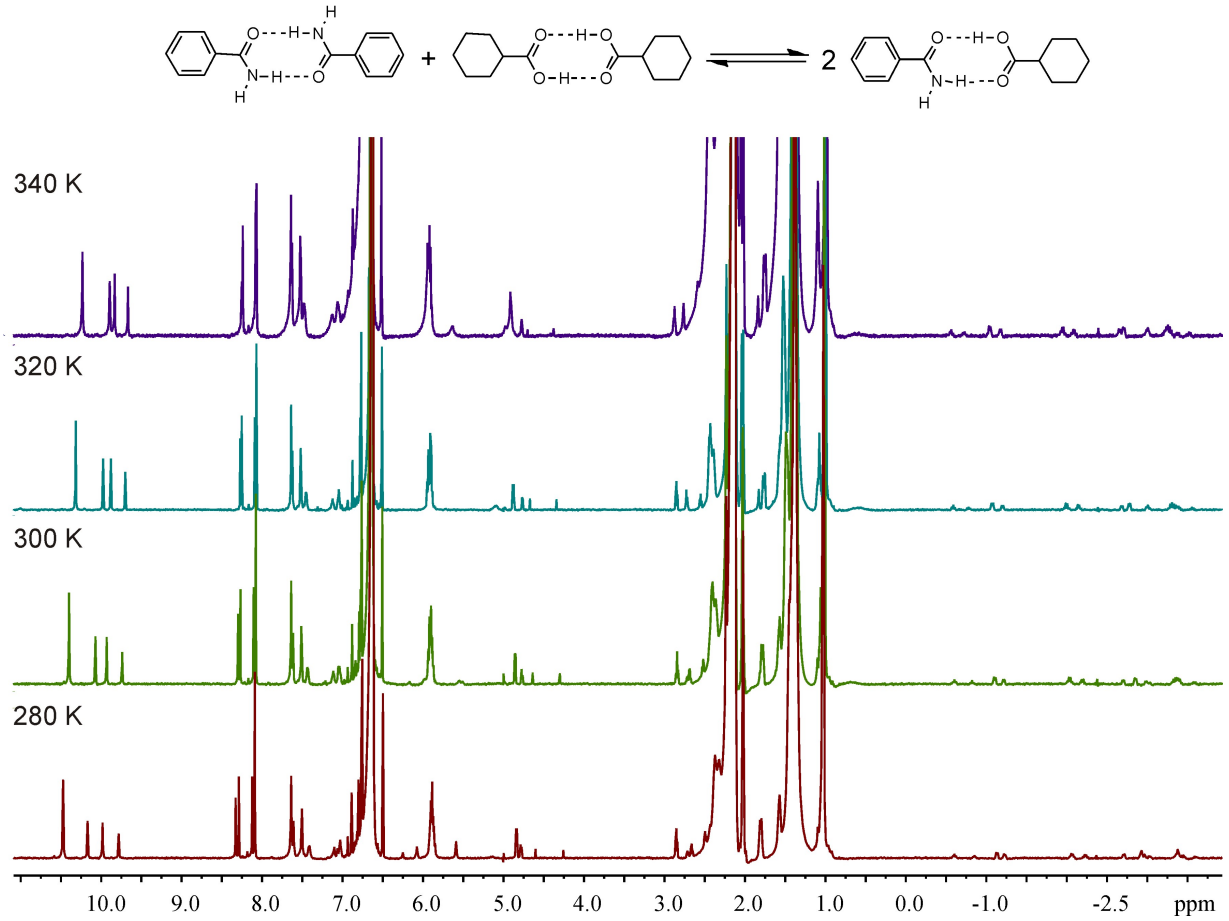

Fig. S15 Variable-Temperature ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}, 300 K) of cyclohexane carboxylic acid and benzamide mixture in the capsule **1.1** ([A]:[C]:[**1**] = 1.5:1.5:1; [**1.1**]=1.0 mM). The ratios of homodimers and heterodimer in the capsules were calculated according to the integration on the capsule peaks at ca. 10.0 ppm.

Table S5 The relative ratios of cyclohexane carboxylic acid and benzamide homodimers and heterodimer in the capsule **1.1** at different temperatures calculated using ^{1}H NMR spectra in Figure S15 and the resulting disproportionation constants (K_d).

	A.A	C.C	A.C	K_d
280 K	49%	12%	39%	2.6
300 K	44%	14%	42%	2.9
320 K	41%	15%	44%	3.2
340 K	38%	16%	46%	3.5

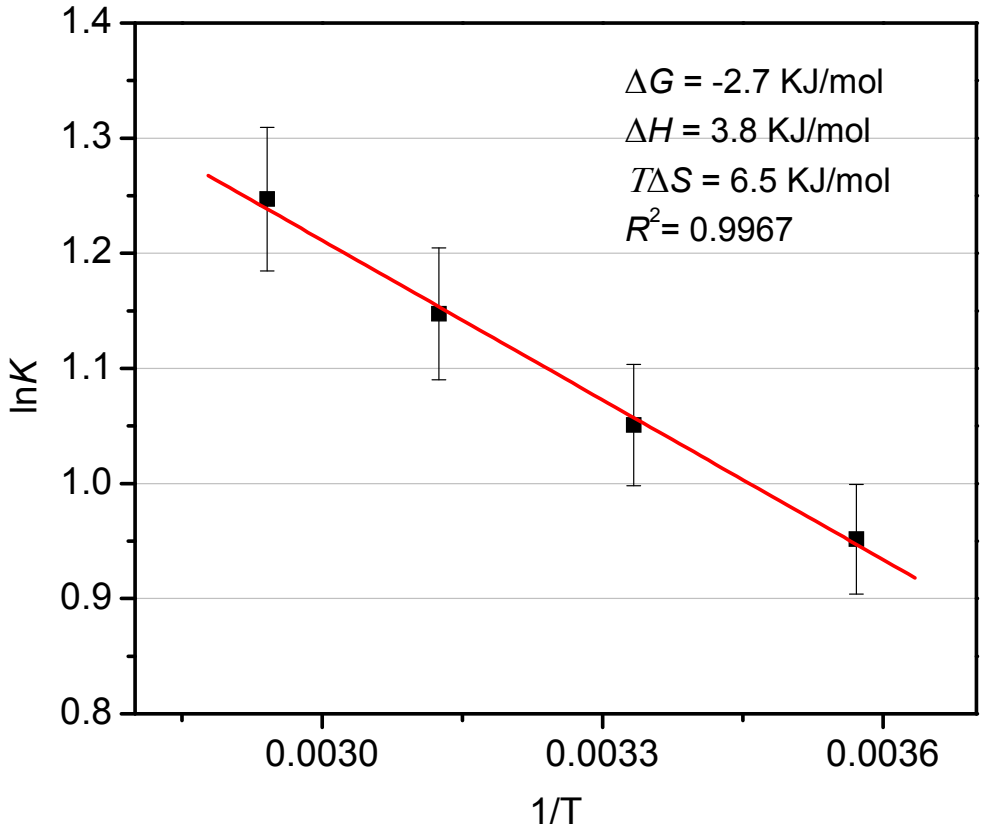

Fig. S16 van't Hoff plot of the disproportionation reaction of cyclohexane carboxylic acid and benzamide homodimers and heterodimer in the capsule **1.1** to calculate the thermodynamic parameters. Error bar was estimated as ±5%.