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Recognition of carboxylic acids and phosphonic acids using 1,8-diphenylnaphthalene-based diguanidine

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ABSTRACT

A diphenylnaphthalene-based diguanidine (**1**) has been designed and synthesized for the recognition of dicarboxylic acids and diphosphonic acids. The diguanidine **1** forms 1:1 complexes with the dicarboxylic acids and the diphosphonic acid derivatives in a DMSO solution, and the formation of the complexes was determined by DOSY NMR spectroscopy. The weak yellowish fluorescence of the diguanidine **1** in a DMSO solution turned to a strong bluish fluorescence after the addition of 1,3-benzenediacetic acids **3**. However, after the addition of other types of aliphatic dicarboxylic acids, such as α,ω-dicarboxylic acids, only a weak yellowish fluorescence was observed and selective recognition of the 1,3-benzenediacetic acids **3** was developed. On the other hand, for the recognition of diphosphonic acid derivatives (**5**–**7**), a light blue, blue or pinkish fluorescence was observed. Interestingly, the binding mode on the guanidyl group (two existing types of binding modes toward three nitrogen atoms) with oxoacids were successfully determined by the 2D NOESY analysis. The fluorescence quantum yields (Φ_{fl}) were moderately increased by the introduction of the guanidyl group and binding with dicarboxylic acids **3** than that of the 1,8-diphenylnaphthalene itself. These fluorescence characteristics of the diguanidine **1** are applicable for the detection of dicarboxylic acids and diphosphonic acids.

1. Introduction

The “oxoacids” and “oxoanions” such as carboxylic acids (carboxylate) and phosphoric acids (phosphate) play many roles in biological systems and in industry. The recognition of carboxylic acids (carboxylate) and phosphoric acids (phosphate) using fluorogenic chemosensor is of particular important because of their applications in the chemical, biological, medical, and environmental sciences [1].

Until recently, numerous reports of fluorogenic chemosensors for “carboxylate” as anionic form have been reported, but the fluorogenic chemosensors for the recognition of “carboxylic acids” are relatively rare [1a-b].

Additionally, the recognition of the “phosphonic acid” is also important target related to the trace of nerve gases that produce phosphonic acid after hydrolysis (i.e., Sarin produces methylphosphonic acid after hydrolysis) [2a-d]. However, only a few examples of the fluorogenic chemosensors for the recognition of the “phosphonic acids” have been reported [2e-h].

On the other hand, the “amidino group” and “guanidyl group” have become extremely advantageous functional binding groups for the oxoacids [3,4]. We previously reported that the synthesis of anthracene-based “diamidine” and “diguanidine”, which recognize dicarboxylic acids and diphosphonic acid derivatives as turn-on and turn-off fluorogenic chemosensors, respectively [2g-h,3f,3h]. Additionally, we developed the diphenylnaphthalene-based diamidine for the recognition of a dicarboxylic acid as a turn-on fluorescent chemosensor with high fluorescent quantum yields [3g]. To explore the applicability of these functional chemosensors for the recognition of oxoacids, we have synthesized the new diphenylnaphthalene-based diguanidine **1** (Scheme 1). The obtained diguanidine **1** recognized “dicarboxylic acids” and “diphosphonic acids” in a DMSO solution, and the formation of 1:1 complexes was determined by a DOSY NMR analysis. The weak yellowish fluorescence of the diguanidine **1** in a DMSO solution turned into a strong bluish fluorescence after the addition of 1,3-benzenediacetic acids **3**. However, after the addition of other types of aliphatic carboxylic acids, such as α,ω-dicarboxylic acids, only a weak yellowish fluorescence was observed and selective

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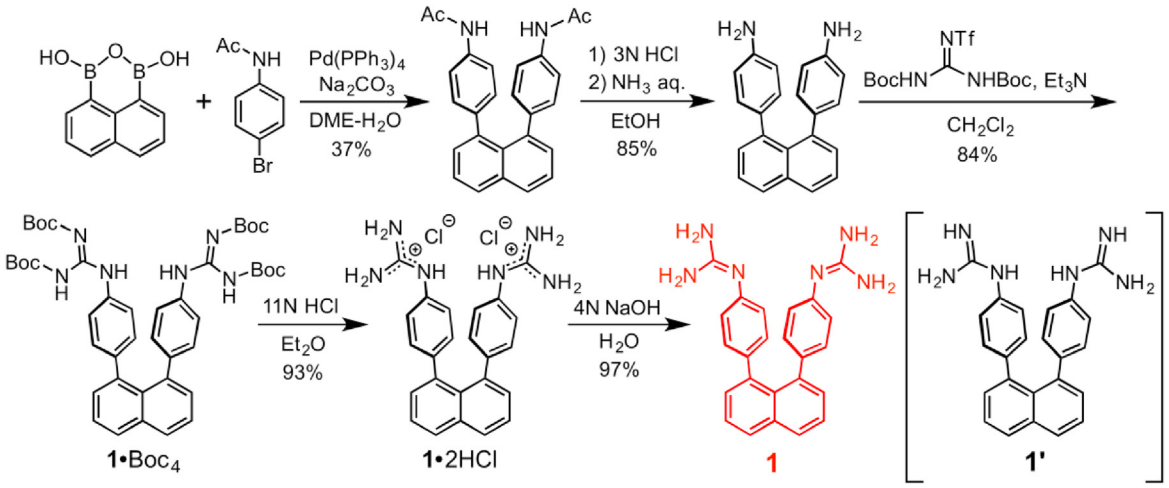

Scheme 1. Synthesis of diguanidine **1**.

recognition of the 1,3-benzenediacetic acids **3** was developed. Additionally, for the recognition of phosphonic acid diethyl ester derivatives, a light blue, blue or pinkish fluorescence was observed. Interestingly, the binding mode (Type I and Type II) on the guanidyl group with oxoacids was successfully determined by the 2D NOESY analysis.

2. Results and discussion

2.1. Synthesis of diguanidine *1*

The diphenylnaphthalene-based diguanidine **1** was prepared according to Scheme 1. The 1,8-di(4′-aminophenyl)naphthalene was prepared using the Suzuki-Miyaura coupling from 1,8-naphthalenediboronic anhydride and 4-bromoacetanilide followed by deprotection of the acetyl group. For the synthesis of the diphenylnaphthalene-based diguanidine **1**, we used Goodman's reagent [5] for the synthesis of the Boc protected diguanidine **1**•Boc_4 and obtained the product in 84% yield by the reaction with 1,8-di(4′-aminophenyl)naphthalene. The ^{1}H NMR spectrum of the Boc protected diguanidine **1**•Boc_4 showed two types of NH signals at 11.6 ppm (H^o) and 9.97 ppm (H^p) in Fig. 1a. The structure of the **1**•Boc_4 (non-conjugated structure of the C=N double bond with diphenylnaphtalene ring) was confirmed by the HMBC correlation between H^p and C^a (see Fig. 1a and supporting information). The obtained Boc protected product **1**•Boc_4 was converted to the diguanidine dihydrochloride **1**•2HCl in an almost quantitative yield. The diguanidine **1** was obtained from the diguanidine dihydrochloride **1**•2HCl by treatment with NaOH aq. (yield: 97%).

There are two isomeric structures for the target diguanidine (**1** and **1′**) that have conjugated and non-conjugated C=N double bonds between the diphenylnaphthalene ring, respectively (Scheme 1). The ^{1}H NMR spectrum of the obtained diphenylnaphthalene-based diguanidine showed only one broad NH signal at 4.88 ppm in DMSO-d_6 (Fig. 1b). The DFT optimized structure of the conjugated structure **1** was 5.0 kcal/mol more

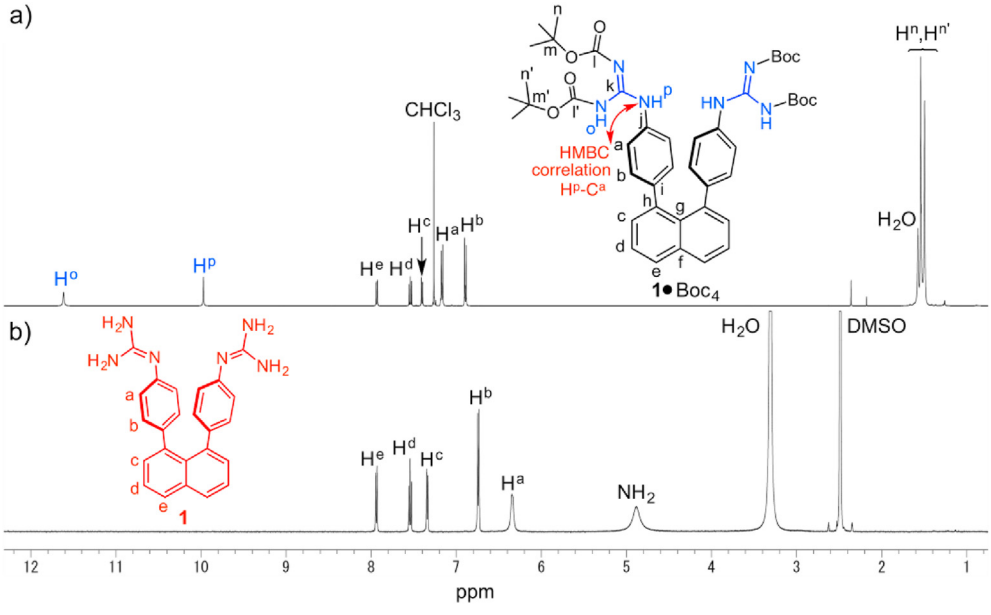

Figure 1. ^{1}H NMR spectra of a) **1**•Boc_4 in $CDCl_3$, and b) diguanidine **1** in DMSO-d_6.

stable than the non-conjugated structure **1'** (B3LYP/6-31G*, Fig. S24). Recently, Antol [6] and co-workers also proposed the conjugated structure of the aromatic guanidine derivatives using DFT calculations.

2.2. Binding experiments of diphenylnaphthalene-based diguanidine *1* with dicarboxylic acids (*2*–*4*)

To investigate the binding ability of the diguanidine **1** toward the dicarboxylic acids (Chart 1), we observed the ^{1}H NMR and DOSY NMR spectra for the complexation of diguanidine **1** with slightly rigid dicarboxylic acids (**2** and **3**). The formation of the 1:1 complex **1•2** was achieved by mixing the DMSO-d_6 solutions ([**1**] = [**2**] = 1.89 mM) of **1** and **2**. The ^{1}H NMR spectrum of the obtained solution showed the characteristic upfield and downfield shifts with respect to those of **1** and **2** (Fig. 2, S1). The downfield shift of the guanidine unit (H^a, H^b) and the upfield shift of the dicarboxylic acid unit (H^A, H^D) in the ^{1}H NMR indicated the formation of a cationic charge and an anionic charge in each unit after complexation.

To obtain information about the formation of the 1:1 complex **1•2**, the DOSY NMR spectroscopy was evaluated. The ^{1}H DOSY spectra showed that the diffusion coefficient of the complex **1•2** is lower than those of the corresponding free building blocks (**1**, **2**), confirming the formation of the binding complex (Fig. 3). The calculated molecular volume of the complex **1•2** derived from the observed diffusion coefficient ($V = 918$ Å^3) is slightly larger than the sum of the volumes of the free building blocks (**1**: $V = 546$ Å^3, **2**: $V = 226$ Å^3), which indicated the formation of the stable 1:1 complex (Fig. 3, Table 1). There are two binding sites (Type I, Type II, see reference 6) for the diguanidine **1**, and two possible structures exist for the formation of the 1:1 complex between the diguanidine **1** and the dicarboxylic acids (Chart 2). Additionally, the conformations of the dicarboxylic acid part also have two possibilities (up and down) and there are four isomeric structures (Chart 2). The DFT calculations of the 1:1 complex **1•2** of the diguanidine **1** and dicarboxylic acid **2** showed that the "Type I-down" is the most stable structure compared to the other structures (Relative energy; Type I-down: 0.00 kcal/mol, Type I-up 2.77 kcal/mol, Type II-down 3.60 kcal/mol, Type II-up 2.31 kcal/mol, see Fig. S25).

The complexation of the diguanidine **1** with the 1,3-benzenediacetic acids **3a** and **3b** also showed the formation of the stable 1:1 complexes **1•3a** and **1•3b** in DMSO-d_6, which were confirmed by ^{1}H NMR and DOSY NMR spectroscopies (Figures S2-3, S11-12, Table 1). The binding mode and the stable conformation of the 1:1 complex **1•3a** was also evidenced by the DFT calculations as the Type I-down structure (Fig. S26).

To explore the applicability of this diguanidine **1** for the recognition of several dicarboxylic acids, we evaluated the recognition of the conformationally flexible α,ω−dicarboxylic acids **4**. The

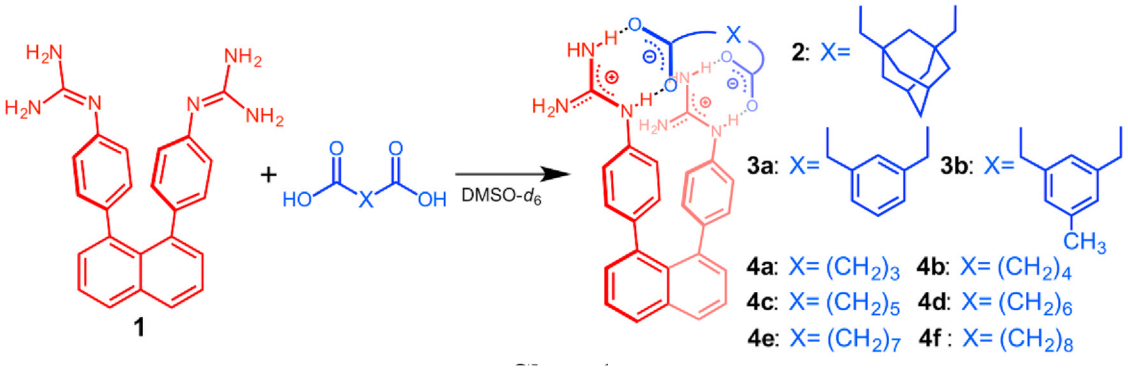

Chart 1.

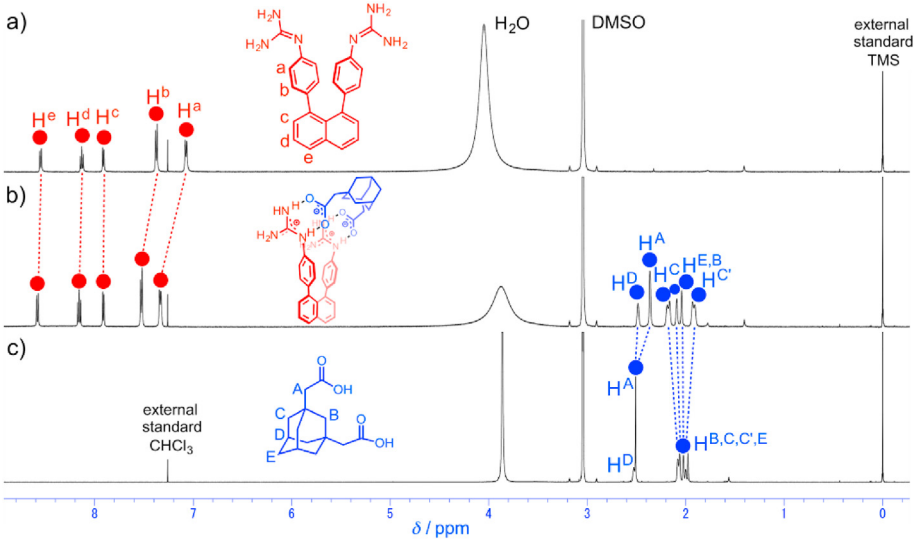

Figure 2. ^{1}H NMR spectra (1.89 mM in DMSO-d_6, 298 K) of a) diguanidine **1**, b) **1•2** obtained by mixing equimolar solutions of **1** and **2**, and c) dicarboxylic acid **2**.

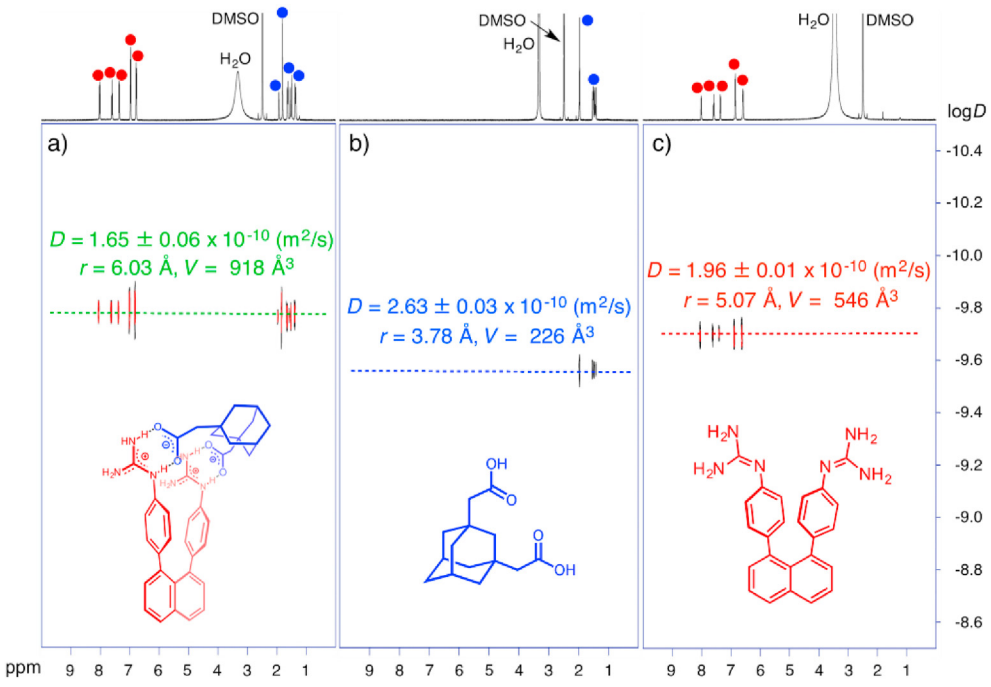

Figure 3. ^{1}H DOSY spectra (1.89 mM in DMSO-d_6, 25 °C, diffusion time Δ = 200 ms) of a) complex **1•2**, b) dicarboxylic acid **2**, c) diguanidine **1**.

Table 1
Comparison of diffusion coefficients, molecular radii and volumes.[a].

Compounds	D (m^2S^{-1})	r_H (Å)	V (Å^3)
1	1.96±0.01 x 10^{-10}	5.07	546
2	2.63±0.03 x 10^{-10}	3.78	226
1•2	1.65±0.06 x 10^{-10}	6.03	918
3a	2.80±0.02 x 10^{-10}	3.55	187
1•3a	1.65±0.02 x 10^{-10}	6.03	918
3b	2.60±0.03 x 10^{-10}	3.82	233
1•3b	1.66±0.02 x 10^{-10}	5.99	900
4c	2.90±0.03 x 10^{-10}	3.43	169
1•4c	1.68±0.05 x 10^{-10}	5.92	869
4d	2.80±0.01 x 10^{-10}	3.55	187
1•4d	1.58±0.09 x 10^{-10}	6.29	1042
4e	2.69±0.03 x 10^{-10}	3.70	212
1•4e	1.63±0.05 x 10^{-10}	6.10	951

[a] Diffusion coefficients were recorded at 298 K in DMSO-d_6 (1.89 mM), and the molecular radii were calculated using the Stokes-Einstein equation.

formation of the 1:1 complex **1•4c** (X=$(CH_2)_5$) was also achieved by mixing the DMSO-d_6 solution (1.89 mM) of both components. The ^{1}H NMR spectrum of the obtained solution showed the characteristic upfield and downfield shifts with respect to those of **1** and **4c**, which indicated the formation of the complex (Fig. S4). The molecular volume of **1•4c** (V = 869 Å^3) derived from the observed diffusion coefficient using DOSY NMR spectroscopy is similar to the sum of the volumes of the free building blocks (**1**: V = 546 Å^3, **4c**: V = 169 Å^3), which also indicated the formation of the stable 1:1 complex (Table 1, Fig. S13). For the complexation of the diguanidine **1** with the dicarboxylic acids **4d** (X=$(CH_2)_6$) and **4e** (X=$(CH_2)_7$), it also showed the formation of the stable 1:1 complexes **1•4d** and **1•4e** in DMSO-d_6, which was also confirmed by the ^{1}H NMR and DOSY NMR spectroscopies (Figures S5-6, S14-15, Table 1).

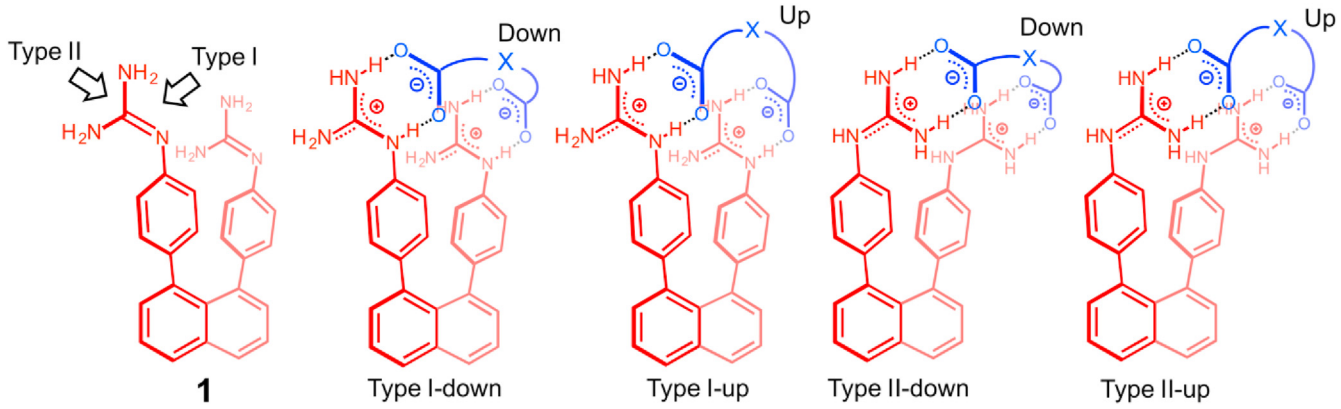

Chart 2.

2.3. Binding experiments of diphenylnaphthalene-based diguanidine **1** with diphosphonic acid diethyl esters (**5**–**7**)

To compare the recognition ability between the "dicarboxylic acids" and "diphosphonic acid derivatives", we examined the recognition of the diphosphonic acid derivatives **5**, **7a** (Y=$(CH_2)_3$), and **7c** (Y=$(CH_2)_5$) which have solubilizing Et groups after the complex formation (protection of the hydroxy group to inhibit the formation of a higher aggregate, Chart 3). The formation of the 1:1 complex **1•5** was also achieved by mixing the DMSO-d_6 solutions (1.89 mM) of both components. The ^{1}H NMR spectrum of the obtained solution showed the characteristic downfield and upfield shifts with respect to those of **1** and **5**, respectively (Fig. 4, S7). The resonance of the NH protons was observed at 10.8 and 8.0 ppm indicating the formation of "guanidinium-phosphonate" salt bridges (i.e., formation of a stable complex, Fig. 4b).

The DOSY spectra of the complex **1•5** confirmed the formation of a stable complex (Fig. 5). The molecular volume of **1•5** derived from the observed diffusion coefficient (V = 1062 Å^3) is similar to the sum of the volumes of the free building blocks (**1**: V = 546 Å^3, **5**: V = 352 Å^3), which indicated the formation of the stable 1:1 complex (Table 2).

The DFT calculations of the 1:1 complex **1•5** of the diguanidine **1** and diphosphonic acid diethyl ester **5** also showed that the Type I-down is a more stable structure than the other binding mode (Chart 2, Fig. S27). The NOESY spectrum of the 1:1 complex **1•5** of the diguanidine **1** and diphosphonic acid diethyl ester **5** showed the NOE correlations between H^a and H^F (or H^E), indicating the formation of the Type I-down structure (Fig. 6, S29).

For the complexation of the diguanidine **1** with the diphosphonic acid diethyl esters having a methylene chain **7c** (Y=$(CH_2)_5$), the ^{1}H NMR spectra of the formed complexes showed reasonable upfield and downfield shifts indicating the formation of stable complexes (Fig. S9). For the 1:1 complex **1•7c**, a slightly larger molecular volume compared to the formation of **1•5** was observed by the DOSY NMR spectroscopy which indicated the formation of a stable 1:1 complex, and also the NOESY correlation was observed for the formation of the Type-I down structure (Figs. S10 and S17, Table 2). On the other hand, for the complexation of diguanidine **1** with the diphosphonic acid diethyl ester **7a** (Y=$(CH_2)_3$) which has a shorter methylene chain length than **7c**, two different diffusion coefficients were observed derived from diguanidine **1** (G) and the diphosphonic acid diethyl ester **7a** (Y=$(CH_2)_3$, P) in the DOSY spectra (Figs. S8 and S16, Table 2) [7]. These observations showed the formation of a weaker complex **1•7a** (Y=$(CH_2)_3$) than **1•7c** (Y=$(CH_2)_5$) and **1•5** that may be caused by the absence and presence of the multiple hydrogen bonding interactions after the complex formation which was estimated by the DFT calculations (Fig. 7, S27-28).

2.4. Fluorescence detection of carboxylic acids using diguanidine **1**

To demonstrate the recognition ability of the diguanidine **1** toward dicarboxylic acids, we observed the fluorescence spectra of the diguanidine **1** with dicarboxylic acids **2**–**4** and benzoic acid **8** (2 eq.) in a DMSO solution. The diguanidine **1** itself shows a very weak yellow fluorescence as a broad band (λ_{max} = 586 nm) in the DMSO solution (Fig. 8). After the addition of 1 equivalent of the 1,3-adamantanediacetic acid **2** and α,ω-dicarboxylic acids **4**, the yellow fluorescence of the diguanidine **1** had only slightly changed and the small increasing of the fluorescence band around 420 nm was observed as a yellowish color. Surprisingly, after the addition of 1 equiv. of 1,3-benzenediacetic acid **3a**, a strong emission was observed at λ_{max} = 417 nm as a bluish color. A similar strong emission was observed after the addition of the 1,3-benzenediacetic acid derivative **3b** to the solution of diguanidine **1** (Fig. 8).

The Job's plot analysis for the complexation of the diguanidine **1** and dicarboxylic acids **3a** and **3b** showed the formation of the 1:1 complex by fluorescence spectroscopy at a high concentration (200 μM, Figs. S20–21). For the complexation with the benzoic acid **8** (aromatic monocarboxylic acid, 2 equiv.) with diguanidine **1**, which corresponds to the formation of guanidinium, and the fluorescence spectrum of the hydrochloric acid salt of **1** (**1**•2HCl, corresponding to protonated guanidinium of **1**), a weak fluorescence was observed around 410 nm (Fig. 8).

To obtain evidence for the formation of the guanidinium-carboxylate bonding and also to assign the fluorescence wavelength (410 nm) of the guanidinium species (i.e., **1**+2H$^+$), we measured the fluorescence spectra of **1•3a** after the addition of H_2O (Fig. 9, Chart 4). The intensity of the fluorescence spectrum of **1•3a** decreased and blue-shifted (λ_{max} = 403 nm) by the addition of H_2O (0–1000 μL) which indicated the formation and dissociation of the guanidinium-carboxylate bonding.

The binding constants of the diguanidine **1** and dicarboxylic acids **2**, **3**, **4c**, **4e** with a 1:1 stoichiometry were determined by fluorescence titrations, and pK_a values of the dicarboxylic acids are summarized in Table 3. The binding constants of the diguanidine **1** and dicarboxylic acids are on the order of 10^4-10^6 (M^{-1}) in the DMSO solution. Surprisingly, higher binding constants were observed for the complexation with the 1,3-benzenediacetic acid derivatives **3a** and **3b** ($K_{1:1}$ = 1.5 × 10^6 M^{-1}) than with the α,ω-dicarboxylic acids **4c** and **4e** (Table 3). These higher binding constants agreed with the observation of the higher fluorescence

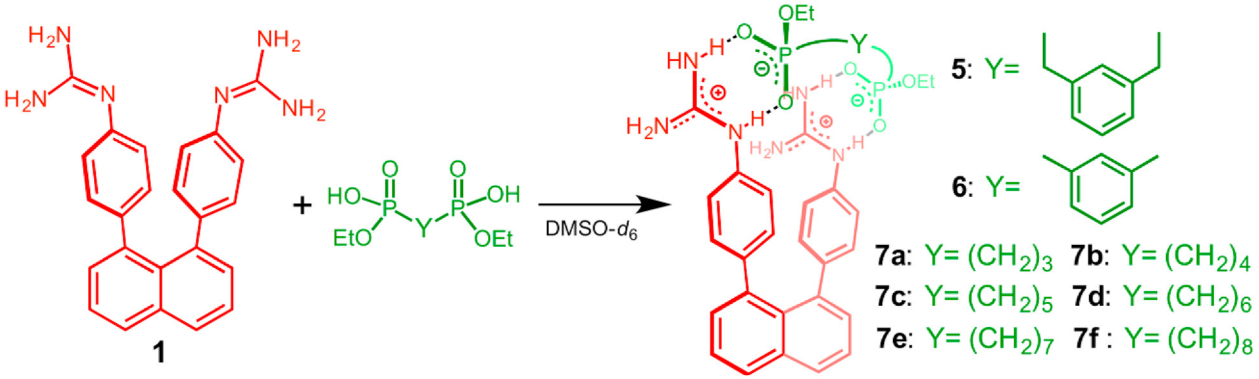

Chart 3.

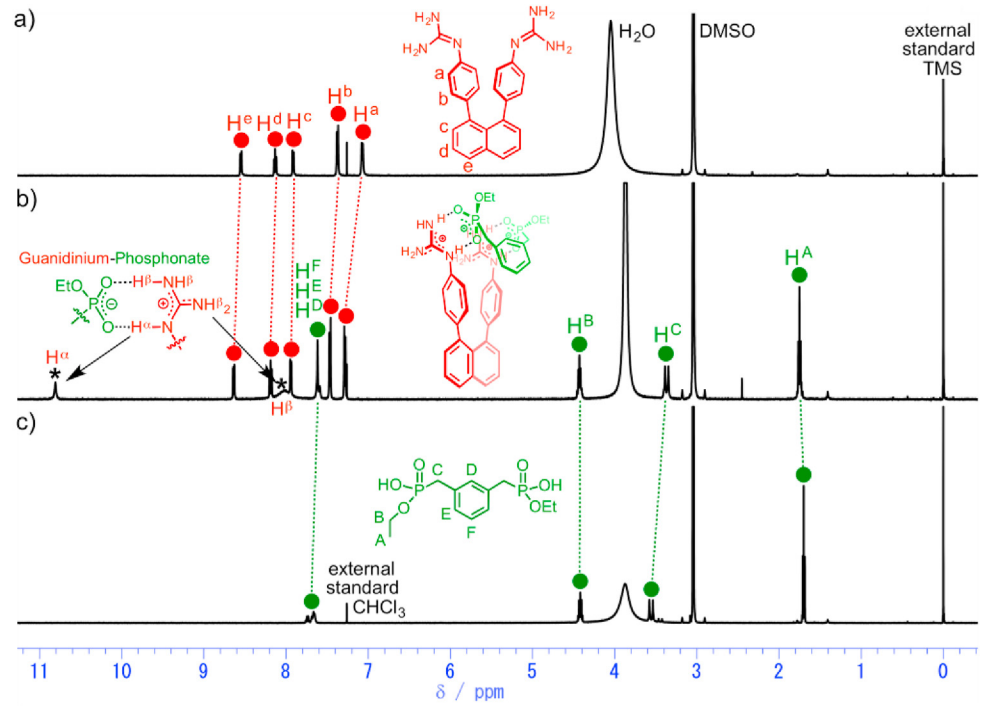

Figure 4. ^{1}H NMR spectra (1.89 mM in DMSO-d_6, 298 K) of a) diguanidine **1**, b) **1•5** obtained by mixing equimolar solutions of **1** and **5**, and c) diphosphonic acid diethyl ester **5**.

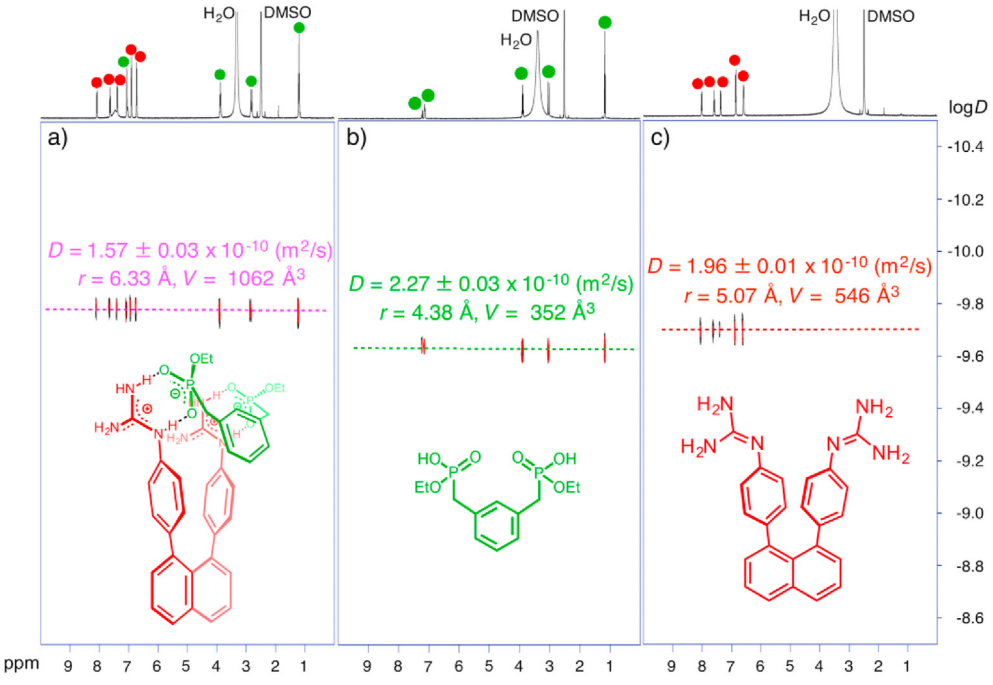

Figure 5. ^{1}H DOSY spectra (1.89 mM in DMSO-d_6, 298 K, diffusion time Δ = 200 ms) of a) complex **1•5**, b) diphosphonic acid diethyl ester **5**, c) diguanidine **1**.

intensities of the mixed solutions of diguanidine **1** with the dicarboxylic acids **3** compared to the dicarboxylic acids **4** (Fig. 8). Relatively higher binding constants were observed for the complexation with carboxylic acids having low pK_a values.

2.5. Fluorescence detection of diphosphonic acids using diguanidine *1*

To further understand the recognition ability of the diguanidine **1** toward diphosphonic acids, we observed the fluorescence spectra

Table 2
Comparison of diffusion coefficients, molecular radii and volumes.[a].

Compounds	D (m^2S^{-1})	r_H (Å)	V (Å^3)
1	1.96±0.01 x 10^{-10}	5.07	546
5	2.27±0.03 x 10^{-10}	4.38	352
1•5	1.57±0.03 x 10^{-10}	6.33	1062
7a	2.50±0.04 x 10^{-10}	3.98	264
1•7a	1.58±0.03 x 10^{-10}(G)[b]	6.29	1042
	1.99±0.03 x 10^{-10}(P)[c]	5.00	524
7c	2.39±0.05 x 10^{-10}	4.16	302
1•7c	1.38±0.06 x 10^{-10}	7.21	1570

[a] Diffusion coefficients were recorded at 298 K in DMSO-d_6 (1.89 mM, diffusion time Δ = 200 ms), and the molecular radii were calculated using the Stokes-Einstein equation.
[b] Derived from diguanidine **1**.
[c] Derived from diphosphonic acid diethyl ester **7a**.

of the diguanidine **1** with diphosphonic acids **5**–**7** in a DMSO solution. The diguanidine **1** itself showed a weak yellow fluorescence as a broad band (λ_{max} = 586 nm) in the DMSO solution as already discussed. After the addition of 1 equivalent of the diphosphonic acids **5**–**7**, the yellow fluorescence of the diguanidine **1** had changed and the increasing of the fluorescence band around 420–430 nm was observed as a light blue, blue or pinkish color (Fig. 10).

The Job's plot analysis for the complexation of the diguanidine **1** and diphosphonic acids **5**, **7c** showed the formation of the 1:1 complex by fluorescence spectroscopy (Figs. S22–23). To obtain evidence for the formation of the guanidinium-phosphonate bonding and to also assign the fluorescence wavelength of the 1:1 complex of the diguanidine **1** and diphosphonic acids, we measured the fluorescence spectra of **1•5** after the addition of H_2O

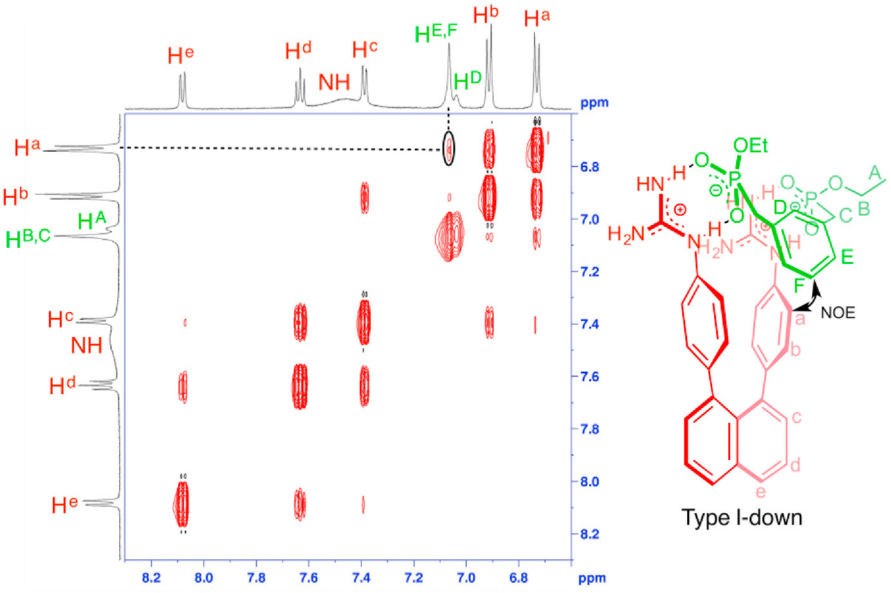

Figure 6. ^{1}H NOESY spectrum (1.89 mM in DMSO-d_6, 298 K, mixing time = 2 sec.) of complex **1•5**.

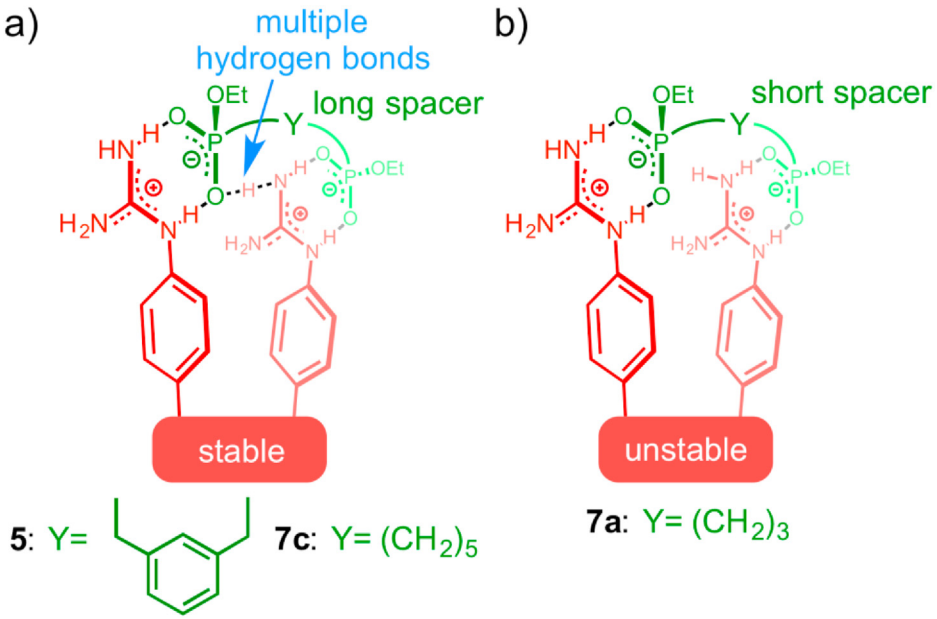

Figure 7. Schematic representation of the formation of the stable and unstable complexes with and without multiple hydrogen bonding interactions.

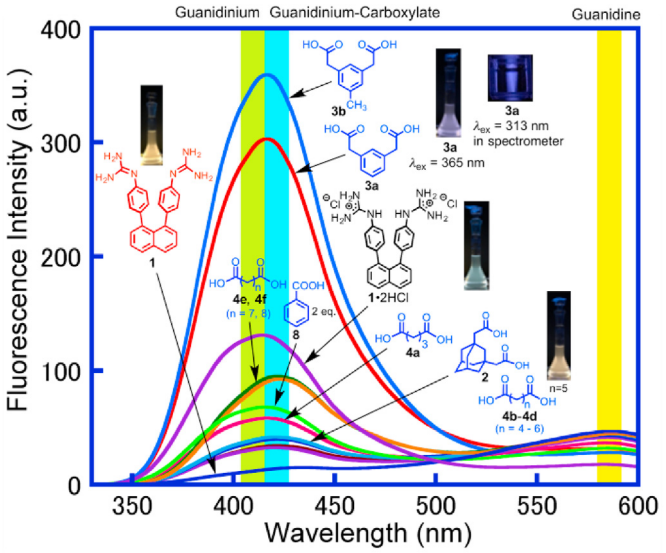

Figure 8. Fluorescence spectra of diguanidine **1** (25 μM in DMSO, λ_{ex} = 313 nm) upon the addition of carboxylic acids, and fluorescence spectrum of **1**•2HCl (25 μM in DMSO).

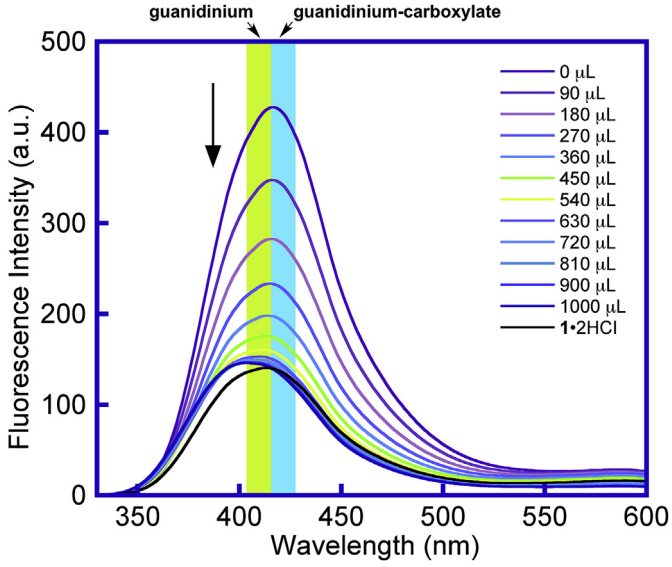

Figure 9. Fluorescence spectra of **1**•**3a** (25 μM, 3 mL in DMSO, λ_{ex} = 313 nm) upon the addition of H_2O.

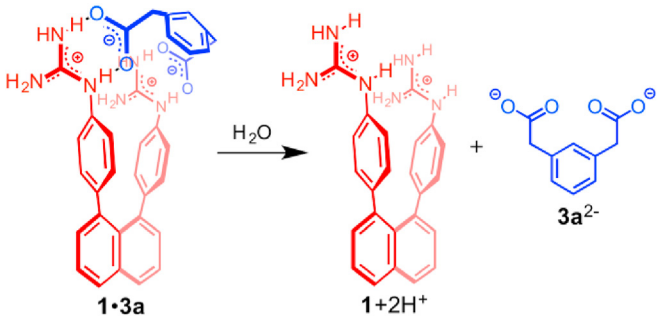

Chart. 4.

Table 3
Binding constants ($K_{1:1}$)[a] of diguanidine **1** with dicarboxylic acids and diphosphonic acids, and pK_a values.[b].

oxoacids	$K_{1:1}$/M^{-1}	p$K_{a\ (obs)}$		p$K_{a\ (calc)}$
2 (1,3-adamantanediacetic acid)	2.8 x 10^4			4.42
3a (1,3-benzenediacetic acid)	1.5 x 10^6			3.93
3b (5-methyl-1,3-benzenediacetic acid)	1.5 x 10^6			3.94
4c (pimelic acid, X= $(CH_2)_5$)	2.4 x 10^4	4.71	5.58	4.43
4e (azelaic acid, X= $(CH_2)_7$)	7.2 x 10^4	4.53	5.33	4.47
5 (Y= *m*-xylylene)	1.7 x 10^6			2.09
7c (Y= $(CH_2)_5$)	1.2 x 10^6			2.65

[a] Binding constants were determined by fluorescent titration in DMSO (**1**: 25 μM,) using the 1:1 model.
[b] p$K_{a\ (obs)}$: pK_a values of carboxylic acids in H_2O, Lide D. R. Ed., *CRC Handbook of Chemistry and Physics*, 88th ed., CRC Press, Boca Raton, FL, 2007-2008; p$K_{a\ (calc)}$: Calculated pK_a values of carboxylic acids and phosphonic acids using Advanced Chemistry Development (ACD/Laboratories) Software V11.02 (1994-2020 ACD/Labs) taken from SciFinder Scholar.

(Fig. S19). The intensity of the fluorescence spectrum of **1•5** slightly decreased and again increased around 400–410 nm by the addition of H_2O (0–1000 μL) which indicated the formation and dissociation of the guanidinium-phosphonate bonding. The binding constants for the complexation of the diguanidine **1** with diphosphonic acid **5** (Y = *m*-xylylene) and **7c** (Y= $(CH_2)_5$) were obtained by the fluorescence titration (**1•5**: K_a = 1.7 × 10^6 M^{-1}, **1•7c**: K_a = 1.2 × 10^6 M^{-1}) as a 1:1 binding model (Table 3, Figs. S35–36).

2.6. Fluorescence quantum yields of carboxylic acids and phosphonic acid binding complexes

The fluorescence quantum yields (Φ_{fl}) of the dicarboxylic acid binding complexes **1•3a**, **1•3b** and diphosphonic acid binding complexes **1•7b** (Y=$(CH_2)_4$), **1•7d** (Y=$(CH_2)_6$) in a DMSO solution were determined by a calibrated integrating sphere (Table 4). Compared to the fluorescence quantum yield of 1,8-diphenylnaphthalene (Φ_{fl} = 0.03 in DMSO) [3g], the introduction of the guanidium-carboxylate and guanidium-phosphonate groups to the 1,8-diphenylnaphthalene unit moderately improved (Φ_{fl} = 0.13–0.27) fluorescence quantum yields in the DMSO solution were observed. The reason for the improvement of the fluorescence quantum yields is not clear at the moment, but there are some possibilities such as the formation of rigid complex or substituent of electron withdrawing groups (i.e., guanidinium-carboxylate or guanidinium-phosphonate groups).

3. Conclusions

We have synthesized the diphenylnaphthalele-based diguanidine **1** for the recognition of carboxylic acids and phosphonic acid derivatives. The diguanidine **1** forms 1:1 complexes with dicarboxylic acids in a DMSO solution and the formation of the complexes were confirmed by the DOSY NMR analysis. For the recognition of the diphosphonic acid diethyl esters, the formation of 1:1 complexes were also evidenced by the DOSY NMR analysis. For the fluorescence detection of the dicarboxylic acids, the weak yellowish fluorescence of the diguanidine **1** in a DMSO solution turned into a strong bluish fluorescence after the addition of the 1,3-benzenediacetic acids **3**, and selective recognition of **3** was developed. On the other hand, after the addition of the diphosphonic acid derivatives, several types of fluorescence colors were observed. Interestingly, the binding mode on the guanidyl group with oxoacids (Type I-down) was successfully determined by the 2D NOESY analysis. These fluorescence characteristics of the diguanidine **1** are applicable for the detection of dicarboxylic acids and diphosphonic acids.

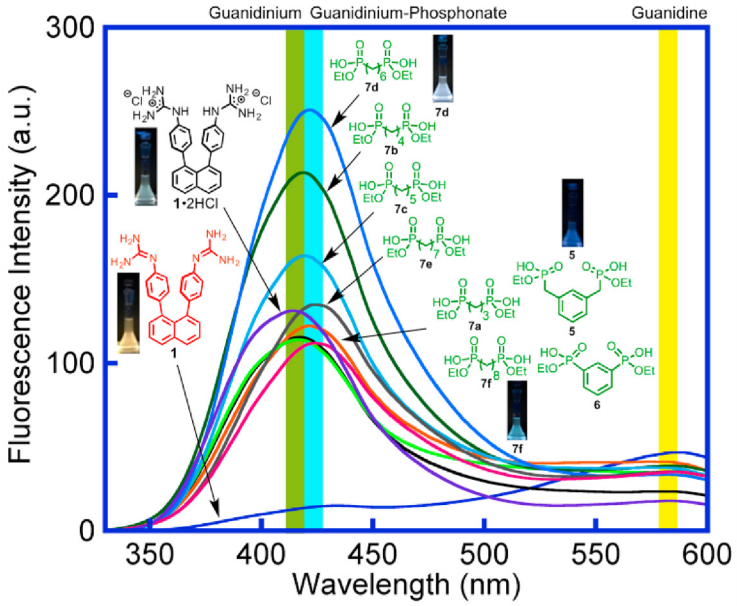

Figure 10. Fluorescence spectra of diguanidine **1** (25 μM in DMSO, λ_{ex} = 313 nm) upon the addition of diphosphonic acids, and fluorescence spectrum of **1**•2HCl (25 μM in DMSO).

Table 4
Fluorescence quantum yields (Φ_{fl}) of dicarboxylic acid-binding complexes and diphosphonic acid-binding complexes in DMSO[a].

compound	Φ_{fl}
1,8-Diphenylnaphthalene	0.03[b]
1	0.07
1•3a	0.27
1•3b	0.26
1•7b (Y=$(CH_2)_4$)	0.13
1•7d (Y=$(CH_2)_6$)	0.20

[a] Fluorescence quantum yields were determined by a calibrated integrating sphere.
[b] in DMSO, from reference 3g.

4. Experimental section

4.1. General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded using Avance III 500 (500 and 125 MHz) spectrometers. The FAB-mass spectra were recorded by a JEOL JMS-700 mass spectrometer. The absorption spectra were recorded by a SHIMADZU UV-2550 UV–Visible spectrometer. The fluorescence spectra were recorded by a JASCO FP-6200 spectrometer, and the fluorescence spectra were corrected using rhodamine B as the reference. The absolute PL quantum yields (Φ_{fl}) were determined by a Quantaurus-QY (Hamamatsu Photonics) instrument. All solvents and reagents were purified according to standard procedures. For the NMR measurement using $CDCl_3$, the acidic impurity in the $CDCl_3$ solvent was removed by passage through basic Al_2O_3 (Merck, 101,076). 1,3-Bis(cyanomethyl)-5-methylbenzene was purchased from TCI (Tokyo Chemical Industry Co., Ltd).

4.1.1. Synthesis of 1,8-naphthalenediboronic anhydride [8]

To a solution of 1,8-diiodonaphthalene (501 mg, 1.32 mmol) in Et_2O (16 mL) was slowly added *n*-BuLi (1.85 M in hexane, 2.14 mL, 3.96 mmol) at −80 °C over 15 min. After stirring the obtained yellow solution for 20 min. at −80 °C, $B(OMe)_3$ (0.58 mL, 5.19 mmol) was smoothly added (attention: melting point of $B(OMe)_3$ is −34 °C). The solution was stirred for 20 min. at −80 °C, then gradually warmed to room temperature over 2 h and stirred overnight at room temperature. The reaction was quenched with H_2O (5 mL) followed by 2 M HCl (10 mL), then stirred at room temperature for 45 min. The organic phase was separated and the water phase was additionally extracted with Et_2O (15 mL x 3). The combined organic phase was extracted with 10% NaOH aq. (10 mL x 3), then the obtained alkaline fraction was acidified with conc. HCl (10 mL). The obtained colorless solids were collected and vacuum dried (208 mg, 80%)

Colorless solid; mp > 300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.14 (s, 2H, B–OH), 8.17 (dd, J = 6.8 Hz, 1.2 Hz, 2H), 8.09 (dd, J = 8.3 Hz, 1.1 Hz, 2H), 7.59 (t, J = 7.5, 2H). ^{13}C NMR (125 MHz, DMSO-d_6); δ = 141.3 (C_q), 134.1 (CH), 131.5 (CH), 131.4 (C_q), 125.5 (CH), missing one carbon (C–B) due to interaction with the boron atom.

4.1.2. Synthesis of 1,8-di(4′-acetoamidophenyl)naphthalene [9]

1,8-Naphthalenediboronic anhydride (303 mg, 1.53 mmol), 4-bromoacetanilide (976 mg, 4.56 mmol), and $Pd(PPh_3)_4$ (175 mg, 0.15 mmol) were mixed in DME (60 mL), then a 0.5 M Na_2CO_3 aqueous solution (15 mL, 7.50 mmol) was added. The obtained mixture was degassed 3 times by a freeze-pump-through method, then the mixture was heated at 85 °C for 20 h in an Ar atmosphere. After removing the solvent in vacuo and adding water (20 mL), the mixture was extracted with CH_2Cl_2 (20 mL x 3), then evaporated. The target product was also precipitated as a gray solid in the water phase, then recovered by filtration. All the fractions were combined, then 1,8-di(4′-acetoamidophenyl)naphthalene was isolated (225 mg, 37%) by column chromatography (SiO_2, $CHCl_3$/MeOH = 19/1).

^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.71 (s, 2H), 8.00 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.36 (d, J = 7.0 Hz, 2H), 7.19 (d, J = 8.5 Hz, 4H), 6.84 (d, J = 8.5 Hz, 4H), 1.99 (s, 6H).

4.1.3. Synthesis of 1,8-di(4′-aminophenyl)naphthalene [9]

1,8-Di(4′-acetoamidophenyl)naphthalene (175 mg, 0.44 mmol), 3 M HCl aq. (1.6 mL), and EtOH (8 mL) were mixed and refluxed for 29 h. After cooling to room temperature, 28% NH_3 aq. (1.5 mL) was

added and extracted with CH_2Cl_2 (10 mL x 3). The combined organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The 1,8-di(4′-aminophenyl)naphthalene (118 mg, 85%) was isolated by column chromatography (SiO_2, AcOEt).

^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 7.86$ (d, $J = 8.2$ Hz, 2H), 7.50 (t, $J = 7.6$ Hz, 2H), 7.28 (d, $J = 7.1$ Hz, 2H), 6.65 (d, $J = 8.4$ Hz, 4H), 6.19 (d, $J = 8.4$ Hz, 4H), 4.78 (s, 4H).

4.1.4. Synthesis of 1•Boc$_4$

1,8-Di(4′-aminophenyl)naphthalene (102 mg, 0.33 mmol), 1,3-bis(*tert*-butoxycarbonyl)-2-(trifluoro-methanesulfonyl)guanidine (Goodman's reagent, 315 mg, 0.81 mmol), and dry-Et_3N (112 μL, 0.82 mmol) were mixed in 3 mL of dry CH_2Cl_2. The obtained mixture was stirred for 1 day under an Ar atmosphere at room temperature. During the course of the reaction, the amount of dry CH_2Cl_2 (should not added a large amount of solvent) was maintained and the reaction was monitored by TLC ($R_f = 0.73$ for **1**•Boc$_4$, $R_f = 0.37$ for monoguanidine•Boc$_2$, $CHCl_3$ as the solvent). To obtain the Boc-protected digauanidine **1**•Boc$_4$, 1,3-bis(*tert*-butoxycarbonyl)-2-(trifluoromethanesulfonyl)guanidine (Goodman's reagent, 88 mg, 0.23 mmol) was additionally added to reaction mixture, and stirred for a total of 6 days under an Ar atmosphere at 40–45 °C. To the reaction mixture, CH_2Cl_2 (10 mL) and 5% $NaHCO_3$ aq. (10 mL) were added, additionally extracted with CH_2Cl_2 (10 mL x 2), and the combined CH_2Cl_2 layer was dried (Na_2SO_4), and evaporated under reduced pressure. The target product **1**•Boc$_4$ (50 mg, 84%) was obtained by column chromatography (SiO_2, toluene).

Colorless solid; mp > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 11.62$ (brs, 2H, NH), 9.97 (brs, 2H, NH), 7.94 (dd, $J = 8.3$, 1.3 Hz, 2H), 7.54 (dd, $J = 8.1$, 7.0 Hz, 2H), 7.40 (dd, $J = 7.0$, 1.3 Hz, 2H), 7.17 (d, $J = 8.5$ Hz, 4H), 6.89 (d, $J = 8.5$ Hz, 4H), 1.53 (s, 18H), 1.49 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$); δ = 163.7 (C_q), 153.6 (C_q), 153.1 (C_q), 151.4 (C_q), 140.0 (C_q), 139.8 (C_q), 135.4 (C_q), 134.3 (C_q), 130.7 (CH), 130.1 (CH), 129.5 (C_q), 128.5 (CH), 125.1 (CH), 122.0 (CH), 86.0 (C_q), 83.2 (C_q), 79.2 (C_q), 28.2 (CH_3), 27.8 (CH_3). HRMS (FAB, NBA) m/z = 795.4083 (calculated for $[M+H]^+$: 795.4081). Anal. Calcd. for $C_{44}H_{54}N_6O_8$•H_2O: C:65.01, H:6.94, N:10.34. Found: C:65.23, H:6.69, N:10.36.

4.1.5. Synthesis of 1,8-di(4′-guanidinophenyl)naphthalene dihydrochloride 1•2HCl

To a suspension of **1**•Boc$_4$ (30 mg, 37.9 μmol) in Et_2O (15 mL) at 0 °C was added 10 mL of 1 M HCl. The reaction mixture was stirred at 0 °C for 10 min, then at room temperature for 7 h. The reaction (water layer) was monitored by ^{1}H NMR (D_2O) to confirm the disappearence of the Boc group. To complete the deprotection, 5 mL of 11 M HCl was added to the reaction mixture and stirred at room temperature for an additional 4 h. After the addition of distilled water (20 mL x 2), the water phase was separated, then concentrated to provide the title compound (17 mg, 93%).

Colorless solid; mp 250.4 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 9.82$ (brs, 2H, NH), 8.10 (dd, $J = 8.3$, 1.2 Hz, 2H), 7.65 (dd, $J = 8.1$, 7.1 Hz, 2H), 7.41 (dd, $J = 7.1$, 1.3 Hz, 2H), 7.35 (brs, 8H, NH), 6.97 (d, $J = 8.5$ Hz, 4H), 6.82 (d, $J = 8.4$ Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6); δ = 155.9 (C_q), 140.7 (C_q), 138.7 (C_q), 135.1 (C_q), 132.7 (C_q), 130.8 (CH), 130.6 (C_q), 129.0 (CH), 128.5 (C_q), 125.5 (CH), 123.2 (CH). Anal. Calcd. for $C_{24}H_{22}N_6$•3.4HCl: C:55.60, H:4.94, N:16.21. Found: C:55.35, H:5.05, N:16.61.

4.1.6. Synthesis of 1,8-di(4′-guanidinophenyl)naphthalene 1

To a stirred solution of 4 M NaOH (13 mL), an aqueous solution of 1,8-di(4′-amidinophenyl)-naphthalene dihydrochloride **1**•2HCl (64 mg, 0.14 mmol, 10 mL) was dropwise added at 0 °C over 15 min, and additionally stirred at 0 °C for 40 min. The resulting precipitate was collected by filtration and washed with cold distilled water (2 mL x 5) to give a colorless solid **1** (49 mg, 91%).

Colorless solid; mp 216.5–217.4 °C; ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 7.95$ (d, $J = 7.5$ Hz, 2H), 7.55 (t, $J = 6.8$ Hz, 2H), 7.35 (d, $J = 6.3$ Hz, 2H), 6.76 (d, $J = 7.1$ Hz, 2H), 6.38 (d, $J = 6.7$ Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 152.2 (C_q), 148.2 (C_q), 140.5 (C_q), 135.3 (C_q), 135.0 (C_q), 130.2 (CH), 130.0 (CH), 128.8 (C_q), 127.7 (CH), 125.2 (CH), 121.5 (CH). HRMS (FAB, NBA) $m/z = 395.1985$ (calculated for $[M+H]^+$: 395.1984). Anal. Calcd. for $C_{24}H_{22}N_6$•0.7H_2O: C:70.81, H:5.79, N:20.64. Found: C:70.84, H:5.44, N:20.41.

4.1.7. Synthesis of 5-methyl-1,3-benzenediacetic acid [10]

1,3-Bis(cyanomethyl)-5-methylbenzene (1.0 g, 5.9 mmol), EtOH (13 mL), and a 2.7 M KOH aqueous solution (13 mL, 35 mmol) were mixed and refluxed for 6 h. After cooling to room temperature, 11 M HCl aq. (4 mL) was added, then extracted with AcOEt (15 mL x 2). The combined AcOEt layer was washed with brine (50 mL x 2), dried (Na_2SO_4), then evaporated under reduced pressure to give the target product 5-methyl-1,3-benzenediacetic acid (778 mg, 63%).

Colorless solid; mp 180.0–181.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 6.93$ (s, 2H), 6.91 (s, 1H), 3.47 (s, 4H), 2.25 (s, 3H).

4.2. Jobs plot analysis (fluorescence spectroscopy)

The stock solutions of **1**, dicarboxylic acids and diphosphonic acids in DMSO were prepared in separate volumetric flasks. Several sample solutions containing both the diguanidine **1** and carboxylic acids (or diphosphonic acids) in different ratios (1/9 to 9/1) were prepared and maintained at 0.2 mM. The fluorescence spectra of the mixtures were recorded, and the intensities were analyzed by the Job's method.

4.3. DOSY measurements

For the DOSY experiments with the free building blocks as well as the complexes, the concentrations of **1**, **2**, **3a**, **3b**, **4c**-**4e**, **5**, **7a**, **7c**, **1•2**, **1•3a**, **1•3b**, **1•4c**-**1•4e**, **1•5**, **1•7a** and **1•7c** were kept constant at 1.89 mM. The ^{1}H DOSY experiments were carried out at 298 K using a Bruker Avance III 500 MHz spectrometer equipped with a 5-mm BBFO probe with a z-axis gradient coil. The data were acquired and processed using the Bruker TopSpin 3.0 software. A series of diffusion ordered spectra were collected of the samples using the LEDbp pulse sequence [11]. The pulse-fields were incremented in 50 steps from 2% to 95% of the maximum gradient strength in a linear ramp. The gradient length was selected between 2.0 and 3.0 ms with a diffusion time of 200 ms and an eddy current delay of 5 ms.

4.4. Fluorescence titrations

A solution of the diguanidine **1** was prepared (3–25 μM in DMSO), and an aliquot (3 mL) was transferred to a 1 cm fluorescence tube. To this solution was dropwise added a stock solution of the dicarboxylic acid or diphosphonic acid (0.3–25 mM in DMSO) in small portions. The fluorescence spectra were recorded by excitation at 313 nm. The association constants were calculated using the program HYPSPEC [12] and are summarized in Table 3.

4.5. Computational methods

The ground-state geometries were fully optimized using the density functional theory (DFT) with the B3LYP hybrid functional at the basis set level of 6–31G*. The frequency calculations allowed verification that these structures did not present imaginary frequencies and we had global minima. All of the calculations were

performed with Gaussian 09W [13].

Author contributions

T.K. designed study (conceptualization); T.K., R.M., M.O., R.S., A.N. implemented study; T.K., R.M., M.O., R.S., A.N. generated data; T.K., R.M., M.O., R.S., A.N. did data curation and formal analysis; T.K. wrote the original draft; T.K. reviewed and edited the manuscript; T.K. took care of <grant-highlight > funding</grant-highlight > acquisition and project management.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131770.

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