Organic and Biomolecular Chemistry

Structure-reactivity relationships in a recognition-mediated [3+2] dipolar cycloaddition reaction

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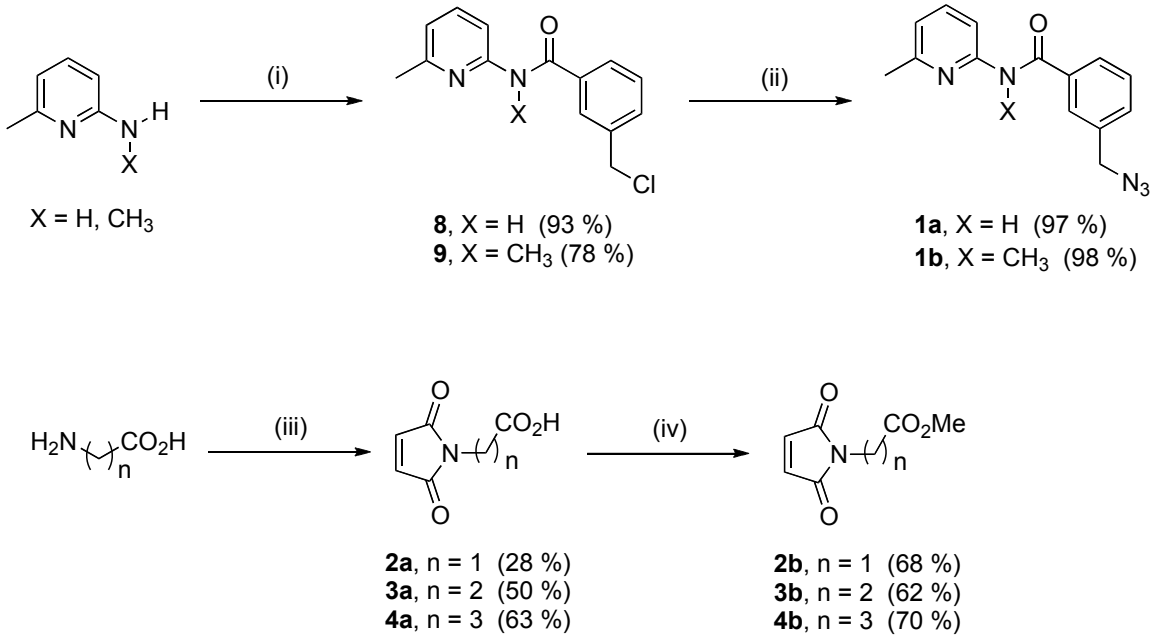
Supporting Information

Synthesis

Compounds **8**, **9**, **1a**, **1b**, **2a**, **3a**, **4a**, **2b**, **3b**, **4b** were prepared according to the following synthetic scheme.



Scheme S1. Reagents and conditions: (i) 3-(chloromethyl)-benzoyl chloride, DCM, 0 °C, 15 h.; (ii) NaN_3, acetone, reflux, 15 h.; (iii) maleic anhydride, AcOH, r.t., 15 h, then reflux, 8 h.; (iv) Cs_2CO_3, MeI, DMF, r.t., 15 h.

Typical procedure for the synthesis of amides 8 and 9 (TP1)

A solution of the appropriate amine (3 equivalents) in dry CH_2Cl_2 was added dropwise over neat 3-(chloromethyl)-benzoylchloride (1 equivalent) under an inert atmosphere and at 0 °C. Once the addition was complete the reaction mixture was allowed to warm to room temperature and it was further stirred for 15 hours. The volatiles were then removed under reduced pressure and the residue was purified by flash chromatography on silica gel to afford the desired compounds, which were dried under high vacuum.

N-(6-Methyl-2-pyridyl)-3-chloromethyl benzamide (8)

Amide **8** was prepared according to **TP1** from 3-(chloromethyl)benzoylchloride (1.00 g, 5.3 mmol) and 2-amino-6-picoline (1.72 g, 15.9 mmol) as a solution in dry CH_2Cl_2 (25 mL). The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2) yielding **8** (1.28 g, 93 %) as a white solid. Mp = 67.5-69.5 °C; Elemental analysis calcd. (%) for $C_{14}H_{13}N_2OCl$: C, 64.49; H, 5.03; N, 10.74; Found: C, 64.34; H, 4.96; N, 10.77; ν_{max} (KBr) (cm^{-1}) = 3264, 3059, 1657, 1577, 793; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.73 (1H, bs, N*H*), 8.20-8.17 (1H, m, ArC*H*), 7.87-7.85 (2H, m, ArC*H*), 7.67-7.62 (1H, m, ArC*H*), 7.51-7.49 (2H, m, ArC*H*), 6.93-6.90 (1H, m, ArC*H*), 4.61 (2H, s, CH_2), 2.43 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.3 (*C*), 157.1 (*C*), 150.8 (*C*), 139.1 (Ar*C*H), 138.5 (*C*), 135.1 (Ar*C*H), 132.4 (Ar*C*H), 129.5 (Ar*C*H), 127.7 (Ar*C*H), 127.3 (Ar*C*H), 119.8 (Ar*C*H), 111.3 (Ar*C*H), 45.7 (*C*H_2), 24.1 (*C*H_3); LRMS (EI+): *m/z* (%) = 260 (19) $[M]^+$, 245 (2), 231 (100), 225 (16), 211 (2), 153 (80), 125 (33), 89 (34); HRMS: found 283.0603 $[M+Na]^+$, $C_{14}H_{13}N_2OClNa$ requires 283.0614.

N-Methyl-*N*-(6-methyl-2-pyridyl)-3-chloromethyl benzamide (9)

Amide **9** was synthesised according to **TP1** from 3-(chloromethyl)-benzoylchloride (0.52 g, 2.7 mmol) and 2-(*N*-methyl)-6-methylpyridine[1] (1.00 g, 8.2 mmol) as a solution in CH_2Cl_2 (20 mL). Purification by flash chromatography on silica gel ($CHCl_3$-2% MeOH) yielded the desired compound as a colourless oil (0.57 g, 78 %). ν_{max} (film) (cm^{-1}) 3062, 2957, 2924, 1649, 1592, 799; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.30-7.08 (m, 5H, ArC*H*), 6.84-6.81 (m, 1H, ArC*H*), 6.51-6.48 (m, 1H, ArC*H*), 4.36 (s, 2H, CH_2), 3.49 (s, 3H, NCH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.1 (*C*),158.1 (*C*), 155.8 (*C*), 137.7 (Ar*C*H), 137.3 (*C*), 136.6 (*C*), 129.9 (Ar*C*H), 128.8 (Ar*C*H), 128.4 (Ar*C*H), 128.3 (Ar*C*H), 120.7 (Ar*C*H), 118.4 (Ar*C*H), 45.6 (*C*H_2), 36.0 (*C*H_3), 24.2 (*C*H_3); LRMS (EI+) *m/z* (%) = 274 (100) $[M+Na]^+$; HRMS: found 297.0776 $[M+Na]^+$, $C_{15}H_{15}N_2ONaCl$ requires 297.0771.

Typical procedure for the synthesis of azides 1a and 1b (TP2)

Sodium azide (3 equivalents) was added to a solution of the appropriate benzylic chloride derivative **8** or **9** (1 equivalent) in dry acetone. This mixture was heated at reflux for 15 hours, cooled to room temperature and the precipitate removed by vacuum filtration. The liquors were concentrated under reduced pressure and the crude residue dissolved in EtOAc. The solution was then washed with water (2 times), the organic layer was dried over $MgSO_4$ and the drying agent filtered. The solvent was evacuated under reduced pressure and the residue was dried under high vacuum. The azided obtained did not require further purification.

N-(6-Methyl-2-pyridyl)-3-methylazidobenzamide (1a)

Azide **1a** was prepared according to **TP2** from sodium azide (0.94 g, 14.4 mmol) and **8** (1.25 g, 4.8 mmol) dissolved in dry acetone (30 mL). The desired azide **1a** (1.24 g, 97 %) was obtained as a colourless solid. Mp = 50.0-52.0 °C; ν_{max} (KBr) (cm^{-1}) = 3412, 2095, 1693, 1555; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.81 (1H, bs, N*H*), 7.87-7.72 (2H, m, ArC*H*), 7.68-7.56 (1H, m, ArC*H*), 7.48-7.35 (2H, m, ArC*H*), 6.92-6.78 (1H, m, ArC*H*), 4.34 (2H, s, CH_2), 2.38 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.3 (*C*), 160.0 (*C*), 150.8 (*C*), 138.8 (Ar*C*H), 136.4 (*C*), 135.1 (*C*), 130.2 (Ar*C*H), 129.3 (Ar*C*H), 128.5 (Ar*C*H), 127.0 (Ar*C*H), 119.6 (Ar*C*H), 111.1 (Ar*C*H), 54.3 (*C*H_2), 23.9 (*C*H_3); LRMS (EI+): *m/z* (%) = 267 (43) $[M]^+$, 238 (100), 210 (38), 197 (30), 160 (49), 104 (81); HRMS: found 290.1019 $[M+Na]^+$, $C_{14}H_{13}N_5ONa$ requires 290.1018.

N-Methyl-(3-methylbenzyl)-3-methylazidobenzamide (1b)

Azide **1b** was prepared according to **TP2** from sodium azide (0.29 g, 5.1 mmol) and benzylic chloride 9 (0.40 g, 1.5 mmol) dissolved in dry acetone (20 mL). Azide **1b** (0.38 g, 91 %) was isolated as a colourless crystalline solid. Mp = 41.0-43.0 ˚C; Elemental analysis calcd. (%) for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.98; Found: C, 68.51; H, 5.95; N, 20.02; ν_{max} (KBr) (cm^{-1}) = 3041, 2957, 2105, 1642; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.29 (1H, s, ArC*H*), 7.25-7.17 (3H, m, ArC*H*), 7.11-7.06 (1H, m, ArC*H*), 6.96-6.94 (1H, m, ArC*H*), 6.87-6.85 (1H, m, ArC*H*) 4.18 (2H, s, CH_2), 3.47 (3H, s, NCH_3), 2.22 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.1 (*C*), 144.6 (*C*), 139.3 (*C*), 136.7 (*C*), 134.9 (*C*), 129.5

[1] 2-(*N*-methyl)-6-methylpyridine was prepared following a procedure similar to that described in: J. Barluenga, A.M. Bayón, G. Asensio, *J. Chem. Soc. Chem. Commun.* **1984**, 1334.

(Ar*C*H), 129.3 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.2 (Ar*C*H), 127.5 (Ar*C*H), 127.4 (Ar*C*H), 124.0 (Ar*C*H), 54.3 (*C*H_2), 38.4 (*C*H_3), 21.2 (*C*H_3); LRMS (EI+): *m/z* (%) = 281 [M +H]$^+$ (36), 253 (13), 239 (6), 224 (2), 161 (82), 133 (97), 105 (100), 92 (43); HRMS: found 303.1213 [M+Na]$^+$, $C_{16}H_{16}N_4ONa$ requires 303.1222.

Typical procedure for the synthesis of dipolarophiles 2a, 3a and 4a[2] (TP3)

A solution of the appropriate amino acid (1 equivalent) and maleic anhydride (1 equivalent) in glacial acetic acid was stirred at room temperature for 15 hours before it was refluxed for 8 hours. The reaction mixture was then allowed to cool to room temperature, the volatiles were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (DCM-5 % ACOH as eluant) to afford the desired product, which was then dried under high vacuum.

2-Maleimidoethanoic acid (2a)

Maleimide **2a** was prepared according to **TP3** from glycine (5.00 g, 66.6 mmol) and maleic anhydride (6.53 g, 66.6 mmol), dissolved in acetic acid (190 mL). The desired product **2a** (2.89 g, 28 %) was obtained as a white solid. Mp = 103.5-104.5 °C (lit. 104-105 °C)[2a, 2b]; ν_{max} (KBr) (cm^{-1}) = 3101, 1755; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.23 (1H, bs, CO_2H), 6.79 (2H, s, 2 x C*H*), 4.32 (2H, s, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.0 (*C*), 168.8 (*C*), 137.4 (2 x *C*H), 40.6 (*C*H_2); LRMS (EI+) *m/z* (%) 155 [M]$^+$ (1), 138 (1), 110 (100), 82 (66); HRMS: found 155.0218 [M]$^+$, $C_6H_5NO_4$ requires 155.0218.

3-Maleimidopropanoic acid (3a)

Maleimide **3a** was prepared according to **TP3** from β-alanine (5.00 g, 56.1 mmol) and maleic anhydride (5.51 g, 56.1 mmol), dissolved in acetic acid (190 mL). The desired maleimide **3a** was isolated as a white solid (4.74 g, 50 %). Mp = 98.0-100.5 °C (lit. 106-107°C)[2a, 2b]; ν_{max} (KBr) (cm^{-1}) = 3096, 1700; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.72 (2H, s, 2 x C*H*), 3.82 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 2.71 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.6 (*C*), 170.5 (*C*), 134.4 (2 x *C*H), 33.4 (*C*H_2), 32.6 (*C*H_2); LRMS (EI +): *m/z* (%) = 169 [M]$^+$ (6), 151 (27), 123 (100), 110 (94), 96 (20); HRMS: found 169.0378 [M]$^+$, $C_7H_7NO_4$ requires 169.0375.

4-Maleimido-*n*-butanoic acid (4a)

Maleimide 4b was prepared according to **TP3** from 4-aminobutyric acid (5.00 g, 48.5 mmol) and maleic anhydride (4.75 g, 48.5 mmol), dissolved in acetic acid (190 mL). The desired maleimide **4a** was isolated as a white solid (5.59 g, 63 %). Mp = 87.5-88.5 °C (lit. 89-90 °C)[2a, 2b]; ν_{max} (KBr) (cm^{-1}) = 3085, 2947, 1713, 1643; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.70 (2H, s, 2 x C*H*), 3.59 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 2.39 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 1.92 (2H, quintet, $^3J_{HH}$ = 7.0 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.6 (*C*), 170.6 (*C*), 134.2 (2 x *C*H), 36.9 (*C*H_2), 31.2 (*C*H_2), 23.5 (*C*H_2); LRMS (EI+): *m/z* (%) = 183 [M]$^+$ (4), 165 (20), 137 (25), 124 (30), 110 (100); HRMS: found 183.0533 [M]$^+$, $C_8H_9NO_4$ requires 183.0533.

[2] (a) D. H. Rich, P. D. Gesellchen, A. Tong, A. Chueng, C. K. Buckner, *J. Med. Chem.* **1975**, *18*, 1004; (b) O. Kellar, J. Rudinger, *Helv. Chim. Acta* **1975**, *58*, 531.

Typical procedure for the synthesis of methyl esters 2b, 3b and 4b (TP4)

Methyl iodide (2.0 equivalents) and Cs_2CO_3 (0.6 equivalent) were added dropwise to a stirred solution of the appropriate carboxylic acid (1.0 equivalent) in freshly distilled dimethylformamide (DMF). The reaction mixture was stirred at room temperature for 15 hours before it was diluted with ethyl acetate and washed with water. The organic phase was dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The residue obtained was purified by flash chromatography on silica gel (7:3 hexane/EtOAc as eluant) to yield the desired methyl ester derivatives, which were then dried under high vacuum.

2-Maleimidoethanoic acid methyl ester (2b)

The procedure outlined above (**TP4**) was followed using 2-maleimidoacetic acid **2a** (0.50 g, 3.2 mmol), methyl iodide (0.92 g, 0.40 mL, 6.4 mmol) and Cs_2CO_3 (0.63 g, 1.92 mmol) dissolved in DMF (40 mL). Purification by flash chromatography yielded the desired ester **2b** (0.37 g, 68 %) as an orange oil. ν_{max} (film) (cm^{-1}) = 3102, 1715, 1601; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.78 (2H, s, 2 x C*H*), 4.26 (2H, s, CH_2), 3.76 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.8 (*C*), 167.7 (*C*), 134.5 (2 x *C*H), 52.7 (*C*H_3), 38.5 (*C*H_2); LRMS (EI+): *m/z* (%) = 169 (71) $[M]^+$, 138 (13), 110 (100), 119 (92); HRMS: found 169.0382 $[M]^+$, $C_7H_7NO_4$ requires 169.0375.

3-Maleimidopropanoic acid methyl ester (3b)

The methyl ester 3b was prepared according to **TP4** from 3-maleimidopropanoic acid **3a** (0.50 g, 2.9 mmol), methyl iodide (0.83 g, 0.36 mL, 5.8 mmol) and Cs_2CO_3 (0.57 g, 1.74 mmol) dissolved in DMF (40 mL). Purification by flash chromatography afforded ester **3b** (0.33 g, 62 %) as an orange oil. ν_{max} (film) (cm^{-1}) = 3099, 3001, 1705, 1610, 1585; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.66 (2H, s, 2 x C*H*), 3.84 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 3.65 (3H, s, CH_3), 2.63 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.1 (*C*), 170.3 (*C*), 134.2 (2 x *C*H), 51.93 (*C*H_3), 33.6 (*C*H_2), 32.7 (*C*H_2); LRMS (EI+): *m/z* (%) = 183 $[M]^+$ (6), 151 (39), 123 (100), 110 (91), 102 (32), 82 (45); HRMS: found 183.0529 $[M]^+$, $C_9H_{11}NO_4$ requires 183.0532.

4-Maleimido-*n*-butanoic acid methyl ester (4b)

The methyl ester derivative **4b** was prepared according to **TP4** from 4-maleimido-*n*-butanoic acid **4a** (0.50 g, 2.7 mmol), methyl iodide (0.77 g, 0.34 mL, 5.4 mmol) and Cs_2CO_3 (0.53 g, 1.62 mmol) dissolved in DMF (40 mL). Purification by flash chromatography gave the title compound **4b** (0.37 g, 70 %) as a colourless solid. Mp = 56.5-57.5 ˚C ; Elemental analysis calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10; found: C, 54.78; H, 5.90; N, 6.84; ν_{max} (KBr) (cm^{-1}) = 3093, 3017, 1709, 1584; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.60 (2H, s, 2 x C*H*), 3.68 (3H, s, CH_3), 3.56 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 2.33 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2), 1.92 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.0 (*C*), 170.7 (*C*), 134.1 (2 x *C*H), 51.7 (*C*H_3), 37.0 (*C*H_2), 31.1 (*C*H_2), 23.8 (*C*H_2); LRMS (EI+): *m/z* (%) = 197 $[M]^+$ (43), 165 (61), 138 (57), 124 (77), 110 (100), 82 (60); HRMS: found 197.0684 $[M]^+$, $C_9H_{11}NO_4$ requires 197.0668.

Determination of Association Constants

General considerations

Association constants for the complexes were determined using the ^{1}H NMR titration method, using 400 MHz ^{1}H NMR spectroscopy at a temperature of 323 K. All solutions were made up in $CDCl_3$ using volumetric flasks with an accuracy of ± 0.02 mL. Samples were equilibrated at 323 K for at least one hour prior to use. The corresponding variation in chemical shift, with respect to guest concentration, was monitored and the association constant was determined by fitting this experimental data to the following equation with a non-linear curve-fitting program:

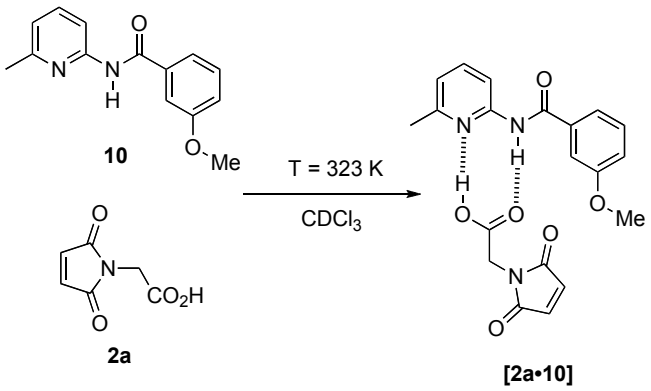
$$\delta_{obs} = \delta_G + \frac{\Delta\delta}{2G_0}\left[K_d + H_0 + G_0 - \sqrt{\left(K_d + H_0 + S_0\right)^2 - 4H_0G_0}\right]$$

This allows the calculation of the dissociation constant, K_d, where δ_{obs} is the chemical shift at concentration G_0 of the guest molecule; H_0 is the concentration of the host molecule, and $\Delta\delta$ is the maximum change in the chemical shift of the bound species. The value of the association constant, K_a is obtained from the best-fit value of K_d:

$$K_d = \frac{1}{K_a}$$

Determination of binding constant for the complex [1a·2a]:

The association constant, between maleimide **2a** and 3-methoxy-*N*-(6-methyl-piridin-2-yl)-benzamide **10** (Scheme S1), was determined by titration as 114 M^{-1}, using 400 MHZ ^{1}H NMR spectroscopy, at 323 K in $CDCl_3$ (Figure S1). The recognition mofit used here is identical to that seen between compounds **2a**/**1a**. Since **2a** and **10** are inert when mixed together we were able to assign any chemical shift changes as a consequence of the association between complementary recognition sites on **2a** and **10**.[3]



Scheme S2

[3] The aromatic substituent constant, σ_m, for the CH_2N_3 group present in **1a** was estimated to be + 0.12 units. The σ_m for a methoxy group exhibits an identical value of + 0.12 units. Accordingly, compound **10** matches **1a** both electronically and sterically. For further reading see: C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165.

The concentration of **10** was varied between zero and 100 mM. Host **2a** was maintained at 10 mM throughout the study. The observed change in chemical shift of the singlet at δ 4.32 from compound **2a** was monitored as the concentration of guest varied. From the data presented in Figure S1, and making use of the equations presented above, the association constant K_a was calculated as 114 M^{-1}.

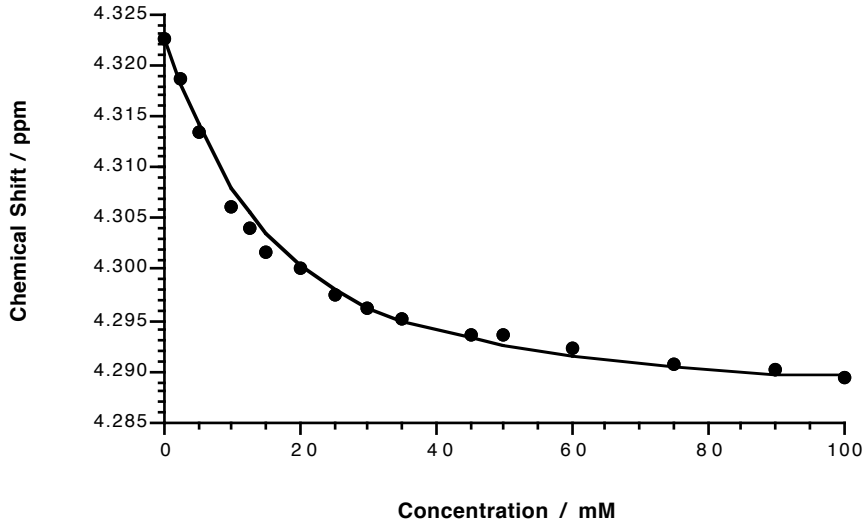
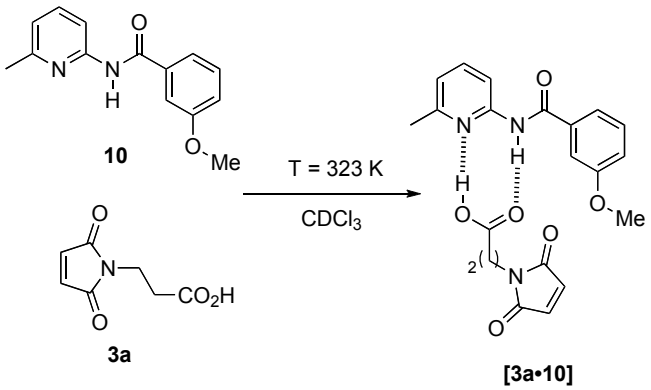


Figure S1. Saturation plot showing the change in chemical shift of the signal at δ = 4.32 ppm arising from compound **2a** as the concentration of **10** increases. The closed circles represent the experimentally determined points and the solid line represents the best-fit value.

Determination of binding constant for the complex [1a·3a]:

The association constant between maleimide **3a** and 3-methoxy-*N*-(6-methyl-piridin-2-yl)-benzamide **10** (Scheme S3) was determined by titration as 45 M^{-1}, using 400 MHz ^{1}H NMR spectroscopy, at 323 K in $CDCl_3$ (Figure S2). This value was used as an estimate for the association constant between components within the complex [**1a**·**3a**].



Scheme S3

The concentration of **10** was varied between 0 and 100 mM. Carboxylic acid **3a** was maintained at 10 mM through the study. The observed change in the chemical shift of the centre of the triplet at δ = 2.71 ppm from **3a** was monitored as the concentration of **10**

varied. From the data represented in Figure S2 the association constant K_a was calculated as 45 M^{-1}.

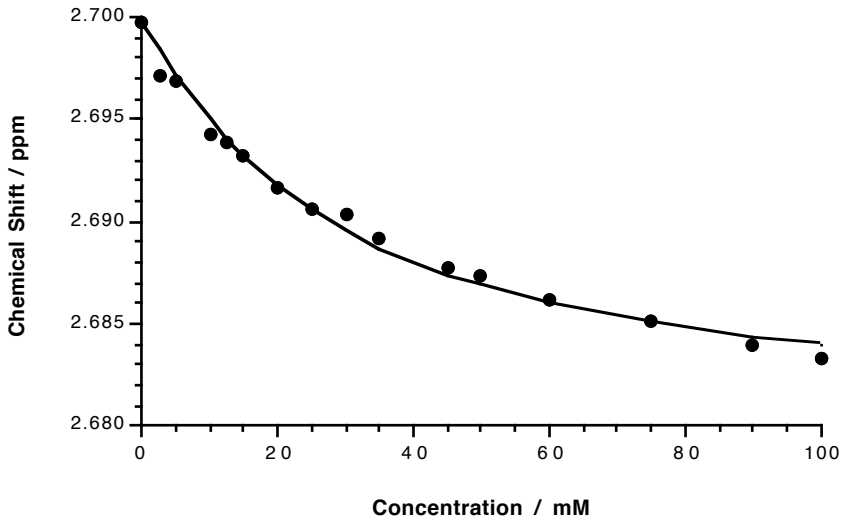


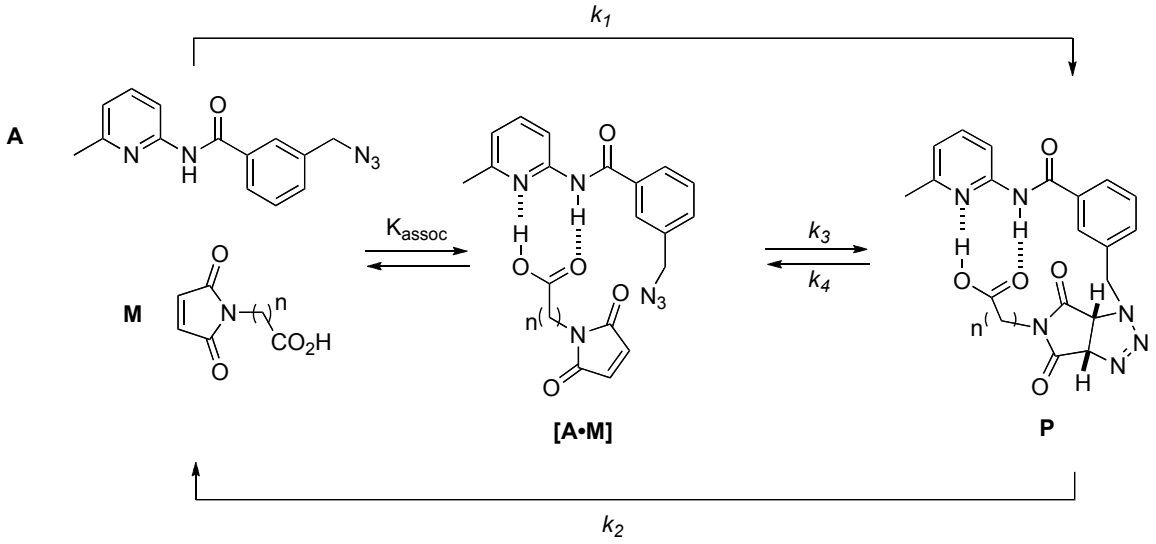
Figure S2. Saturation plot showing that change in chemical shift of the signal at δ = 2.71 ppm arising from compound **3a** as the concentration of **10** increases. The closed circles represent the experimentally determined points and the solid line represents the best-fit value.

Determination of binding constant for the complex [1a·4a]:

An association constant value of 45 M^{-1}, estimated for the complex [**1a**·**3a**], was equally used as an approximation for the association constant between components within the [**1a**·**4a**] complex. Although another methylene spacer has been added, it was viewed that the resultant change in electronic properties would be negligible and that the binding constant used for the [**1a**·**3a**] complex would also serve as a good approximation in this case.

THERMODINAMIC RELATIONSHIPS:

The thermodynamic profiles represented in Figure 2 were calculated from the thermodynamic equations expressed below.



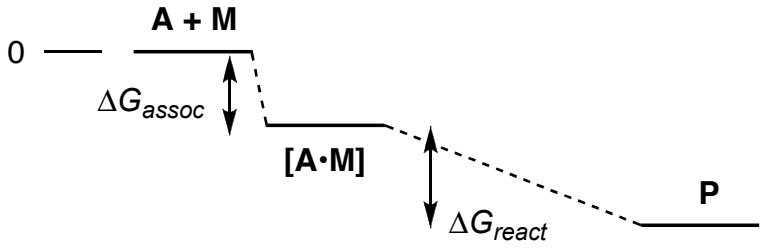
Ground state calculation:

For the starting materials $\Delta G = 0$ was considered.

$$\Delta G_{assoc} = -RT \ln K_{assoc}$$

$\Delta G_P = \Delta G_{assoc} + \Delta G_{react}$, being $\Delta G_P = -RT \ln K$ where $K = \frac{k_3}{k_4}$

Gas constant: $R = 8.314$ J·K^{-1}·mol^{-1}

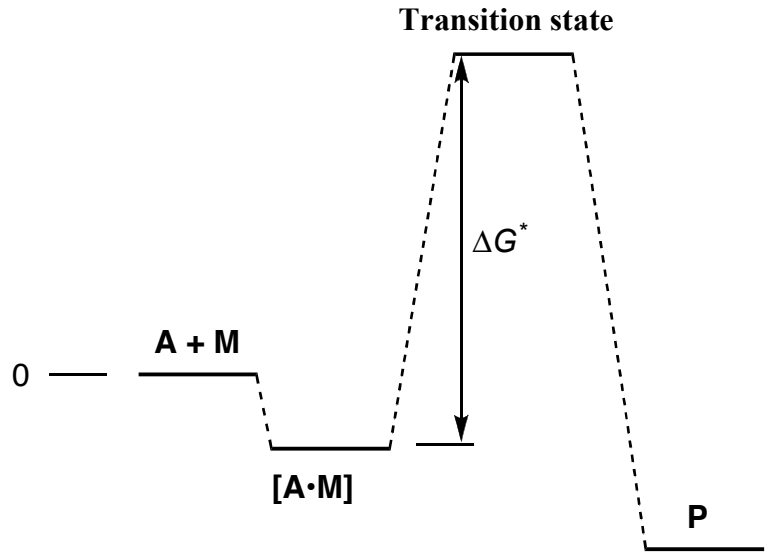


Transition state calculation:

For the calculation of the energy of the transition state the Eyring equation was used.

$$\Delta G^{*} = -RT \ln\left(\frac{k_3 h}{k_B T}\right), \text{ where}$$

Gas constant: $R = 8.314$ J·K^{-1}·mol^{-1}
Plank's constant: $h = 6.626 \times 10^{-34}$ J·s
Boltzman's constant: $k_B = 1.380 \times 10^{-23}$ J·K^{-1}



Revisiting the Eyring equation, ΔG^* can be expressed in terms of ΔH^* and ΔS^*.

Thus, $k_3 = \frac{k_B T}{h} e^{\left(-\frac{\Delta G^*}{RT}\right)}$ becomes $k_3 = \frac{k_B T}{h} e^{\left(-\frac{\Delta H^*}{RT}\right)} e^{\left(\frac{\Delta S^*}{R}\right)}$

If changes in ΔG^* are assumed to result from only changes in ΔS^* (for instance, when there is a variation in the number of rotors in a certain system) then $\Delta H^* = 0$. In this case, two different systems *A* and *B* can be compared in based on Δ(ΔS)

$$\Delta\left(\Delta S^*\right) = \Delta S_A^* - \Delta S_B^* = R\left[\ln k_A - \ln k_B\right] \quad \text{or} \quad k_A = k_B e^{\frac{\Delta(\Delta S^*)}{R}}$$