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

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Synthesis

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

\[
\begin{align*}
\text{H}_2\text{NCO}_2\text{H} & \xrightarrow{\text{(iii)}} \text{CO}_2\text{H} \\
\text{X} = \text{H, CH}_3 & \xrightarrow{\text{(iv)}} \text{CO}_2\text{Me}
\end{align*}
\]

Scheme S1. Reagents and conditions: (i) 3-(chloromethyl)-benzoyl chloride, DCM, 0 °C, 15 h.; (ii) \text{NaN}_3, acetone, reflux, 15 h.; (iii) maleic anhydride, \text{AcOH}, r.t., 15 h, then reflux, 8 h.; (iv) \text{Cs}_2\text{CO}_3, \text{MeI}, \text{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 \text{CH}_2\text{Cl}_2 was added dropwise over neat 3-(chloromethyl)-benzoyl chloride (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.

\(\text{N-}(6\text{-Methyl-2-pyridyl)-3-chloromethyl benzamide (8)}\)

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 \text{CH}_2\text{Cl}_2 (25 mL). The crude residue was purified by flash column chromatography on silica gel (\text{CH}_2\text{Cl}_2) yielding 8 (1.28 g, 93 %) as a white solid. Mp = 67.5-69.5 °C; Elemental analysis calcd. (%) for \text{C}_{14}\text{H}_{13}\text{N}_2\text{OCl}: C, 64.49; H, 5.03; N, 10.74; Found: C, 64.34; H, 4.96; N, 10.77; \nu_{\text{max}} (\text{KBr}) (\text{cm}^{-1}) = 3264, 3059, 1657, 1577, 793; ^1\text{H NMR (300 MHz, CDCl}_3) \delta = 8.73 (1\text{H, bs, NH}), 8.20-8.17 (1\text{H, m, ArC}_H), 7.87-7.85 (2\text{H, m, ArC}_H), 7.67-7.62 (1\text{H, m, ArC}_H), 7.51-7.49 (2\text{H, m, ArC}_H), 6.93-6.90 (1\text{H, m, ArC}_H), 4.61 (2\text{H, s, CH}_2), 2.43 (3\text{H, s, CH}_3); ^13\text{C NMR (75 MHz, CDCl}_3) \delta = 165.3 (\text{C}), 157.1 (\text{C}), 150.8 (\text{C}), 139.1 (\text{ArC}), 138.5 (\text{C}), 135.1 (\text{ArC}), 132.4 (\text{ArC}), 129.5 (\text{ArC}), 127.7 (\text{ArC}), 127.3 (\text{ArC}), 119.8 (\text{ArC}), 111.3 (\text{ArC}), 45.7 (\text{CH}_2), 24.1 (\text{CH}_3); \text{LRMS (EI+): } m/z \% = 260 (19) [\text{M}]^+, 245 (2), 231 (100), 225 (16), 211 (2), 153 (80), 125 (33), 89 (34); \text{HRMS: found 283.0603 [M+Na]^+}, \text{C}_{14}\text{H}_{13}\text{N}_2\text{OClNa requires 283.0614.}
N-Methyl-N-(6-methyl-2-pyridyl)-3-chloromethyl benzamide (9)

Amide 9 was synthesised according to TP1 from 3-(chloromethyl)-benzoyl chloride (0.52 g, 2.7 mmol) and 2-(N-methyl)-6-methylpyridine\(^1\) (1.00 g, 8.2 mmol) as a solution in CH\(_2\)Cl\(_2\) (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%). \(\nu_{\text{max}}\) (film) (cm\(^{-1}\)) 3062, 2957, 2924, 1649, 1592, 799; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.30-7.08\) (m, 5H, ArC\(\text{H}\)), 6.84-6.81 (m, 1H, ArC\(\text{H}\)), 6.51-6.48 (m, 1H, ArC\(\text{H}\)), 4.36 (s, 2H, C\(\text{H}_2\)), 3.49 (s, 3H, NC\(\text{H}_3\)), 2.41 (s, 3H, C\(\text{H}_3\)); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 170.1\) (C), 158.1 (C), 155.8 (C), 137.7 (ArC), 137.3 (C), 136.6 (C), 129.9 (ArC), 128.9 (ArC), 128.4 (ArC), 128.3 (ArC), 120.7 (ArC), 118.4 (ArC), 45.6 (CH\(_2\)), 36.0 (CH\(_3\)), 24.2 (CH\(_3\)); LRMS (EI\(^+\)) \(m/z\) (%) = 274 (100) [M+Na]\(^+\); HRMS: found 297.0776 [M+Na]\(^+\), C\(_{15}\)H\(_{15}\)N\(_2\)O 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 azide 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 \(^\circ\)C; \(\nu_{\text{max}}\) (KBr) (cm\(^{-1}\)) = 3412, 2095, 1693, 1555; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 8.81\) (1H, bs, NH), 7.87-7.72 (2H, m, ArC\(\text{H}\)), 7.68-7.56 (1H, m, ArC\(\text{H}\)), 7.48-7.35 (2H, m, ArC\(\text{H}\)), 6.92-6.78 (1H, m, ArC\(\text{H}\)), 4.34 (2H, s, C\(\text{H}_2\)), 2.38 (3H, s, C\(\text{H}_3\)); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 165.3\) (C), 160.0 (C), 150.8 (C), 138.8 (ArC), 136.4 (C), 135.1 (C), 130.2 (ArC), 129.3 (ArC), 128.5 (ArC), 127.0 (ArC), 119.6 (ArC), 111.1 (ArC), 54.3 (CH\(_2\)), 23.9 (CH\(_3\)); 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\(_5\)O 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 = 50.0-52.0 \(^\circ\)C; \(\nu_{\text{max}}\) (KBr) (cm\(^{-1}\)) = 3041, 2957, 2105, 1642; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.29\) (1H, s, ArC\(\text{H}\)), 7.25-7.17 (3H, m, ArC\(\text{H}\)), 7.11-7.06 (1H, m, ArC\(\text{H}\)), 6.96-6.94 (1H, m, ArC\(\text{H}\)), 6.87-6.85 (1H, m, ArC\(\text{H}\)) 4.18 (2H, s, CH\(_2\)), 3.47 (3H, s, NCH\(_3\)), 2.22 (3H, s, CH\(_3\)); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 170.1\) (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.
(ArCH), 129.3 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 124.0 (ArCH), 54.3 (CH2), 38.4 (CH3), 21.2 (CH3); 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]+, C16H16N4O requires 303.1222.

**Typical procedure for the synthesis of dipolarophiles 2a, 3a and 4a**

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; νmax (KBr) (cm⁻¹) = 3101, 1755; 1H NMR (300 MHz, CDCl₃) δ = 9.23 (1H, bs, CO₂H), 6.79 (2H, s, 2 x CH), 4.32 (2H, s, CH₂); 13C NMR (75 MHz, CDCl₃) δ = 171.0 (C), 168.8 (C), 137.4 (2 x CH), 40.6 (CH₂); LRMS (EI+): m/z (%) = 155 [M] + (1), 138 (1), 110 (100), 82 (66); HRMS: found 155.0218 [M]⁺, C₆H₅NO₄ 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; νmax (KBr) (cm⁻¹) = 3096, 1700; 1H NMR (300 MHz, CDCl₃) δ = 6.72 (2H, s, 2 x CH), 3.82 (2H, t, JHH = 7.0 Hz, CH₂), 2.71 (2H, t, JHH = 7.0 Hz, CH₂); 13C NMR (75 MHz, CDCl₃) δ = 176.6 (C), 170.5 (C), 134.4 (2 x CH), 33.4 (CH₂), 32.6 (CH₂); LRMS (EI+): m/z (%) = 169 [M] + (6), 151 (27), 123 (100), 110 (94), 96 (20); HRMS: found 169.0378 [M]⁺, C₇H₇NO₄ 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; νmax (KBr) (cm⁻¹) = 3085, 2947, 1713, 1643; 1H NMR (300 MHz, CDCl₃) δ = 6.70 (2H, s, 2 x CH), 3.59 (2H, t, JHH = 7.0 Hz, CH₂), 2.39 (2H, t, JHH = 7.0 Hz, CH₂), 1.92 (2H, quintet, JHH = 7.0 Hz, CH₂); 13C NMR (75 MHz, CDCl₃) δ = 178.6 (C), 170.6 (C), 134.2 (2 x CH), 36.9 (CH₂), 31.2 (CH₂), 23.5 (CH₂); LRMS (EI+): m/z (%) = 183 [M]⁺ (4), 165 (20), 137 (25), 124 (30), 110 (100); HRMS: found 183.0533 [M]⁺, C₈H₉NO₄ requires 183.0533.

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

Methyl iodide (2.0 equivalents) and Cs₂CO₃ (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 MgSO₄ 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 Cs₂CO₃ (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; ¹H NMR (300 MHz, CDCl₃) δ = 6.78 (2H, s, 2 x CH), 4.26 (2H, s, CH₂), 3.76 (3H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ = 169.8 (C), 167.7 (C), 134.5 (2 x C), 52.7 (CH₂), 38.5 (CH₂); LRMS (EI⁺): m/z (%) = 169 (71) [M]+, 138 (13), 110 (100), 119 (92); HRMS: found 169.0382 [M]+, C₇H₇NO₄ 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 Cs₂CO₃ (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; ¹H NMR (300 MHz, CDCl₃) δ = 6.66 (2H, s, 2 x CH), 3.84 (2H, t, JHH = 7.0 Hz, CH₂), 3.65 (3H, s, CH₃), 2.63 (2H, t, JHH = 7.0 Hz, CH₂), 13C NMR (75 MHz, CDCl₃) δ = 171.1 (C), 170.3 (C), 134.2 (2 x CH), 51.93 (CH₃), 33.6 (CH₂), 32.7 (CH₂); LRMS (EI⁺): m/z (%) = 183 [M]+ (6), 151 (39), 123 (100), 110 (91), 102 (32), 82 (45); HRMS: found 183.0529 [M]+, C₉H₁₁NO₄ 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 Cs₂CO₃ (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 C₉H₁₁NO₄: 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; ¹H NMR (300 MHz, CDCl₃) δ = 6.60 (2H, s, 2 x CH), 3.68 (3H, s, CH₃), 3.56 (2H, t, JHH = 7.0 Hz, CH₂), 2.33 (2H, t, JHH = 7.0 Hz, CH₂), 1.92 (2H, m, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ = 173.0 (C), 170.7 (C), 134.1 (2 x CH), 51.7 (CH₃), 37.0 (CH₂), 31.1 (CH₂), 23.8 (CH₂); LRMS (EI⁺): m/z (%) = 197 [M]+ (43), 165 (61), 138 (57), 124 (77), 110 (100), 82 (60); HRMS: found 197.0684 [M]+, C₉H₁₁NO₄ 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:

$$
\delta_{\text{obs}} = \delta_0 + \frac{\Delta\delta}{2G_0} \left[ K_d + H_0 + G_0 - \sqrt{(K_d + H_0 + S_0)^2 - 4H_0G_0} \right]
$$

This allows the calculation of the dissociation constant, $K_d$, where $\delta_{\text{obs}}$ 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 motif 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](image)

$^3$ The aromatic substituent constant, $\sigma_m$, for the CH$_2$N$_3$ group present in 1a was estimated to be $+0.12$ units. The $\sigma_m$ 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](image)

**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 ¹H NMR spectroscopy, at 323 K in CDCl₃ (Figure S2). This value was used as an estimate for the association constant between components within the complex [1a·3a].

![Scheme S3](image)

**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$^{-1}$.

![Chemical Shift vs Concentration](image)

**Figure S2.** Saturation plot showing that change in chemical shift of the signal at $\delta = 2.71$ 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.

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**Ground state calculation:**

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

\[
\Delta G_{assoc} = -RT \ln K_{assoc}
\]

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

Gas constant: \( R = 8.314 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1} \)

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**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: \( R = 8.314 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1} \)
Plank’s constant: \( h = 6.626 \times 10^{-34} \text{ J} \cdot \text{s} \)
Boltzman’s constant: \( k_B = 1.380 \times 10^{-23} \text{ J} \cdot \text{K}^{-1} \)
Revisiting the Eyring equation, $\Delta G^*$ can be expressed in terms of $\Delta H^*$ and $\Delta S^*$.

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 $\Delta G^*$ are assumed to result from only changes in $\Delta S^*$ (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 $\Delta(\Delta S)$

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