Electronic Supplementary Material (ESI) for Photochemical & Photobiological Sciences

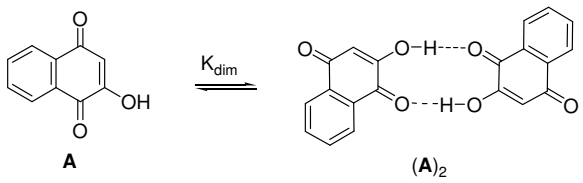

# Supplementary Information

## Chirogenic [3+2]-photocycloaddition reactions of 2-substituted naphthoquinones with cyclic alkenes

Christiane Müller, Andreas Bauer, Thorsten Bach

## 1. Determination of $K_{dim}$ – NMR dilution experiment

Dimerisation constants ($K_{dim}$) can be obtained from dilution experiments. A number of samples have to be prepared, each with a different concentration of the substrate. The NMR-shift of the most sensitive nucleus (here the O–H proton) was measured for each sample.




Scheme 1: Proposed dimerisation equilibrium of substrate **2a** (**A**)

Table 1: Dilution experiment for the determination of $K_{dim}$ (T=303 K)

| Entry | $[A]_0$ [mol/L] | $\delta_{OH}$ [ppm] |
|---|---|---|
| 1 | 7.07E-02 | 6.276 |
| 2 | 4.72E-02 | 6.276 |
| 3 | 3.54E-02 | 6.276 |
| 4 | 2.83E-02 | 6.273 |
| 5 | 2.02E-02 | 6.273 |
| 6 | 1.41E-02 | 6.273 |
| 7 | 2.80E-03 | 6.271 |
| 9 | 5.00E-04 | 6.268 |

The changes in chemical shift over the complete concentration range were close to or even below the detection limit. The data could hardly be analyzed using nonlinear regression.[1] The analysis delivered binding constants from 0-100 L/mol with only minor changes in the signal residuals. A flat minimum was detectable around 40 L/mol. For the best fit, a maximum signal change of only 0.012 ppm is expected ($\delta_A$ =6.268 ppm, $\delta_{A2}$ = 6.280 ppm).

[1] A. Bakowski, M. Dressel, A. Bauer, T. Bach, *Org. Biomol. Chem.*, 2011, DOI: 10.1039/c0ob01272f.

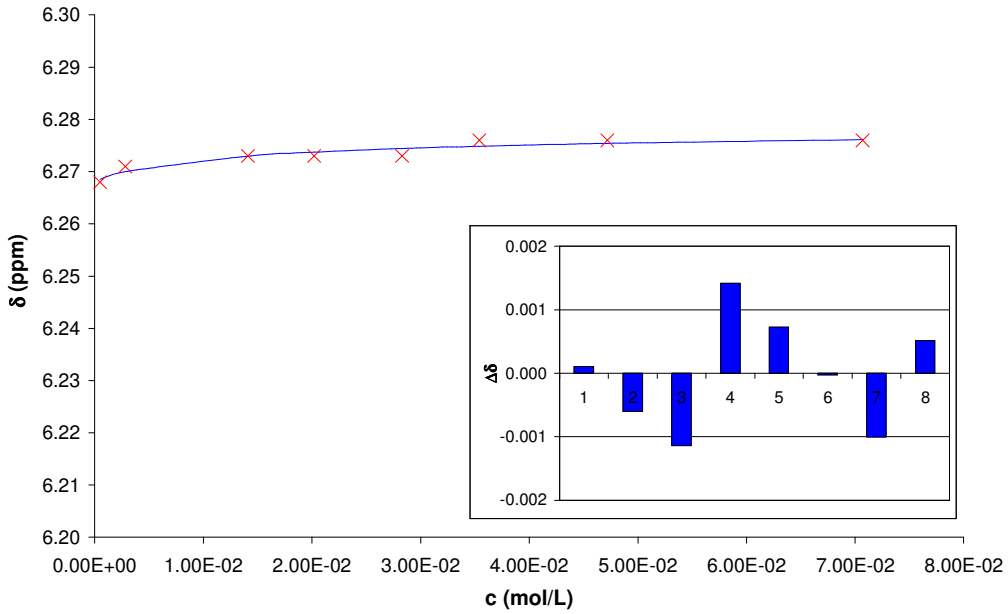
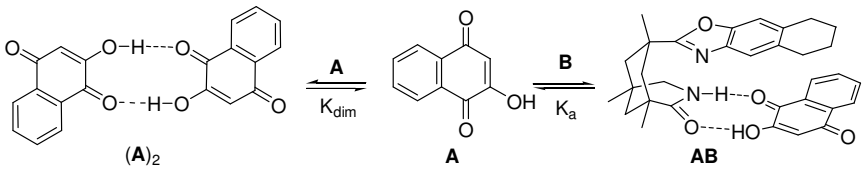



Figure 1: Measured values (red), calculated chemical shift (blue line, $K_{dim}$ = 40 L/mol, $\delta_A$ =6.268 ppm, $\delta_{A2}$ = 6.280 ppm) and signal residuals for the dimerisation experiment.

## Determination of $K_a$ – NMR titration of template with substrate

Association constants were obtained from a titration experiment of template (+)-**1** (**B**) with substrate **2a** at constant template concentration ($[B]_0$ = 27.9 mmol/L). The substrate concentration was varied from 2.65 mmol/L (i. e. a substrate to template ratio 1:10) to 59.1 mmol/L (i. e. a substrate to template ratio of 2:1).




Scheme 2: Dimerisation and expected association of substrate **2a** (**A**) and template (+)-**1** (**B**)

Table 3: Titration experiments for the determination of $K_a$ (T=303 K), $[B]_0$=28 mM

| Entry | $[A]_0$ [mol/L] | $\delta_{OH}$ [ppm] |
|---|---|---|
| 0 | 0.00E+00 | 4.156 |
| 1 | 2.65E-03 | 4.446 |
| 2 | 5.07E-03 | 4.592 |
| 3 | 7.30E-03 | 4.701 |
| 4 | 1.12E-02 | 4.835 |
| 5 | 1.89E-02 | 5.105 |
| 6 | 2.86E-02 | 5.325 |
| 7 | 3.46E-02 | 5.341 |
| 8 | 4.15E-02 | 5.345 |
| 9 | 4.53E-02 | 5.350 |
| 10 | 5.91E-02 | 5.337 |

The data could not be analyzed based on the assumption of a 1:1 complex and the boundary condition of a small dimerisation constant. Only if large dimerisation constants would be considered ($K_{Dim}$ > 6000 L/mol), a fit could be obtained which shows at least no systematic errors (systematic change in the signal residuals) but still large signal residuals (mean absolute signal residual of 0.05 ppm).

Much better results are obtained, if a 2:1 complex was taken into account. As described recently,[1] analytical solutions can be deduced for the individual species in the solution which allows to determine association constants using standard nonlinear regression. The method was modified to deal with the equilibrium shown in Scheme 3 (cf. Annex).

$$\mathbf{B} \underset{K_{a,1}}{\overset{\mathbf{A}}{\rightleftharpoons}} \mathbf{AB} \underset{K_{a,2}}{\overset{\mathbf{A}}{\rightleftharpoons}} \mathbf{A_2B}$$

Scheme 3: Association of substrate **2a** (**A**) and template (+)-**1** (**B**)

Using equation (6), two binding constants could be tentatively assigned, a small binding constant for the 1:1 complex ($K_{a,1} \approx 100$ L/mol) and a large binding constant for the 1:2 complex ($K_{a,2} \approx 2000$ L/mol). The signal residual showed no systematic trend (i. e. no obvious indication for a systematic error) and the mean absolute signal residual is 0.027 ppm.

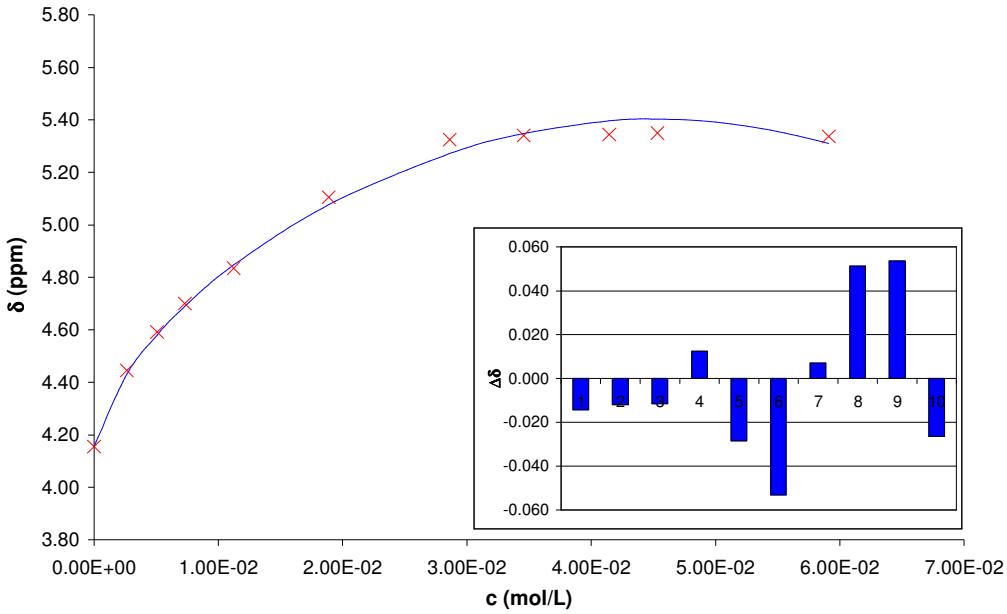



Figure 2: Measured values (red), calculated chemical shift (blue line, $K_{a,1}$ = 93 L/mol, $K_{a,2}$ =2139 L/mol, $\delta_{AB}$ =12.11 ppm, $\delta_{A2B}$ = 5.012 ppm) and signal residuals for the association experiment.

These values are to be taken as a rather qualitative indication for the stoichiometry and the magnitude of the association constants. As four parameters had to be fitted using only ten data points no quantitative estimation of the error (Monte-Carlo error analysis[1,2]) was possible. Given the limited results (yields, stereoselectivity) a further refinement (more data points, higher substrate to template ratios, …) of these values was not attempted.

[2] J. S. Alper and R. I. Gelb, *J. Phys. Chem.*, 1990, 94, 4741.

## Annex – Equations for $K_{a,1}$ and $K_{a,2}$

$$\mathbf{B} \underset{K_{a,1}}{\overset{\mathbf{A}}{\rightleftharpoons}} \mathbf{AB} \underset{K_{a,2}}{\overset{\mathbf{A}}{\rightleftharpoons}} \mathbf{A_2B}$$

$$K_{a,1}=\frac{[AB]}{[A]\cdot[B]} \quad \Rightarrow \quad [AB]=K_{a,1}\cdot[A]\cdot[B] \qquad (1), (2)$$

$$K_{a,2}=\frac{[A_2B]}{[A]\cdot[AB]}=\frac{[A_2B]}{K_{a,1}\cdot[A]^2\cdot[B]} \quad \Rightarrow \quad [A_2B]=K_{a,1}\cdot K_{a,2}\cdot[A]^2\cdot[B] \qquad (3), (4)$$

Using the boundary $[B]_0=[B]+[AB]+[A_2B]$ an equation for $[B](K_{a,1},K_{a,2},[A])$ can be obtained:

$$[B]=\frac{[B]_0}{K_{a,1}\cdot K_{a,2}[A]^2+K_{a,1}\cdot[A]+1} \qquad (5)$$

Using the boundary $[A]_0=[A]+[AB]+2\cdot[A_2B]$ together with expression (5) a third order equation in [A] can be obtained:

$$0=K_{a,1}\cdot K_{a,2}\cdot[A]^3-K_{a,1}\cdot(K_{a,2}\cdot[A]_0-2\cdot K_{a,2}\cdot[B]_0-1)\cdot[A]^2+(K_{a,1}\cdot[A]_0-K_{a,1}\cdot[B]_0-1)[A]-[A]_0 \qquad (6)$$

This equation is solved analytically. It can be shown that for values $K_{a,1}>0$, $K_{a,2}>0$, $[A]_0>0$ and $[B]_0>0$ only one real solution and two complex solution exist, the latter being of no relevance to this problem.

The chemical shift of the proton under investigation is described as weighted average of the individual species:

$$\delta_{calc}=\delta_B\cdot\frac{[B]}{[B]_0}+\delta_{AB}\frac{[AB]}{[B]_0}+\delta_{A_2B}\frac{[A_2B]}{[B]_0} \qquad (7)$$

As $\delta_B$ is directly accessible (template with the given constant concentration, without substrate) only $\delta_{AB}$ and $\delta_{A2B}$ are unknown. The optimization has therefore to deal with four parameters ($K_{a,1}$, $K_{a,2}$, $\delta_{AB}$ and $\delta_{A2B}$) resulting in very weak stabilities in a Monte-Carlo error analysis with the given small set of data points.