

## Supporting Information

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## Potentiometric Titration Method for the Determination of Solubility Limits and $pK_a$ Values of Weak Organic Acids in Water

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### Calculation of free hydrogen ion concentration

The concentration of free hydrogen ions was determined from the pH with the following equation:

$$[H^+] = 10^{-pH} \quad (1)$$

### Derivation of equation for the determination of crystallized compound

When the dosing was stopped and the solution was in a supersaturated state with respect to the neutral, protonated compound, the constant pH<sub>1</sub> was recorded and converted with equation (1) to describe the ratio of neutral, protonated compound (AH) and anionic, deprotonated compound (A<sup>-</sup>) with the mass action law:

$$\frac{[H^+]_1}{K_a} = \frac{[AH]_1}{[A^-]_1} \quad (2)$$

After the addition of seed crystals and sufficient time for crystallization and pH equilibration, the recorded constant pH<sub>2</sub> was utilized to describe this ratio at dissolution equilibrium:

$$\frac{[H^+]_2}{K_a} = \frac{[AH]_2}{[A^-]_2} \quad (3)$$

If we want to combine those two stages with each other, following considerations are necessary: As AH precipitates from solution ( $n_{cryst}$ ) in the volume  $V_{tot}$  when seed crystals are present, the protonated compound concentration  $[AH]_1$  is lowered. Each crystallized compound molecule withdraws one proton from solution  $[H^+]_{ex}$  so the pH increases and lowers  $[AH]_1$  even further:

$$[AH]_2 = [AH]_1 - \frac{n_{cryst}}{V_{tot}} - [H^+]_{ex} \quad (4)$$

At the same time the rising pH value increases the concentration of  $[A^-]_1$  by the concentration  $[H^+]_{ex}$ :

$$[A^-]_2 = [A^-]_1 + [H^+]_{ex} \quad (5)$$

If we insert equations (4) and (5) into (3), we receive the following expression:

$$\frac{[H^+]_2}{K_a} = \frac{[AH]_1 - \frac{n_{cryst}}{V_{tot}} - [H^+]_{ex}}{[A^-]_1 + [H^+]_{ex}} \quad (6)$$

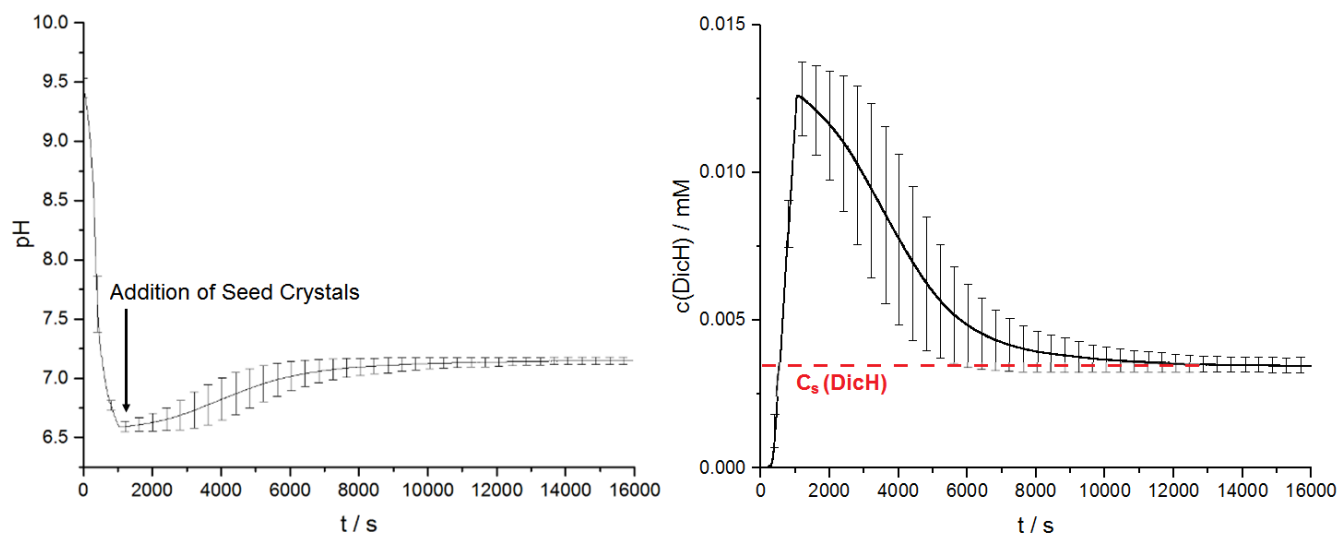
As the amount of protons withdrawn  $[H^+]_{ex}$  equals the amount of compound crystallized, we can write the following:

$$\frac{[H^+]_2}{K_a} = \frac{[AH]_1 - 2 \frac{n_{cryst}}{V_{tot}}}{[A^-]_1 + \frac{n_{cryst}}{V_{tot}}} \quad (7)$$

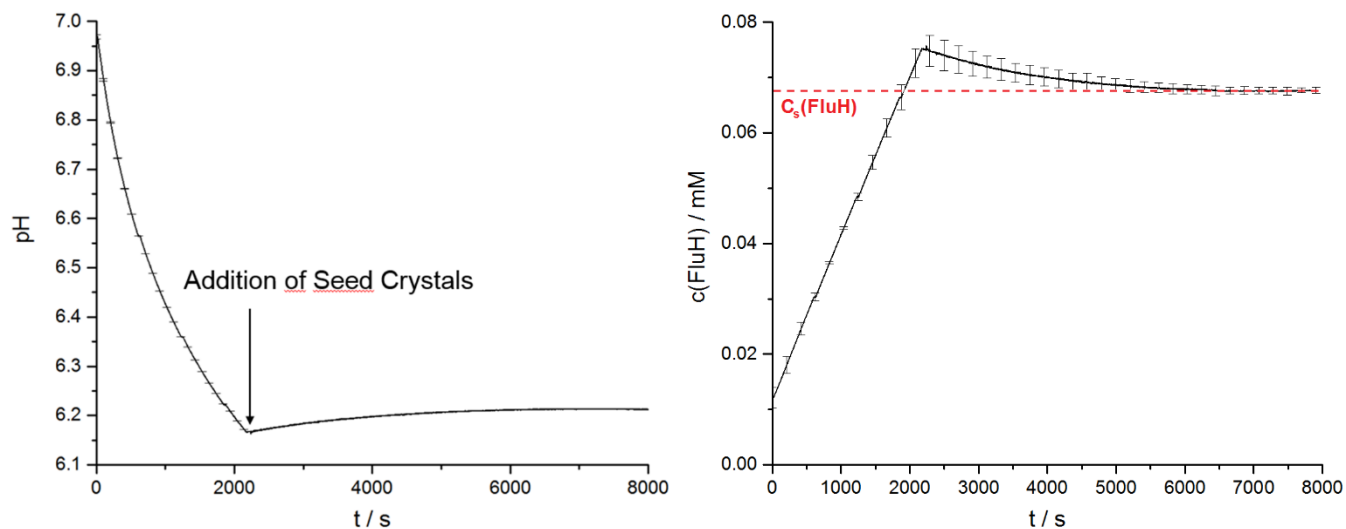
Rearrangement of the equation above yields the following equation for the calculation of the amount of crystallized compound in the volume:

$$\frac{n_{cryst}}{V_{tot}} = \frac{[AH]_1 - \frac{[H^+]_2}{K_a} [A^-]_1}{2 + \frac{[H^+]_2}{K_a}} \quad (8)$$

### Stop titration experiments of diclofenac and flurbiprofen



**Figure S1.** Stop titration experiments of 5 mM diclofenac sodium solution titrated with 8.0 mL of 10 mM diclofenac sodium solution and 1 mM HCl solution with subsequent addition of seed crystals (*HD2*). Left: pH equilibration of diclofenac after addition of the respective seed crystal powder. Right: Concentration of the neutral, protonated compound and intrinsic solubility limit of diclofenac (*HD2*) determined by equation (3) and a  $pK_a$  value of 3.99<sup>1</sup> with the initial total diclofenac concentration.



**Figure S2.** Stop titration experiments of 5 mM flurbiprofen sodium solution titrated with 7.0 mL of 10 mM flurbiprofen sodium solution and 1 mM HCl solution with subsequent addition of seed crystals. Left: pH equilibration of flurbiprofen after addition of the respective seed crystal powder. Right: Concentration of the neutral, protonated compound and intrinsic solubility limit of flurbiprofen determined by equation (3) and a  $pK_a$  value of 4.35<sup>2</sup> with the initial total flurbiprofen concentration.

## References

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- (2) Ràfols, C.; Rosés, M.; Bosch, E., *Anal. Chim. Acta* **1997**, 338 (1), 127-134.