

# Diclofenac Solubility: Independent Determination of the Intrinsic Solubility of Three Crystal Forms

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The solubility in water of diclofenac ( $\{2-[(2,6\text{-dichlorophenyl})\text{amino}]\text{phenyl}\}$ acetic acid), a potent nonsteroidal anti-inflammatory drug, has been investigated. The various solid forms have been characterized by thermogravimetric analysis, differential scanning calorimetry, and X-ray diffraction. The commercially available form of diclofenac is the anhydrous sodium salt. This was recrystallized from ethanol and precipitated as a hydrate containing four diclofenac anions, four sodium cations, and nineteen water molecules per unit cell. This crystal structure is similar to but different from an earlier report of the structure. Crystals of the acid form of diclofenac were anhydrous and corresponded to an earlier crystal structure. Separate solubility measurements on all three of these solid forms of diclofenac gave consistent results for the intrinsic solubility. The aqueous solubility values reported in the literature for diclofenac are spread over a large range, with a factor of 100 separating the largest and the smallest. Our value is at the smaller end of this range. It is the only one supported by three independent procedures and rigorous characterization of the solid forms. The experimental conditions were precisely controlled.

## Introduction

Measurements of solubility reported in the literature can differ dramatically.<sup>1</sup> The measurements are difficult because it is hard to ensure thermodynamic conditions have been reached, as supersaturated solutions may form readily. The conditions used for the experiments must be precisely reported, as small changes in pH, dissolved salts, and temperature, among other things, can substantially affect solubility. The characterization of the solute must be done precisely to ensure that hydration and polymorph effects have been adequately monitored. In addition, there are many types and definitions of solubility, and it is essential to be clear which has been chosen. Aqueous solubility,  $S_{\text{aq}}$ ,<sup>a</sup> refers to the solution of the solute in distilled water. Measurements may also be made in pH-buffered water, and this may give dramatically different results, especially when the Henderson–Hasselbach relationship is not followed due to precipitation of an ionic salt or when high ionic strengths are used (i.e., divalent buffer systems) as shown recently by Bergström.<sup>2</sup> In this study we focus on intrinsic solubility,  $S_0$ , which is defined as the solubility of a compound in its free acid or free base form.<sup>3</sup>

## Results and Discussion

We have investigated the solubility in water of diclofenac, a potent nonsteroidal anti-inflammatory drug. Three different solid

forms (anhydrous sodium salt, 4.75 hydrate sodium salt, and the anhydrous free acid) have been characterized by thermogravimetric analysis, differential scanning calorimetry, and X-ray diffraction. Separate solubility measurements on all three of these solid forms of diclofenac gave consistent results for the intrinsic solubility. The aqueous solubility values reported in the literature for diclofenac are spread over a large range, with a factor of 100 separating the largest and the smallest. Our value is at the smaller end of this range. It is the only one supported by three independent procedures and rigorous characterization of the solid forms. The experimental conditions were precisely controlled.

Many methods and protocols have been described in the literature for measuring and representing solubility–pH profiles.<sup>5</sup> We represent titrations by plotting the concentration of the un-ionized diclofenac (moles of bound proton ions per mole of sample) against the pH (a Bjerrum plot, Figure 1). The amount of strong acid and base added at any point is known, and we know how many dissociable protons diclofenac brings to the solution, together with the hydrogen ion concentration from water autoprotolysis. The free hydrogen ion concentration is determined by measuring the pH (after converting it to  $\text{pH} = -[\log [\text{H}^+]]$ ). The difference between the total number of dissociable protons and the free concentrations is equal (after a small correction for water autoprotolysis) to the concentration of the bound hydrogen ions (un-ionized diclofenac). Dividing this concentration by the concentration of the sample, the average number of bound hydrogen atoms per molecule of substance,  $n_{\text{H}}$ , is readily calculated. In this work, we use an intrinsic solubility determination method based on a potentiometric acid–base titration originally described by Stuart and Box<sup>6</sup> and further developed commercially by Sirius. This method has already been described.<sup>6</sup> The process works by dissolving a material in water and partially reprecipitating it. Figure 1 shows the Bjerrum curve for diclofenac. For fully dissolved diclofenac the titration curve is calculated from the  $\text{p}K_{\text{a}}$  of diclofenac (measured previously at the same conditions as the

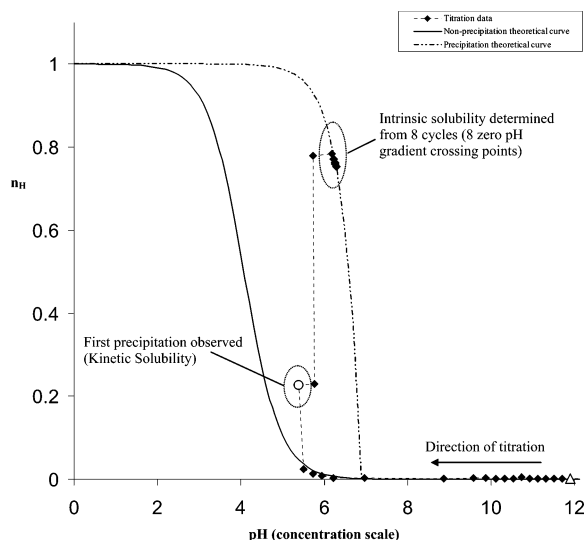
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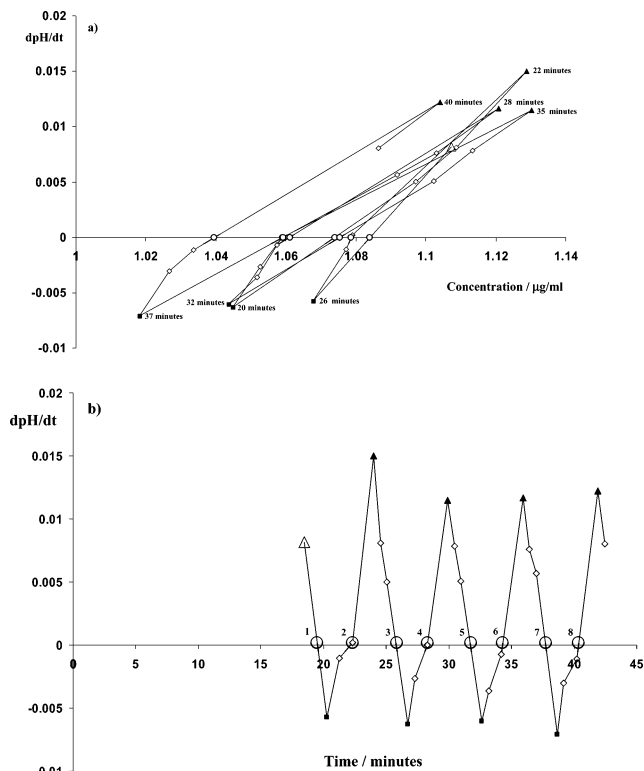
<sup>a</sup> Abbreviations:  $S_{\text{aq}}$ , aqueous solubility;  $S_0$ , intrinsic solubility; TGA, thermogravimetric analysis; DSC, differential scanning calorimetry;  $n_{\text{H}}$ , average number of bound hydrogen atoms per molecule of substance; EtOH, ethanol; CV, coefficient of variation;  $K_{\text{a}}$ , acid dissociation constant;  $K_{\text{w}}$ , water autoprotolysis constant;  $S_{\text{H}}$ , solubility in water at a specific pH;  $[\text{H}^+]$ , concentration of protons.



**Figure 1.** Bjerrum curve for diclofenac. The experimental data follow the theoretical curve up to the precipitation point (full circle), when it jumps onto the precipitation curve. The direction of titration is toward the acidic region (right to left).

solubility experiments) and corresponds to the continuous line in Figure 1. Diclofenac is titrated with acid (Figure 1, direction of titration right to left) until precipitate is turbidimetrically detected by light scattering using a spectroscopic dip probe (full circle). At this point the measurements depart suddenly from the calculated Bjerrum curve, because of the change in the amount of dissolved diclofenac. New Bjerrum curves corresponding to the amount of dissolved diclofenac are calculated by the CheqSol program during data acquisition and displayed on screen. The solution is then repeatedly switched from subsaturated to supersaturated states by precise control and monitoring of the pH of the solution. A very accurate determination of the  $pK_a$  of the sample is needed, because the ionization state of the sample is affected by the pH of the mixture. The measurements are performed under nitrogen, and both the reagents and the water are degassed to minimize the effect of dissolved  $CO_2$ . The temperature is precisely controlled throughout (i.e.,  $25.0 \pm 0.1$  °C). The cycling between subsaturated and supersaturated states continues (“chasing equilibrium”, Figure 2) until the value for the transition between the states, the solubility itself, has converged. The intrinsic solubility is calculated as the mean concentration of all crossing points. The Bjerrum curve for the saturated solution is illustrated as the dotted–dashed line in Figure 1. The experiment was repeated 10 times, and a new intrinsic solubility value is calculated as the mean of all 10 converged intrinsic solubility values.

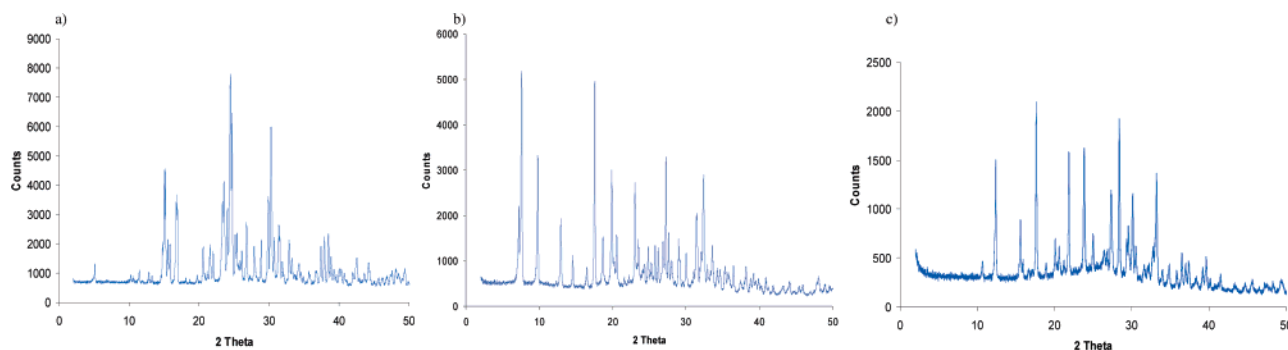
The commercially available form of diclofenac is the anhydrous sodium salt (**1**, ( $\{2-[(2,6\text{-dichlorophenyl})\text{amino}]\text{-phenyl}\}\text{acetic acid}$ )), supplied by Sigma-Aldrich. This salt was purified by recrystallization from EtOH: 50 mg was dissolved in 5 mL of ethanol. After a week of standing at room temperature, crystals appeared in the solution (**3**). Single-crystal X-ray diffraction analysis indicated that this crystal is a hydrate, containing four diclofenac anions, four sodium cations, and nineteen water molecules per unit cell. The molecular arrangement is distinct from, but very similar to, the pentahydrate that has previously been reported, AKOTAV<sup>7</sup> (Cambridge Structural Database<sup>8</sup>). Both crystals are monoclinic and have similar lattice parameters. The primary difference from the pentahydrate is in the arrangement of sodium ions and water molecules, which are disordered in the pentahydrate but are ordered in the material we have isolated. Three of the sodium ions are octahedrally



**Figure 2.** Chasing equilibrium of diclofenac (1 of 10 runs). The pH gradient ( $d(pH)/dt$ ) changes from a positive value (neutral form **5** is precipitating) in the supersaturated region to a negative one (neutral form **5** is redissolving) in the subsaturated one. The rate of pH change is zero at the crossing points (O). In this run eight cycles were performed (eight crossing points). Each crossing point in plot a corresponds to an intrinsic solubility value in plot b; i.e., the first crossing point (point 1 in plot a) occurs at around 20 min after the experiment has started, giving an intrinsic solubility value (first crossing point) of  $1.06 \mu\text{g/mL}$  (plot b): point 2, 22 min,  $1.07 \mu\text{g/mL}$ ; point 3, 26 min,  $1.08 \mu\text{g/mL}$ ; point 4, 28 min,  $1.07 \mu\text{g/mL}$ ; point 5, 32 min,  $1.06 \mu\text{g/mL}$ ; point 6, 35 min,  $1.07 \mu\text{g/mL}$ ; point 7, 37 min,  $1.06 \mu\text{g/mL}$ ; point 8, 40 min,  $1.04 \mu\text{g/mL}$ . Full triangles represent when acid titrant is added and full squares when base titrant is added. Empty tilted squares mean no titrant is added. Empty circles are the crossing points, when the pH does not change, and the large empty triangle is where the experiment starts.

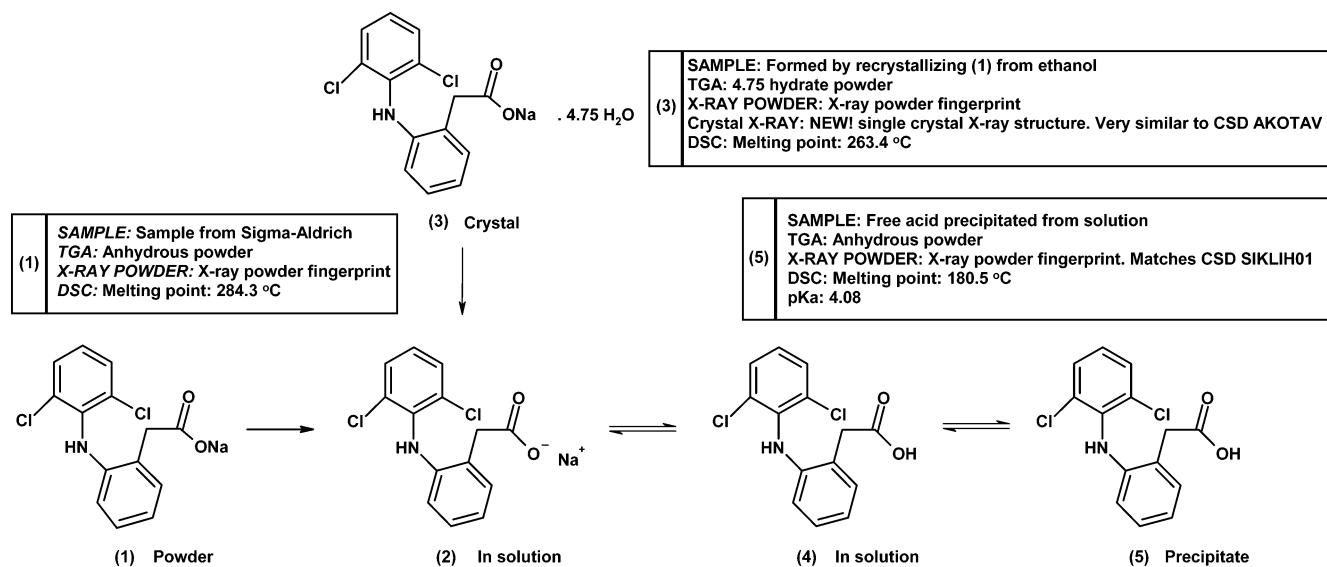
coordinated by water, whereas the fourth is surrounded by five water molecules in a distorted trigonal bipyramidal manner. As a result of this ordering of water molecules, the current crystal structure adopts the  $P2$  space group, whereas the pentahydrate adopts  $P2_1/m$ . This suggests that either we have identified a new crystal form, with 5% less water than an earlier form, or the higher  $R$  factor in the earlier determination led to the assumption that there were five water molecules in the unit cell, rather than nineteen in a unit cell 4 times the size. [The CIF file for the diclofenac sodium 4.75 hydrate can be found in the Supporting Information and can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif) (code CCDC 630862).]

X-ray powder experiments were performed on the commercial sample of diclofenac (**1**) and on the powder from the recrystallized diclofenac (**3**; Figure 3), demonstrating that they are different materials. Attempts to index the patterns were unsuccessful, but the pattern from **3** was almost identical to the pattern simulated from the single-crystal X-ray data. Both **1** and **3** were characterized using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). TGA shows that the commercial sample is the anhydrous form of the sodium salt, with a melting point of  $284.3$  °C (lit.<sup>9</sup> mp  $283\text{--}285$  °C), while



**Figure 3.** Powder X-ray diffraction patterns (STOE, STADI-P, Cobalt 1.79 Å): (a) commercial sample of diclofenac sodium salt (**1**); (b) single crystal of diclofenac sodium salt (**3**); (c) neutral form of diclofenac precipitated (**5**).

**Scheme 1.** Diclofenac: Summary of New Experimental Data



the recrystallized form is a hydrate form with 4.75 water molecules with a melting point, after loss of the water molecules, of 263.38 °C, which means that even when the crystalline form has lost its 4.75 water molecules, the resultant anhydrous form is still different from the commercial one. To determine the intrinsic solubility by chasing equilibrium, an accurate  $pK_a$  value is required. Literature  $pK_a$  values are readily available, but the conditions of these measurements are not always exactly the same as in the solubility experiments, so we measured the  $pK_a$  values ourselves. Aqueous pH titration was not used because of precipitation problems. Instead, several titrations were performed at different concentrations of cosolvent (methanol), and the aqueous  $pK_a$  was obtained by extrapolation to zero methanol concentration (Yasuda–Shedlovsky method).<sup>10</sup> An average  $pK_a$  (10 experiments) of  $4.08 \pm 0.04$  was obtained using this procedure at 0.15 M ionic strength and 25 °C, which agrees closely with previous reported data of 3.99.<sup>11</sup>

The results for the first solubility determination of the sodium salt of diclofenac (**1**) are illustrated in Figure 2, which represents the pH gradient against the concentration of the neutral species. Each crossing point represents the transition from super- to subsaturated (or vice versa), so the concentration of the neutral species at zero pH gradient is the intrinsic solubility of diclofenac. All crossing points should lie close together and give essentially the same answer. The agreement in Figure 2 is extremely good, with a coefficient of variation (CV)<sup>6</sup> of 1.2%. The spread of these crossing points is used to determine the CV of the mean intrinsic solubility result. This method is extremely useful to check that equilibrium has been reached. If

the crossing points lie closely together (low CV), then the sample has reached equilibrium, but if the crossing points are not in a tight bunch (high CV) or they are not randomly distributed (showing a tendency toward one single intrinsic solubility value), then our system needs more time to evolve toward the steady state.

The neutral form of diclofenac, the acid (**5**), was isolated by stopping the solubility experiment after eight cycles at pH 6.5. At the end of the experiment (around 60 min), and at this pH (6.5), the solid precipitated is in equilibrium with the neutral form in solution. Differential scanning calorimetry, thermogravimetric analysis, and powder X-ray diffraction (Figure 3) were performed on this precipitate to fully characterize it. The crystal structure of this solid (**5**) corresponded to the structure SIKLIH01<sup>12</sup> (Cambridge Structural Database).<sup>8</sup> Characterization showed that the precipitated solid **5** is the anhydrous form of the acid of diclofenac, space group  $C2/c$ , with an observed melting point of 180.5 °C.

Solubility experiments were performed using **1**, **3**, and **5**. Since intrinsic solubility corresponds to the solubility of the free acid, we expected to obtain the same intrinsic solubility result for all the materials (Scheme 1). Each experiment was repeated 10 times to be able to apply statistical treatment to the results obtained.

The results obtained demonstrate that the method is very robust, obtaining very high quality data (Table 1). The agreement between the data for the different forms of diclofenac shows that the system is at equilibrium and that the intrinsic solubility is independent of the form originally introduced at the beginning

Table 1. <sup>a</sup>

starting material diclofenac	X-ray structure	mp(DSC) (°C)	TGA	sample mass <sup>b</sup> (mg)	ionic strength <sup>c</sup> (M)	kinetic solubility (μg/mL)	intrinsic solubility(μg/mL)
sodium salt (1)		267.4	anhydrous	10–30	0.165 ± 0.01	40 ± 5	1.1 ± 0.1
sodium salt crystal (3)	new	263.4	4.75H <sub>2</sub> O	10–30	0.165 ± 0.01	65 ± 7	1.0 ± 0.1
acid (5)	SIKLIH01	180.5	anhydrous	10–30	0.165 ± 0.01	12 ± 4	1.0 ± 0.1

<sup>a</sup> Experiments were done at 25 °C and  $I = 0.15$  M. <sup>b</sup> Experiments were repeated more than 10 times; therefore, the sample mass used varied from 10 to 30 mg. The volume at the beginning of the experiment was 10 mL. <sup>c</sup> The *initial* ionic strength is 0.15 M. At the *end* of the experiment the ionic strength will have changed; the amount of change depends on the amount of starting material and how many cycles we have performed. The value given in the table is the average of all the experiments. Solubility values refer to the free acid form of diclofenac (MW = 296.16).

Table 2. Summary of Solubilities for Diclofenac

	solubility(μg mL <sup>-1</sup> )	comments	ref
1	2.36	solubility of the neutral acid at pH 3.00, $I = 0.5$ M (NaCl), and 25 °C, shake flask method	14
2	1.00	acidic pH	13
3	0.9 ± 0.1	intrinsic solubility by chasing equilibrium, $I = 0.15$ M (KCl) and 25 °C	6
4	0.8 ± 0.2	intrinsic solubility by potentiometric titration, $I = 0.15$ M (KCl) and 25 °C	5
5	17.80	neutral pH	15
6	1771	solubility of the salt, $I = 0.5$ M (NaCl) and 25 °C, shake flask method	13
7	1113	solubility of the sodium salt, neutral Ph	13
8	1.03 ± 0.7	intrinsic solubility by chasing equilibrium, $I = 0.16$ M (KCl) and 25 °C	this work
9	857.7	aqueous solubility at pH 7 derived from eq 1 (pH 7, $pK_a = 4.08$ , $S_0 = 1.03$ μg/mL)	this work
10	6.06	aqueous solubility in pure distilled water (pH 4.77) derived from eq 1 (pH 4.77, $pK_a = 4.08$ , $S_0 = 1.03$ μg/mL)	this work

of the experiment. These results agree quite well with some previously reported intrinsic solubilities of diclofenac of 0.9 ± 0.1 μg mL<sup>-1</sup> (Box),<sup>6</sup> 0.8 ± 0.2 μg mL<sup>-1</sup> (Avdeef),<sup>5</sup> and 1 μg mL<sup>-1</sup> (Fini)<sup>13</sup> but clearly disagree with others: 2.36 μg mL<sup>-1</sup> (Fini).<sup>14</sup>

When the aqueous solubilities are compared, the situation is worse. It is not clear whether some of the measurements were done in buffers, at a specific pH, or in pure water, leaving the system to reach whatever pH at equilibrium by itself. Reporting aqueous solubilities without stating clearly the conditions of pH is confusing, because carbonate-saturated water could significantly affect the pH and hence the reported solubility value. The reported aqueous solubility values range from 17.8 to 1771 μg mL<sup>-1</sup> (Fini).<sup>13,15</sup>

The aqueous solubility is the concentration of a compound in a saturated solution of pure water when excess solid is present. It can be calculated from the intrinsic solubility, if it is assumed that ionized species are perfectly soluble.<sup>16</sup> For a monoprotic acid the aqueous solubility is given by

$$S_{\text{aq}} = S_0 \left( 1 + \frac{K_a}{(S_0 K_a + K_w)^{1/2}} \right) \quad (1)$$

where  $S_{\text{aq}}$  is the aqueous solubility,  $S_0$  is the intrinsic solubility,  $K_a$  is the acid dissociation constant, and  $K_w$  is the water autoprotolysis constant.<sup>17</sup> Using this equation, the aqueous solubility of diclofenac at 25 °C and 0.15 M ionic strength is 6.06 μg mL<sup>-1</sup> (20.5 μM), which is around one-third of the reported value by Chiarini (Table 2, entry 5) at neutral pH and about 300 times less than the one reported by Fini (Table 2, entry 6).

This saturated solution will have a pH of 4.77, calculated using

$$[\text{H}^+] = (S_0 K_a + K_w)^{1/2} \quad (2)$$

We can calculate the aqueous solubility at any pH,  $S_{\text{H}}$ , using the following equation:

$$S_{\text{H}} = S_0 (1 + K_a / [\text{H}^+]) \quad (3)$$

where  $S_{\text{H}}$  is the solubility in water at a specific pH and  $[\text{H}^+]$  is the concentration of protons at the same pH.

Using our value of the mean intrinsic solubility,  $S_0$  (1.03 μg mL<sup>-1</sup>), at pH 7, the solubility,  $S_{\text{H}}$ , is 857.7 μg mL<sup>-1</sup> ( $2.9 \times 10^{-3}$  M). The value is fairly close to the values reported by Fini of 1771 and 1113 μg mL<sup>-1</sup> (Table 2, entries 6 and 7).<sup>13</sup>

Intrinsic solubility and aqueous solubility are thermodynamic properties. Kinetic solubility, a measure of the ability of a compound to form supersaturated solutions, is also of interest, but is hard to define precisely. The values reported in Table 1 record the moment at which the solute first precipitates at the beginning of our experiments. The pH at which this happens varies from run to run, and these values are strongly time dependent. We used consistent conditions for repeating the runs (rate of addition, stirring speed, equilibration time, etc.), so the results are similar. The kinetic solubilities are much larger than the intrinsic solubilities, indicating that diclofenac is prone to supersaturation, and the results have a larger variation between runs. Despite this, the kinetic solubilities for the three compounds **1**, **3**, and **5** are distinct, as the differences between the mean values are much larger than the standard deviations.

Assuming that the errors in the three independent measurements of the intrinsic solubility are random, we may conclude that the best value to use is 1.03 ± 0.07 μg mL<sup>-1</sup>.

## Experimental Section

**Solubility Measurements.** The apparatus used to perform the solubility determinations was a GLpKa titrator and a D-PAS spectrometer controlled from a computer running Refinement Pro and CheqSol software (Sirius Analytical Instruments Ltd.). All experiments were performed in 0.15 M KCl solution under a nitrogen atmosphere, at 25 ± 0.1 °C, using standardized 0.5 M HCl and 0.5 M KOH solutions.

**Differential Scanning Calorimetry.** Differential scanning calorimetry was performed on powdered samples using a Metler Toledo DSC 821<sup>e</sup>, with Metler Toledo STAR<sup>e</sup> software. Around 5–10 mg of each sample was run in a sealed aluminum pan with a hole pierced in the lid. Each run was carried out under a nitrogen purge at a heating rate of 10 °C/min.

**Thermogravimetric Analysis.** TGA was carried out on powdered samples (5–10 mg) using a Metler MT5 balance. Data were processed using Metler Toledo STAR<sup>e</sup> software.

**X-ray Powder Diffraction.** X-ray powder diffraction was performed using Co K $\alpha_1$  radiation ( $\lambda = 1.79 \text{ \AA}$ ) on a Stoe Stadi-P diffractometer operating in Debye–Scherrer geometry. The sample was contained in a 0.7 mm diameter borosilicate capillary (Lindemann glass). Data sets with relatively high signal to noise ratios suitable for structure solution were collected at 290 K (approximate counting time 24 h per data set).

**Single-Crystal X-ray Diffraction.** Single crystals of **3** were immersed in perfluoropolyether oil, which protects them from atmospheric oxygen and moisture,<sup>18</sup> mounted on thin glass fibers, and placed in a low-temperature N<sub>2</sub> stream. [CCDC 630862 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).] The crystals were examined on a Nonius Kappa CCD diffractometer using thin slice K and  $\Omega$  scans at 150(2) K utilizing Mo K $\alpha$  radiation. Low temperatures were achieved using an Oxford Instruments Cryostream cooler. Data for this sample were corrected for absorption anomalies using the SORTAV utility. Structures were solved by direct methods using SHELXTL software. Refinements were made on F<sup>2</sup> with all non-H atoms refined anisotropically.<sup>19</sup>

**Acknowledgment.** Financial support by Pfizer is gratefully acknowledged.

**Supporting Information Available:** Details of the method, example of a Bjerrum curve for **1**, crystal structures of **1**, **3**, and **5**, thermogravimetric analysis, differential scanning calorimetry, and powder diffraction patterns for **1**, **3**, and **5**, and CIF file for structure **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Avdeef, A. Physicochemical profiling (solubility, permeability and charge state). *Curr. Top. Med. Chem.* **2001**, *1*, 277–351.
- (2) Bergström, C. A. S.; Luthman, K.; Artursson, P. Accuracy of calculated pH-dependent, aqueous drug solubility. *Eur. J. Pharm. Sci.* **2004**, *22*, 387–398.
- (3) Hörter, D.; Dressman, J. B. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. *Adv. Drug Delivery Rev.* **1997**, *25*, 3–14.
- (4) Avdeef, A. pH-metric solubility. 1. Solubility-pH profiles from Bjerrum plots. Gibbs buffer and pK<sub>a</sub> in the solid state. *Pharm. Pharmacol. Commun.* **1998**, *4*, 165–178.
- (5) Avdeef, A.; Berger, C. M.; Brownell, C. pH-metric solubility. 2: Correlation between the acid-base titration and the saturation shake-flask solubility-pH methods. *Pharm. Res.* **2000**, *17*, 85–89.
- (6) Stuart, M.; Box, K. Chasing equilibrium: Measuring the intrinsic solubility of weak acids and bases. *Anal. Chem.* **2005**, *77*, 983–990.
- (7) Muangsin, N.; Prajaubsook, M.; Chaichit, N.; Siritaedmukul, K.; Hannongbua, S. Crystal structure of a unique sodium distorted linkage in diclofenac sodium pentahydrate. *Anal. Sci.* **2002**, *18*, 967–968.
- (8) Bruno, I. J.; Cole, J. C.; Edgington, P. R.; Kessler, M.; Macrae, C. F.; McCabe, P.; Pearson, J.; Taylor, R. New software for searching the Cambridge Structural Database and visualizing crystal structures. *Acta Crystallogr., B* **2002**, *58*, 389–397.
- (9) Sallman, A.; Pfister, R. Antiinflammatory phenylacetates. U.S. Patent 3558690, 1971.
- (10) (a) Yasuda, M. Dissociation constants of some carboxylic acids in mixed aqueous solvents. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 429–432. (b) Shedlovsky, T. The behavior of carboxylic acids in mixed solvents. *Electrolytes, Proc. Int. Symp., 1959* **1962**, 146–151. (c) Shedlovsky, T. In *Electrolytes*; Pesce, B., Ed.; Pergamon Press: New York, 1962; pp 146–151.
- (11) *Sirius Technical Application Notes*; Sirius Analytical Instruments Ltd.: East Sussex, U.K., 1995 and 1996; Vols. 1 and 2 (ISBN 901125 00 9 and 1 901125 05 X).
- (12) Kovala-Demertzi, D.; Mentzafos, D.; Terzis, A. Metal complexes of the anti-inflammatory drug sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (diclofenac sodium). Molecular crystal structure of cadmium diclofenac. *Polyhedron* **1993**, *12*, 1361–1370.
- (13) Fini, A.; Laus, M.; Orienti, I.; Zecchi, V. Dissolution and partition thermodynamic functions of some nonsteroidal anti-inflammatory drugs. *J. Pharm. Sci.* **1986**, *75*, 23–25.
- (14) Fini, A.; Fazio, G.; Feroci, G. Solubility and solubilization properties of non-steroidal anti-inflammatory drugs. *Int. J. Pharm.* **1995**, *126* (1, 2), 95–102.
- (15) Chiarini, A.; Tartarini, A.; Fini, A. pH-solubility relationship and partition coefficients for some anti-inflammatory arylaliphatic acids. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 268–273.
- (16) The equations have been implemented as a Java applet and are available: Goodman, J. M. (University of Cambridge, U.K.). Solubility Simulator. <http://www.ch.cam.ac.uk/magnus/solubility.html>, 2006.
- (17) Marshall, W. L.; Frank, E. U. Ion product of water substance, 0–1000 °C, 1–10,000 bars, new international formulation and its background. *J. Phys. Chem. Ref. Data* **1981**, *10*, 295–304.
- (18) Kottke, T.; Lagow, R. J.; Stalke, D. Low-cost conversion of a coaxial nozzle arrangement into a stationary low-temperature attachment. *J. Appl. Crystallogr.* **1996**, *29*, 465–468.
- (19) Sheldrick, G. M.; Schneider, T. R. SHELXL: high-resolution refinement. *Methods Enzymol.* **1997**, *277* (Macromolecular Crystallography, Part B), 319–343.

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