Measuring pK_a values in 2-propanol to gain process understanding

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Purpose

2-propanol (isopropyl alcohol, isopropanol, IPA) is a water-miscible solvent used during synthesis of active pharmaceutical ingredients (APIs). During process synthesis, it is essential to know the pK_a of the API in the solvent, for example to understand the effect of speciation to control supersaturation during crystallisation. Much work is required to measure pK_a values in organic solvents accurately. However, the accuracy required for process development is usually lower than that to which an aqueous pK_a is typically determined. Some pK_a values in 2-propanol have been published. In this work, we sought a rapid way to determine pK_a in 2-propanol using an aqueous pK_a measurement procedure, and calibrating it with published values. The presence of water at low levels can change the solubility of organic compounds in organic solvents, and it is expected that water will also have a significant effect on speciation; however until recently the change in pK_a caused by small amounts of water in organic solvents had not been measured.

Methods

10mL solutions of test compounds (0.5 to 3.0 mM) were prepared in anhydrous 2-propanol, and titrated pH-metrically with 0.1 M tetrabutylammonium hydroxide in 2-propanol, using a combination pH electrode calibrated in aqueous pH7 buffer solution, and filled with 2.0 M tetrabutylammonium bromide in anhydrous 2-propanol. Test compounds for these measurements included phenols, carboxylic acids and acidic APIs. Experiments took about 30 minutes. To study the effect of water, selected compounds were titrated in 2-propanol containing up to 17% volume of added water.

Results

pK_a values on an aqueous scale ($^{s}_{w}pK_a$) were calculated from the experimental data by refinement, and plotted vs. accurately measured values on a 2-propanol scale ($^{s}_{s}pK_a$) taken from the literature (Figure 1). Good linearity was observed. It is thought that by measuring $^{s}_{w}pK_a$ of unknown compounds and comparing against the calibration graph, approximate $^{s}_{s}pK_a$ could be estimated. Water appeared to affect the measured pK_a systematically, probably due to improved solvation of the ionised species.

Conclusion

A fit-for-purpose method to measure $^{s}_{s}pK_a$ values in 2-propanol has been described and an understanding of the impact of water present at low levels on speciation in organic solvents has been gained.

Acknowledgement

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pK_a measurements in 2-propanol were made using Sirius GLpKa (above). During the titrations the measurement cell was purged with an inert gas atmosphere. Probes and samples were moved under full automation to minimise user exposure to 2-propanol.

Working with 2-propanol as a titration solvent

2-propanol mixes with water in any proportions. The autoprotolysis constant for 2-propanol is 10^{-22} , compared with 10^{-14} for water. This influences the span and extent of the pH scale in 2-propanol, leading to pK_as significantly higher than aqueous values. Its dielectric constant is 18.3, compared with 78.3 for water. This low value inhibits the freedom of ionic species in 2-propanol, and favours the formation of ion pairs.

We used the Sirius GLpKa to titrate solutions within the concentration range $5x10^{-4}$ M to $3x10^{-3}$ M, prepared by dissolving 1 to 6 mg of the test compound in 10 mL anhydrous 2-propanol (Sigma Aldrich). Working at these low concentrations minimises the formation of ion-pairs. The test solutions were titrated pH-metrically with 0.1 M tetrabutylammonium hydroxide (Sigma Aldrich), diluted with 2-propanol. In aqueous pH-metric pK_a determination, acid (or base) is generally added prior to titration to convert the sample to a single ionised form. However, to minimise the creation of water via neutralisation, no pH adjustment with acid was performed; only very small amounts of water were then created by titrating the sample itself. The pH electrode was stored in 2-propanol before use. Prior to each titration it was standardised in aqueous buffer solution at pH 7. The electrode was filled with 2 M tetrabutylammonium bromide (Acros Organics) in 2-propanol. After each titration, $^{s}_{w}pK_a$ results were calculated using Sirius RefinementPro software, and compared with published measured values. It is proposed that $^{s}_{w}pK_a$ for any acidic drug soluble in 2-propanol could be measured by this method, and compared with the graph in Figure 1 to determine the $^{s}_{s}pK_a$ on an absolute 2-propanol scale.

Published values for pK_a in 2-propanol

We reviewed the literature from 1951 to date, and identified 66 papers that discuss potentiometric titrations in various non-aqueous solvents including pure 2-propanol, methods for calculating pH values in 2-propanol, buffer solutions, and methods for investigating ion-pair formation and the effects of water. The knowledge gained helped us to understand pH scales, the pK_a values of drugs in pure 2-propanol, and the effect of the solvent on salt formation. Of particular interest, two papers [1, 2] published pK_a values expressed on an absolute 2-propanol scale for a number of organic acids, taking account of ion-pair formation (determined conductometrically) when computing the pK_a values. While rigorous, the methods used were time-consuming and laborious, and not suited to automation.

Opportunities for further work

Only a few $^{s}_{s}pK_a$s (all acids) in 2-propanol have been published in the literature. The eight compounds in the pK_a correlation cover the range from pH 11.43 to15.31 on the 2-propanol scale. This range is not wide enough to give confidence to extrapolations made for compounds with low pK_a values. No literature reports for pK_a values of bases in 2-propanol or for models of the effect of water on $^{s}_{s}pK_a$ have been identified.

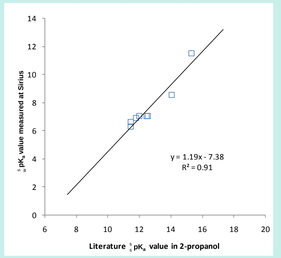
References

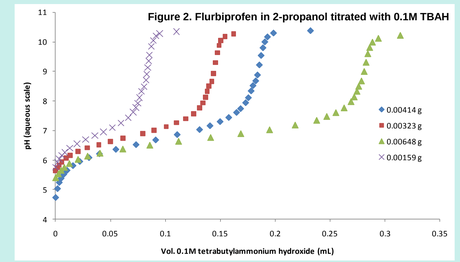
[1] Rafols, C.; Roses, M.; Bosch, E., Anal. Chim. Acta 1997, 338 (1-2), 127-134.
[2] Bosch, E.; Rafols, C.; Roses, M., Talanta 1989, 36 (12), 1227-31.

Results

The table and Figure 1 show pK_a results for eight acids in 2-propanol. Figure 2 shows titration curves for different weights of flurbiprofen. The $^{s}_{w}pK_a$ can be estimated as the half-neutralisation point of each curve. No correlation was observed between sample weight and pK_a, indicating the effect of ion pairing is negligible.

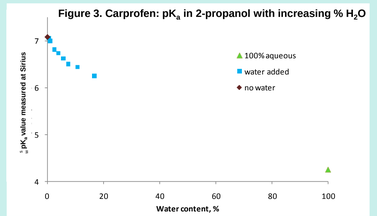
	pK_a on absolute 2-propanol scale (lit.)	$^{s}_{w}pK_a$ (this work)	n	SD
Flurbiprofen [1]	11.43	6.63	4	0.08
Ketoprofen [1]	11.45	6.29	6	0.15
Ibuprofen [1]	11.77	6.88	5	0.11
Carprofen [1]	11.99	7.05	5	0.17
4-nitrophenol [1]	12.45	7.06	9	0.29
2,4,6-trichlorophenol [2]	12.55	7.04	4	0.05
3,5-dichlorophenol [1]	14.05	8.54	4	0.19
4-chlorophenol [1]	15.31	11.54	6	0.34

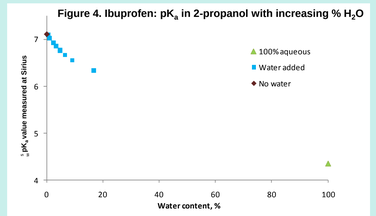




Effect of water

To investigate the effects of water on the pK_a values, similar weights of carprofen, ibuprofen and flurbiprofen were titrated with known volumes of water added. Figures 3 and 4 show the effect of increasing water content on the $^{s}_{w}pK_a$ of carprofen and ibuprofen. The presence of 5% water caused a pK_a shift of approximately 0.4 pH units. A similar trend was observed for flurbiprofen.





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