Pion

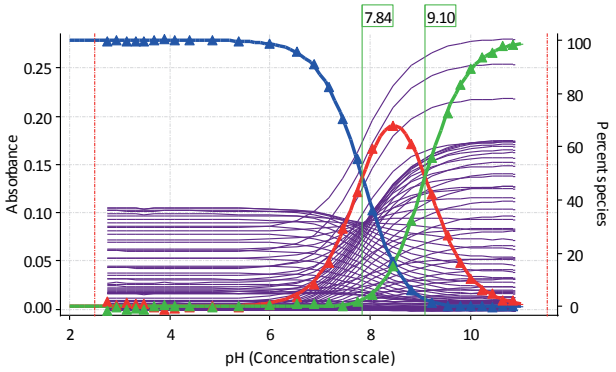

# *SiriusT3*

***From Pion Inc.***

For compound screening and
detailed PhysChem characterisation

SiriusT3 measures $pK_a$, log P, log D and solubility of ionisable drugs and small molecules, needing little amounts of sample. SiriusT3 instruments are used in labs that support drug discovery, crop science research, by universities, biochem and CROs.

*Five miniature probes entering sample vial*




*Spectral data vs. pH for sample with two $pK_a$s*

## Use it for

### Early stage compound screening

- In synthetic chemistry, measuring $pK_a$ helps in selecting the best structures for development
- Good compound selection reduces the risk of costly late stage failures
- Up to 80 $pK_a$ samples a day; automation reduces operator time

### PhysChem characterisation

- Understand the ionisation state of a drug, how it varies with pH and its effect on absorption
- Learn how the $pK_a$ changes due to solvent interactions, partitioning, precipitation or binding
- Improve ADME predictions and evaluate how changes to the molecule can affect the log P for a desired application.

### Pre-formulation

- Preparing detailed PhysChem profiles
- Learn about the molecule's capacity for supersaturation and LLPS (liquid-liquid phase separation) formation

### Importance of $pK_a$

Most small-molecule drugs ionize in aqueous solutions. Ionization occurs when the molecules acquire or lose hydrogen ions in response to changes in the pH. When pH goes up (e.g. in the GI Tract), bases convert from ionised to neutral and become more lipophilic and less soluble. These changes affect the rate of absorption. $pK_a$ values affect many other properties, too. Chemists often improve drug candidates by making substitutions to change their $pK_a$.

### Screening

SiriusT3 is ideal for high throughout $pK_a$ measurement in support of drug discovery. In most labs, 80% of samples will succeed first time by a Fast UV/cosolvent method. Failures can be re-measured by pH-metric, or flagged for future attention if the compound gets through DMPK.

## What customers say

"SiriusT3 integrates perfectly in our analytical workflow".

"It is a good fit, filled the gap we had in the company".

"…a pre-requisite for DMPK studies".

"It has become a part of our screening cascade to aid in selection of compounds to move forward into further PK testing".

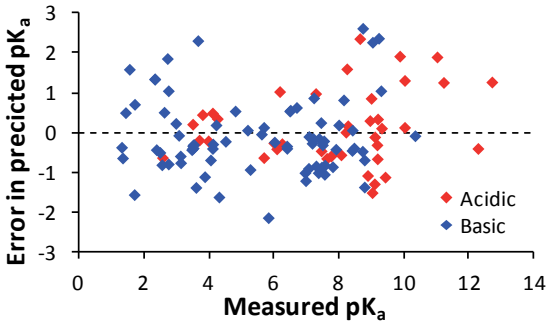
"The SiriusT3 is an integral part of a pool of instruments for physicochemical compound characterisation. For $pK_a$ and log P/D measurements, SiriusT3 is the Golden Standard".

### Measuring $pK_a$

If a molecule has a $pK_a$ between 2 and 12, we will find it. Many drugs absorb UV, and the intensity vs. wavelength changes when they ionise. Our UV-metric methods determine $pK_a$ values from these changes. Around 80% of drug $pK_a$ values can be successfully measured in about 15 minutes by our Fast UV method, which requires only 5µL of 10 mM stock solution (typically 10 µg). Those $pK_a$s that are not associated with UV change can be measured by our pH-metric method, which requires less than 1 mg of solid sample.

### Prediction and measurement

Scientists often use software to predict $pK_a$ values. It's powerful and fast, but it doesn't always get things right. This graph shows measured vs. predicted $pK_a$ for 115 $pK_a$s measured in our Applications Laboratory in 2013. We're confident in the measured values, but it would be risky to base development strategies on some of the predictions




### log P and solubility – find out more

Pion pH-metric methods for measuring log P and solubility of ionisable compounds are supported by several validation studies. Methods are described on www.pion-inc.com, along with recordings of webinars about $pK_a$, log P and solubility.

## TECHNICAL SPECIFICATION

| SIRIUST3 TECHNICAL SPECIFICATION | |
|---|---|
| pH electrode | Ag/AgCl, double junction reference |
| pH range | 1.8 - 12.2, standardised by Sirius Four-Plus™ |
| Electrode storage | Home position for electrode storage pH7 buffer positions for calibration |
| Stirrer | Overhead, variable speed, computer controlled |
| Temperature | Measured by thermocouple at every datapoint.<br>Controlled by Peltier, range 12°C to 70°C |
| Turbidity detection | Pass-through light detection – percentage light detected reported to 0.1% |
| Reagents | Water, Acid, Base, partition solvent, CoSolvent |
| Partition solvents | Supports 7 including Octanol, Dodecane, Toluene |
| CoSolvents | Supports 10 including Methanol, Acetonitrile, DMSO and MDM. Six can be installed, via automated valve. |
| Dispensers | Precision dispensers, 0.5 mL syringes, multi-tip capillary bundle, minimum volume of 0.024 L |
| Probe movement | Fully automated X-Y axis on titrator module |
| Washes | Wash station provides static and flowing washes |
| Autoloader | Holds up to 192 samples, automatic gripper arm for transfer to sample position |
| Purge gas | Two internal flow meters, nitrogen or argon supply required |
| Assay volume | 1.0 to 3.5 mLs |
| Environment | For indoor use only<br>Altitude ≤2000m<br>Temp. 5°C to 40°C<br>Max relative humidity 80% @ 31°C<br>Mains voltage fluctuation +/- 10%<br>Installation overvoltage Cat II<br>Pollution degree 2 |

| SIRIUST3 ASSAY SPECIFICATION | |
|---|---|
| Analytical methods | Templates supplied for all supported assays.<br>Users can save customised templates if required.<br>1-2-3 template for setting up cosolvent pKa assays. |
| $pK_a$ | Determine $pK_a$ values to the highest commercially available accuracy<br>• Results in 15 minutes by Fast UV for most samples<br>• UV-metric method for pKas range of 0.5 to 13.5<br>• pH-metric assays for samples without pH/UV activity<br>• Cosolvent methods for poorly soluble samples<br>• Yasuda-Shedlovsky plots for cosolvent $pK_a$s<br>• Generate distribution of species plots<br>• Determine buffer capacity<br>Standard assay conditions: 0.15 M KCl, 25 or 37°C.<br>Sample requirement: UV, 10 µg; pH-metric, 1 mg |
| log P | • Determine log P and log D vs. pH<br>• Study octanol/water & many other mixtures<br>• Built-in methods for high, medium and low log P<br>• No need for time-consuming shake-flask style experiments in multiple pH buffers.<br>• Sample requirement: 1 - 2 mg |
| Solubility | • Determine intrinsic solubility and kinetic solubility<br>• Derive pH vs. solubility profile<br>• Determine supersaturation<br>• Sample requirement: 1 -10 mg, depends on solubility |
| Assay Expert | Optional integrated software prediction module (powered by ACD) to analyse structure and identify ionizable groups, identify whether they are acidic or basic and estimate $pK_a$ and log P values. Predicted properties are used to automatically optimize the design of experiments. |
| Reagents | • Minimal running costs - uses off the shelf reagents with no special "kits" required. |
| Getting samples to dissolve | • Built in ultra-sonic bath to aid measurements of insoluble compounds.<br>Automated acid and base pre-dose can be programmed. |
| Clean-up assays | Short automated procedures for cleaning electrode and probes.<br>Low to high and high to low pH with cosolvent present; surfactant wash at end. |

| PHYSICAL DIMENSIONS | WEIGHT | HEIGHT | WIDTH | DEPTH |
|---|---|---|---|---|
| DISPENSER MODULE | 35kg/77.16lbs | 700mm | 260mm | 460mm |
| TITRATOR | 23kg/50.71lbs | 490mm | 215mm | 460mm |
| AUTOLOADER | 27kg/59.52lbs | 490mm | 350mm | 460mm |
| TOTAL | 85kg/187.39lbs | 700mm | 825mm | 460mm |

**Please contact your appropriate region below to find out more about Pion products.**

***Pion stands behind the science. Let us prove it to you. Contact us today.***

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