

# Tips and tricks

## Karl Fischer titration

### Recognizing and preventing side reactions

Karl Fischer water determination is only specific if there are no side reactions. Side reactions are any reactions with substances in the sample that

- interfere with the stoichiometry of the KF reaction.
- change the pH range, which is buffered at pH 5–6.
- produce or use up water themselves.
- oxidize on the anode of the generator electrode.
- reduce on the cathode of the generator electrode.
- react with the substances in the Karl Fischer reagent.

The following side reactions between substances in the sample and substances in the Karl Fischer reagent may occur:

- Reaction with iodine, i.e., the sample may be oxidized by iodine
- Reaction with iodide, i.e., the sample may oxidize iodide to form iodine and be reduced in the process
- Reaction with alcohol
- Reaction with the acids in the reagent

How pronounced a side reaction is depends not only on the side reaction itself but also on the proportion of interfering component in the sample and the sample size. In some cases, side reactions can be minimized through the use of smaller sample sizes and a fresh reagent for each titration so that no further special treatment is required.

### Recognizing KF side reactions

If a side reaction is suspected, it is important to clarify whether the water has been completely released from the sample or whether the observations are to be attributed to slow and incomplete water release. In the case of samples that are completely dissolved in the KF reagent, the water is also completely released.

« *Karl Fischer water determination is only specific if there are no side reactions.*

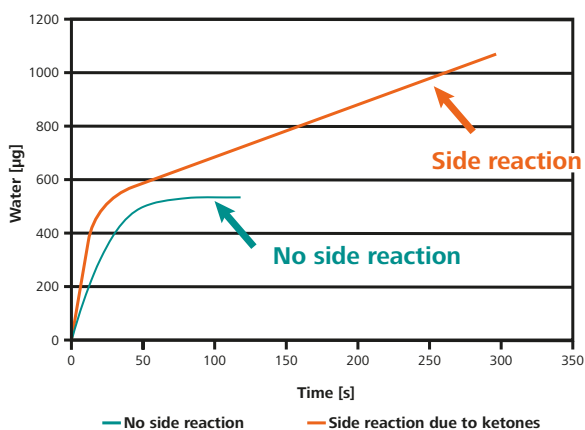
### Titration does not finish

If there is a pronounced side reaction with continuous iodine consumption, the system titrates over a longer period without reaching the endpoint parameters and the end of the titration. In this case, the determination must be stopped by adjusting the live parameters, e.g., the termination time.



### Anomalies of the titration curve

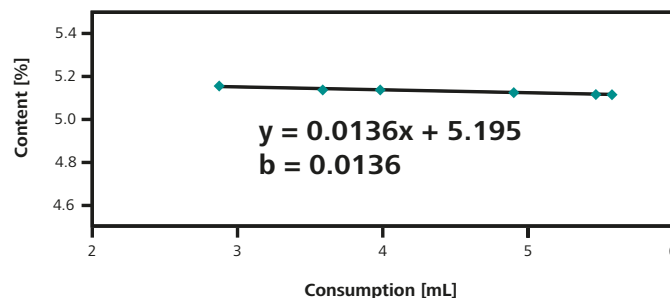
Side reactions can be indicated by a longer titration time compared to the titration of a water standard, slow endpoint detection, and a higher drift after the titration than before the titration. Comparing the titration curve of a sample with that of a standard with a similar water quantity makes it easier to evaluate the situation. If a graph plotting volume against time (or  $\mu\text{g}$  water against time in the case of coulometry) shows a titration curve that increases rapidly to begin with before continuing to increase steadily, this can indicate a side reaction (Figure 1).



**Figure 1.** Side reactions can often be identified from the titration curve.

### Linearity

If there is a side reaction, the water content found may be dependent on the sample weight or the titrant consumption. In this case, a trend can be seen in the regression line of the water content / titrant consumption value pairs. Significant positive or negative slopes in the regression line indicate an apparent dependency of the water content on the size of the titrant consumption / sample weight, which can in turn indicate the occurrence of side reactions (Figure 2). Ideally, the slope (b) should be 0.000.



**Figure 2.** If the slope of the regression line for the water content / titrant consumption value pairs deviates significantly from 0, this indicates a side reaction.



### Spiking

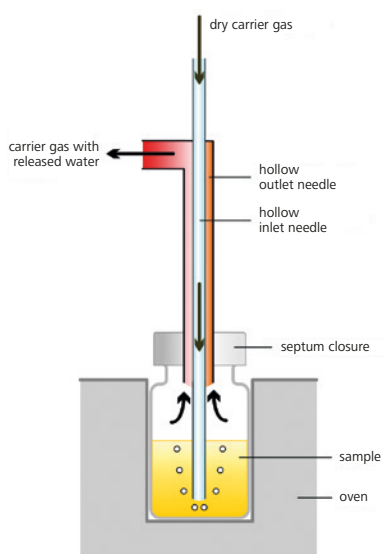
If the water recovery rate found after spiking the samples is not within  $100 \pm 3\%$ , this can indicate a side reaction. Depending on the type and speed of the side reaction, the recovery may be too high or too low. For example, samples which contain DMSO (dimethyl sulfoxide) result in false low readings. It is worth noting, however, that a recovery rate of almost 100% does not guarantee the absence of a side reaction, as side reactions that take place very rapidly will not be detected. The process for determining the recovery after spiking is described in detail in the suitability test in chapter 2.5.12 of the European Pharmacopoeia.

### Preliminary tests

Preliminary tests in a weakly acidic (alcoholic) environment indicate whether substances in the samples reduce iodine or oxidize iodide. Simply adding drops of iodine or potassium iodide solution can help to detect side reactions based on the coloring.

### Evaluating the redox potentials

By comparing the redox potentials of the redox pairs of sample substances with the redox potential of iodine/iodide, it is possible to assess whether an undesired redox reaction may occur. If the standard potential is more positive than that of iodine/iodide – as in the case of chlorine, for example – the oxidation of the iodide may result in false low readings. If it is more negative, the reduction of the iodide may result in additional consumption.



The Karl Fischer oven method (diagram on left) can be used to extract water from liquid and solid samples and to separate it from interfering components that are thermally stable at oven temperature.

### Remedy in the event of KF side reactions

Most undesired and disruptive side reactions can be suppressed by taking suitable measures.

- Ketones and substances that react with the methanol in the KF reagent: Use methanol-free reagents.
- Samples that lower the pH range of the KF reagent: Add buffer solution for acids or a stoichiometric excess of imidazole.
- Samples that raise the pH value (e.g., aminic bases): Add buffer solution for bases or a stoichiometric excess of salicylic acid / benzoic acid with sufficient acidity.
- High afterdrift: Afterdrift correction may help. This involves canceling the titration at a set time and recording the additional consumption over several minutes. This makes it possible to calculate the drift after the titration. This afterdrift is then used to correct the water quantity found.
- Samples that reduce iodine: Subtract the iodine consumption of the reductant in the sample from the overall iodine consumption of the sample.
- Samples that oxidize iodide: Reduce the oxidant, e.g.,  $\text{Cl}_2$ , in advance with an excess of  $\text{SO}_2$ , for example, by treating the sample with the solvent of a two-component reagent.
- General: Carry out the titration in a thermostatically controlled cell connected to a circulation thermostat at, e.g.,  $-20\text{ }^\circ\text{C}$  in order to slow down the side reaction. Note that the titration parameters should be adjusted to the low temperatures.
- General: Extract the water with the KF oven method if the interfering components are thermally stable at oven temperature.
- General: Mask/eliminate the interfering component, e.g., by adding *N*-ethylmaleimide in the case of thiols.

**Table 1.** Side reactions in Karl Fischer titration

Substance in sample	KF reagent	Side reaction	Effect	Remedy
Ketones	Alcohol	Reaction to form ketals	Slow release of water, no stable endpoints, results in false high readings	Use of methanol-free reagents for ketones and aldehydes, afterdrift correction
Aldehydes	Alcohol	Reaction to form acetals	Slow release of water (faster than for ketones), no stable endpoints, results in false high readings	Use of methanol-free reagents for ketones and aldehydes, afterdrift correction
Aldehydes	SO <sub>2</sub> and water	Addition of bisulfite	Water is part of the adduct, results in false low readings	Use of methanol-free reagents for ketones and aldehydes, titrate quickly
Polyvalent phenols, aminophenols	Iodine	Oxidation by iodine or on the anode (coulometry)	Increased consumption of iodine, no stable endpoints, results in false high readings	Addition of benzoic acid / salicylic acid, the oxidation should be considered in relation to the pH value: for coulometry, only use benzoic acid
Acids, stronger carboxylic acids	Alcohol, pH change	Esterification	pH value changes to < pH 4, slowing of KF reaction speed, water formed through esterification, results in false high readings	Buffering the acid with stoichiometric excess, e.g., with imidazole
Organic bases (nitrogen compounds)	pH change	Disproportionation of the iodine (I <sup>••</sup> /I <sup>-</sup> ) and oxidation of the amine	pH value changes to > pH 8, no stable endpoints, results in false high readings	Buffering the base with a stoichiometric excess of sufficiently strong acid, e.g., with benzoic acid or stronger salicylic acid
Alcoholates	pH change	Disproportionation of the iodine (I <sup>••</sup> /I <sup>-</sup> ) and oxidation of the amine	pH value changes to > pH 8, no stable endpoints, results in false high readings	Buffering the base with a stoichiometric excess of salicylic acid/benzoic acid, for example
Oxides, hydroxides, carbonates, and hydrogen carbonates	Acids, e.g., HI	Neutralization reaction	Rapid formation of water causes false high readings	Oven method with KF oven
Thiols (mercaptans) and sulfides, thioesters, cysteines	Iodine	Oxidation of the thiol groups by iodine to form disulfides	Increased consumption of iodine, results in false high readings	Indirect procedure with KF oven; jamming of the sulphydryl group (SH group) with <i>N</i> -ethylmaleimide
Silanols/siloxanes	Alcohol	Esterification	Slow separation of water, no stable endpoints, results in false high readings	Use of methanol-free reagents for ketones and aldehydes, afterdrift correction
Boron compounds	Alcohol	Esterification	Slow separation of water, no stable endpoints, results in false high readings	Use of methanol-free reagents for ketones and aldehydes, afterdrift correction
Metal salts	Iodine/iodide	Redox reaction	Resulting iodine can react with the water in the sample, results in false low readings; additional consumption of iodine, results in false high readings	Oven method with KF oven
Metal peroxides (M <sub>2</sub> O <sub>2</sub> )			Slow release of water, no stable endpoints, results in false high readings	Oven method with KF oven, as long as the substances release their water at < 250 °C
Organic peroxides		Sample can oxidize iodide to form iodine	Resulting iodine can react with the water in the sample, results in false low readings	Sufficient SO <sub>2</sub> and sufficient buffering in the measuring solution, as well as titration in cold conditions in order to «freeze» possible side reactions
Strong oxidants	Iodide	The sample may oxidize iodide to form iodine and be reduced in the process	Resulting iodine can react with the water in the sample, results in false low readings	Organic peroxides: titration in cold conditions, large excess of SO <sub>2</sub> and imidazole buffer as well as afterdrift correction if necessary (exception: although hydroperoxides such as H <sub>2</sub> O <sub>2</sub> form iodine, they also form an equivalent quantity of H <sub>2</sub> O) Chlorine/bromine: reduce with excess of SO <sub>2</sub> Dichromates, chromates, permanganates: oven method with KF oven
Strong reductants	Iodine	Sample is oxidized by iodine	Increased consumption of iodine, results in false high readings	Oven method with KF oven, calculate the difference between the iodine consumption for the reductant and the overall iodine consumption for water and reductant