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Counterion effects in the preparation of aldehyde-bisulfite adducts

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Graphical Abstract
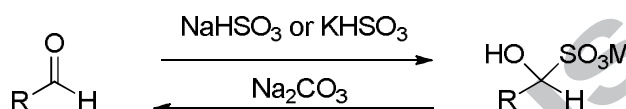
Abstract

The identification and development of an aldehyde-bisulfite adduct as an isolable starting material in the synthesis of the CETP inhibitor Evacetrapib is described. The physical properties of the sodium and potassium analogs are compared, and the extension of the scope of this study to include an investigation into the solid state properties of a range of sodium and potassium bisulfite adducts of commonly encountered aldehydes is discussed.

Keywords: aldehyde-bisulfite adduct, Rosenmund reduction, solid state properties, Evacetrapib

Introduction

Aldehydes are an important class of compounds in organic synthesis due to their functional reactivity and participation in a range of reactions such as condensations, oxidations, reductions and hydrations.[1] Aldehydes are extensively utilized in the pharmaceutical industry, in transformations such as organometallic coupling reactions,[2] allylations,[3] Wittig reactions[4] and reductive aminations.[5] However, the long term storage of synthetically useful aldehydes can be problematic as aldehydes often suffer from instability and non-crystallinity issues.[6] These issues can lead to challenges affecting variability in product purity and supply robustness. Many of these challenges can be conveniently overcome by the preparation of aldehyde bisulfite adducts, most commonly as the sodium salt by reaction of the aldehyde with sodium bisulfite.[7-9] Bisulfite adducts are generally crystalline solids that are easy to handle and can be stored for prolonged

periods of time due to their enhanced stability.[6, 10-11] In most cases, the bisulfite adducts are readily cleaved back to their aldehyde precursors.

As part of an ongoing project into the synthesis of the CETP inhibitor Evacetrapib, multikilogram quantities of aldehyde **1a** were required. However, **1a**, which is an oil, is rather unstable due to its ability to epimerize readily and its potential to oxidize in air to the carboxylic acid, and was thus deemed to be unsuitable for long term storage. It was hoped that the conversion of **1a** to the corresponding sodium bisulfite adduct **2a** would lead to a crystalline solid with the stability and solid state characteristics necessary for prolonged storage of the material. It was found that **1a** was easily converted to **2a** by reaction with $NaHSO_3$ in THF and water. Unfortunately, the solid state characteristics of **2a** were not very favourable; in particular **2a** was found to be quite hygroscopic, with a weight gain as high as 30% at relative humidities of up to 95%. This would have a major impact on the long term storage of **2a**, as controlled storage conditions would be required. Additionally, a thick slurry is formed during the preparation of **2a** resulting in long filtration times. As a result of these issues with the solid state properties, we were interested in investigating if changing the counterion of the bisulfite adduct would lead to a solid with improved physical properties. Although not as common as its sodium counterpart, the preparation of potassium bisulfite adducts have also been reported.[12-14] The potassium bisulfite adduct **3a** was prepared and was found to have much improved solid state characteristics compared to **2a**. Herein is reported the study on the solid state characteristics of the sodium and potassium bisulfite adducts of **1a**. The scope of this study was also extended to include an investigation into the solid state properties of a range of sodium and potassium bisulfite adducts of commonly encountered aldehydes.

Results and Discussion
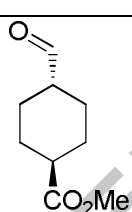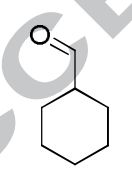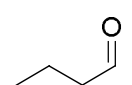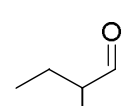
The aldehyde **1a** was prepared as outlined in Scheme 1.[15] Conversion of the monoacid **4** to the acid chloride **5** is achieved by reaction of **4** with 1.14 eq. of oxalyl chloride and 0.1 eq. of 2,6-lutidine in toluene at rt for 17 h. The acid chloride then undergoes a Rosenmund reduction by reaction with 0.26 eq. of 5% Pd/C, 1.2 eq. of 2,6-lutidine in toluene to afford the aldehdye **1a**,[16] with yields over the 2 steps typically 88-92%. Aldehyde **1a** formed in this manner is typically quite pure, with levels of the undesired cis-isomer consistently less than 0.5%.
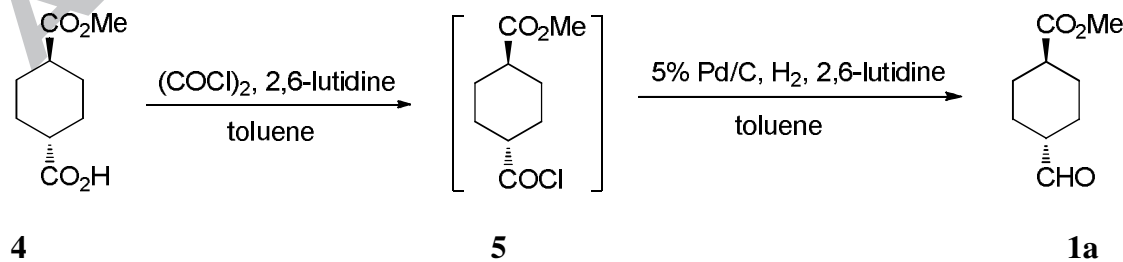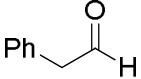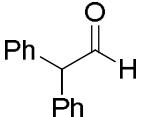
Scheme 1 Preparation of 1a

The sodium and potassium bisulfite adducts of the aldehyde **1a** were easily prepared by reaction of 1 equivalent of sodium or potassium bisulfite with 1 equivalent of **1a** in a THF-water mixture to give the sodium bisulfite adduct **2a** and potassium bisulfite adduct **3a** in yields of >90% following stirring at room temperature for 2-16 h and filtration. The purity (determined by quantitative NMR in DMSO using maleic acid as an in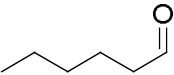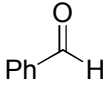ternal standard) of **3a** is usually up to 10% greater than that of **2a**, with water and suspended inorganic salts presumably accounting for the remaining mass (by NMR spectroscopy and HPLC there are no other organic impurities present). Additionally, aldehyde regenerated from either the sodium or potassium adduct is typically equivalent in purity to the crude material emanating from the Rosenmund reduction. This procedure is very amenable to scale-up and has been demonstrated successfully for both **2a** and **3a** on multikilogram scales.

Table 1 Preparation of aldehyde bisulfite adducts

Entry	Aldehyde	Na adduct	K adduct	% yield Na	% purity Na[a]	% yield K	% purity K[a]
1		2a	3a	quant.	85	90	95
2		2b	3b	quant.	88	84	93
3		2c	3c	79	92	93	84
4		2d	3d	77	72	77	90

5		2e	3e	67	84	75	94
6		2f	3f	quant	97	92	93
7		2g	3g	91	91	89	100
8		2h	3h	91	89	86	98

a. Determined by quantitative NMR in DMSO or D_2O using maleic acid as an internal standard

In addition to an enhanced purity profile, the filterability properties of **3a** were found to be much more favorable than those of **2a**. As mentioned earlier in the introduction, a thick slurry is formed during the preparation of **2a** which leads to long filtration times. In contrast, the slurry formed during the preparation of **3a** is much more flowable, leading to filtrations which are up to 6 times faster. The filtration of **2a** and **3a** was studied using a 200 mL Pocket Pressure Filter with 4.0 cm diameter and Tetco filter medium at pressures of 30, 15 and 5 psi (see Table 2 and Table 3). For **2a**, the filtration flux ranged from 280-832 L/hm^2 and the filtration rate from 0.09-0.26 g/s, while the corresponding values for **3a** were 678-1700 L/hm^2 and 0.22-0.54 g/s respectively. Further optimisation of the preparation of **3a** to include a co-addition of aqueous potassium bisulfite and a THF solution of **1a** to a solution of THF and water containing a seedbed of **3a** at 45 °C have led to further enhancement of the filtration properties, with a filtration flux of up to 11,200 L/hm^2 and a filtration rate of up to 3.6 g/s obtained.

Table 2 Filtration study of 2a

Pressure (psi)	30	15	5
Filtration rate (g/s)	0.26	0.17	0.09
Filtration flux (L/hm^2)	832	551	280

Table 3 Filtration study of 3a

Pressure (psi)	30	15	5

Filtration rate (g/s)	0.54	0.43	0.22
Filtration flux (L/hm^2)	1700	1341	678

With the benefits of enhanced filterability, we desired to further explore the physical property difference of the sodium and potassium bisulfite adducts. In a variable humidity solid state experiment, the sodium bisulfite adduct **2a** was found to be quite hygroscopic, with a weight gain of 27% at relative humidity of up to 95%. The corresponding moisture sorption pattern for the potassium bisulfite adduct **3a** showed it to be much less hygroscopic, with a weight gain of just 2% at relative humidity of up to 95% (entry 1, Table 5). Presumably, the sodium adduct exists as a variable hydrate, while the potassium adduct exists in the solid state as a hemihydrate, which was further confirmed by single crystal analysis on a sample that was crystallized from EtOH-H$_2$O. The X-ray also verified the sulfonate structure (Figure 1 and Figure 2). Despite repeated attempts, we were unable to grow a crystal of **2a** suitable for single crystal analysis.
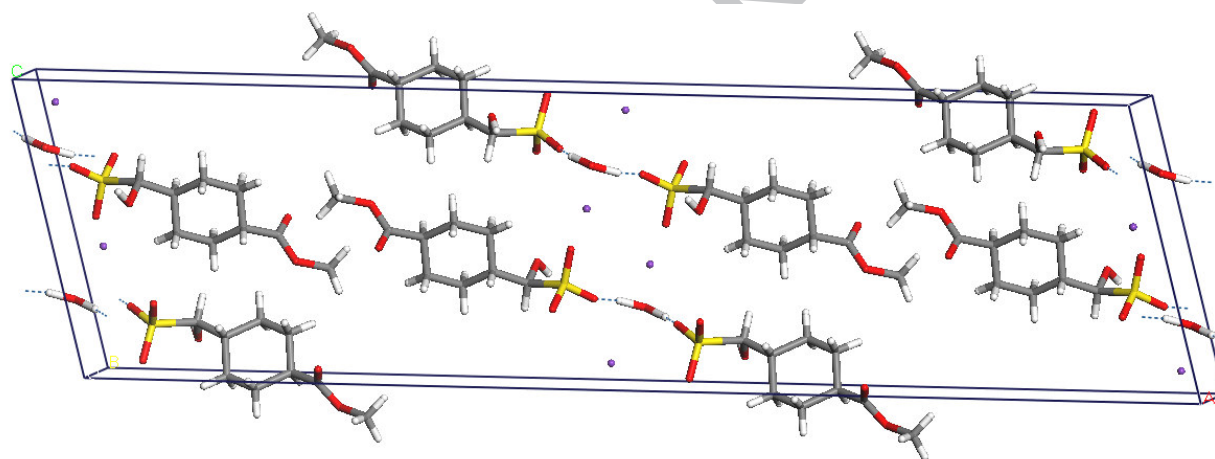

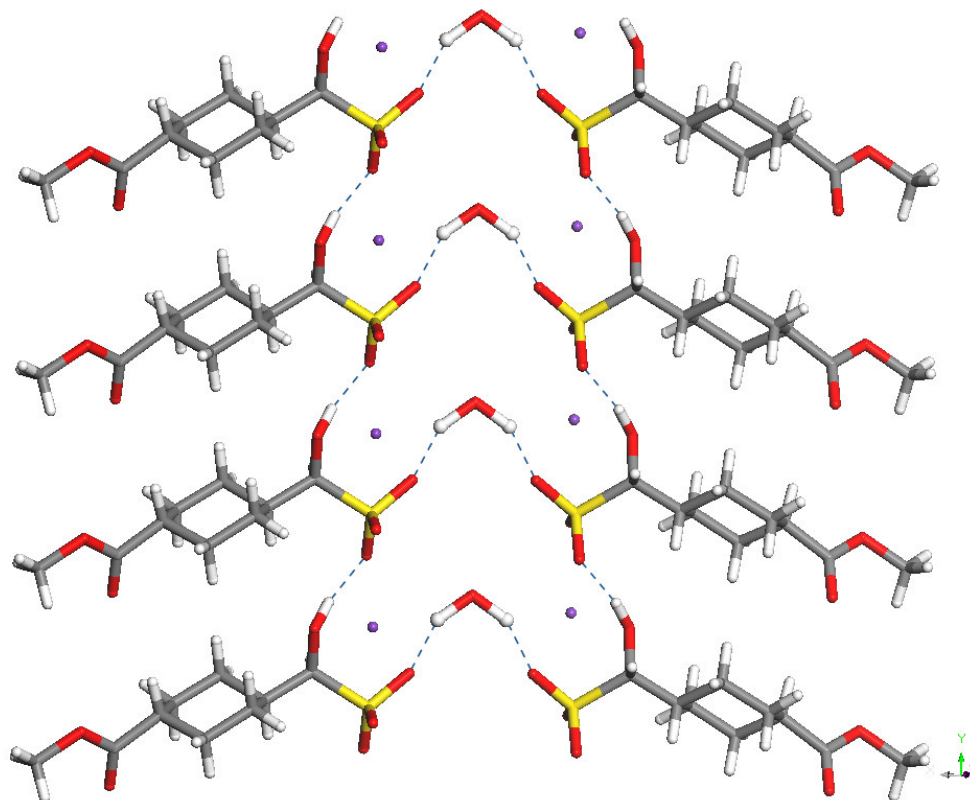**Figure 1 X-Ray structure of 3a (unit cell viewed down the *y*-axis)**

Figure 2 Hydrogen bonded ribbons propagate along the *b*-direction

The thermal profile of both **2a** and **3a** was recorded using TGA-DSC analysis. As shown in Figure 1 and Figure 2, the potassium bisulfite adduct **3a** is usually isolated as the hemihydrate, and TGA analysis confirms this with a 4.1% loss in mass observed between 80-130 °C, although this is a little higher than the calculated wt% water for a hemihydrate (2.9%). Meanwhile, the sodium bisulfite adduct **2a** showed a 9.1% mass loss between 50-100 °C in the TGA profile (the calculated wt% water for a monohydrate is 6.2%). Interestingly, decomposition rather than a phase transition from solid to liquid was observed for both salts, with a significant mass loss accompanying each major thermal event. The onset temperature of decomposition for **2a** was 152 °C, while the corresponding temperature for **3a** was 168 °C (entry 1, Table 6).

The amount of water present was further verified by oven Karl Fisher coulometric titrations (standard volumetric Karl Fisher titrations were not possible due to interactions between the bisulfite ion and the Karl Fisher titrant). The average water content in samples of the sodium bisulfite adduct **2a** is usually 8% (the theoretical amount for the monohydrate is 6%), while the amount of water present in samples of the potassium bisulfite adduct **3a** is typically 3%, which corresponds to the theoretical amount for the hemihydrate (see Table 6).

Table 4 pH Measurements of bisulfite adducts

Entry	Na adduct	K adduct	pH Na[a]	pH K[a]
1	**2a**	**3a**	6.5	5.2
2	**2b**	**3b**	5.7	5.1
3	**2c**	**3c**	5.8	5.0
4	**2d**	**3d**	6.4	4.9
5	**2e**	**3e**	7.3	6.1
6	**2f**	**3f**	5.8	4.9
7	**2g**	**3g**	6.0	3.7
8	**2h**	**3h**	5.3	4.6

a. pH of a 1% aqueous solution

Following the successful preparation of **2a** and **3a**, the scope of this study was extended to include an investigation into the solid state properties of a range of sodium and potassium bisulfite adducts of commonly encountered aldehydes. To that end, the sodium and potassium bisulfite adducts of cyclohexane carboxaldehyde,[11] butyraldehyde, 2-methylbutyraldehyde, hexanal, benzaldehyde,[11] phenylacetaldehyde[10] and diphenylacetaldehyde were prepared (Table 1, entries 2-9) in yields ranging from 67-100% and purities of 72-100%. In general, the preparation of the potassium bisulfite aldehyde adducts gave material of higher purity than the sodium counterparts. The pH values of 1% aqueous solutions of each of **2a**-**2h** and **3a**-**3h** were measured, and in most instances the potassium bisulfite adducts were found to be more acidic than their sodium analogues (Table 4, entries 2-8).

The sodium and potassium bisulfite adducts of cyclohexane carboxaldehyde **2b** and **3b** had similar filterability properties to **2a** and **3a**, with **2b** forming a thick slurry and had longer filtration times than **3b**. For all the other adducts **2c**-**2h** and **3c**-**3h**, the filtration properties were comparable for the sodium and potassium salts.

We were particularly interested in determining if a similar trend to that observed in the moisture sorption patterns of **2a** and **3a** would be seen for **2b**-**2h** and **3b**-**3h**. The sodium bisulfite adducts of cyclohexane carboxaldehyde **2b**, hexanal **2e**, phenylacetaldehyde **2g** and diphenylacetaldehyde **2h** were found to absorb moisture much more readily than the corresponding potassium bisulfite adducts (Table 5). The sodium and potassium bisulfite adducts of butyraldehyde **2c** and **3c** and 2-methylbutyraldehyde **2d** and **3d** were both found to be quite

hygroscopic, with a weight gain of up to 63% observed at 95% relative humidity for **2c** and **3c** (Table 5, entry 3) and a weight gain of up to 37% observed for **2d** and **3d** (Table 5, entry 4), while a low mass increase (up to 3%) was seen for the bisulfite adducts **2f** and **3f** at similar relative humidity (Table 5, entry 6)-see supporting information for moisture sorption patterns.

Table 5 Moisture sorption of aldehyde bisulfite adducts

Entry	Na	K	Moisture sorption Na[a] (%wt gain)	Moisture sorption K[a] (%wt gain)
1	**2a**	**3a**	26.7	2.0
2	**2b**	**3b**	29.6	7.0
3	**2c**	**3c**	61.3	63.2
4	**2d**	**3d**	32.9	37.4
5	**2e**	**3e**	19.5	2.5
6	**2f**	**3f**	3.3	3.4
7	**2g**	**3g**	7.0	1.3
8	**2h**	**3h**	17.7	0.2

a. At 95% relative humidity

The thermal profiles of **2b**-**2h** and **3b**-**3h** were also recorded using TGA-DSC analysis. As the decomposition of **2d** had an onset temperature of 71 °C and **2h** had an onset temperature of 75 °C, it was not possible to determine how much water was present in these samples from TGA analysis (Table 6, entries 4 and 8). The cyclohexane carboxaldeyde adducts **2b** and **3b** behaved similar to **2a** and **3a**, with a mass loss of 10.3% in the TGA of **2b** indicative of a monohydrate, while the 3.4% mass loss in the TGA of **3b** corresponds to the hemihydrate (Table 6, entry 2). The potassium bisulfite adduct of 2-methylbutyraldehyde **3d** was also isolated as the hemihydrates (confirmed by the 3.7% loss in mass in the TGA, Table 6, entry 4). All other adducts had minimal loss in mass around 100 °C. Again, similar to **2a** and **3a**, decomposition rather than a phase transition from solid to liquid was observed for each salt, with a significant mass loss accompanying each major thermal event. The onset temperatures of the decomposition varied from 75 °C for **2h** up to 170 °C for **3g** (Table 6, entries 2-9).

The amount of water in each sample was also measured by oven KF, with good correlation in all instances between the KF data and the TGA data. As the oven KF was measured at 90 °C, which is above the onset temperatures of degradation for **2d** and **2h**, the KF values are likely not representative of the amount of water present in these samples.

Table 6 Thermal analysis and oven KF of aldehyde bisulfite adducts

Entry	Na adduct	K adduct	T decomp Na (° C)	T decomp K (° C)	% H$_2$O Na		% H$_2$O K	
					TGA[a]	KF[b]	TGA[a]	KF[b]
1	**2a**	**3a**	152	168	9.1	8	4.1	3
2	**2b**	**3b**	127	157	10	11.8	3.4	2.0
3	**2c**	**3c**	139	142	1.7	1.8	0.6	0.9
4	**2d**	**3d**	71	113	-	8.3	3.7	4.0
5	**2e**	**3e**	157	143	0	<0.4	0	<0.4
6	**2f**	**3f**	127	153	0	<0.4	0	<0.4
7	**2g**	**3g**	187	170	0.4	<0.4	0.7	<0.4
8	**2h**	**3h**	75	147	-	11.9	0.3	<0.4

a. Estimated from TGA by loss in mass at 100 °C

b. Measured by oven KF at 90-115 °C

As multigram quantities of the free aldehyde **1a** were required for subsequent chemistry, the generation of **1a** from **2a** and **3a** was investigated. The use of NEt$_3$ led to <25% conversion to **1a**,[11] while TMSCl led to >95% conversion but was accompanied by 30% isomerisation to the cis isomer.[10] Aqueous basic hydrolytic cleavage proved to be much more successful, with K$_2$CO$_3$ and Na$_2$CO$_3$ giving complete conversion to the desired aldehyde with minimal formation of the cis isomer. Na$_2$CO$_3$ is now the preferred base as better layer separations are observed. The optimized conditions involve reaction of the bisulfite adduct with 3 equivalents of Na$_2$CO$_3$ in 5 volumes of water and 5 volumes of toluene or 2-MeTHF at room temperature for 0.5-2 h to give **1a** in yields of >90% (entries 1 and 2, Table 7). Under these conditions, the level of epmierization is typically <0.5%. The regeneration of cyclohexanecarboxaldehyde **1b** from bisulfite adducts **2b** and **3b** (entries 3 and 4, Table 7) and diphenylacetaldehyde **1h** from **2h** and **3h** (entries 5 and 6, Table 7).

Table 7 Regeneration of aldehyde from bisulfite adduct

Entry	Bisulfite Adduct	Aldehdye	% Yield
1	**2a**	**1a**	90-95
2	**3a**	**1a**	90-95
3	**2b**	**1b**	57
4	**3b**	**1b**	55
5	**2h**	**1h**	89
6	**3h**	**1h**	95

Conclusion

An aldehyde-bisulfite adduct was identified and developed as a stable, isolable starting material in the synthesis of the CETP inhibitor Evacetrapib. Both the sodium and potassium bisulfite adducts were prepared in multikilogram scales, and the potassium bisulfite was found to have more favorable solid state properties in terms of its filterability and hygroscopicity. The scope of the study was extended to include an investigation into the solid state properties of a range of sodium and potassium bisulfite adducts of commonly encountered aldehydes. In general, the solid state properties of the potassium bisulfite adducts were more advantageous.

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Acknowledgements

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