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Reaction of cyclic ketals with ceric ammonium nitrate in acetonitrile/water

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Abstract—The possibility of performing the hydrolysis of cyclic acetals and ketals under basic or mildly alkaline conditions by ceric ammonium nitrate (CAN) in MeCN/H_2O or in 10% aq. methanol is rejected. However a role for Ce(IV) as Lewis acid is evidenced at pH 4.4. Under these conditions, which allow hydrolysis of cyclic ketals leaving glycosidic bonds unaltered, a selectivity of ketal cleavage due to steric hindrance is also observed. Similar yields are obtained when acetone/water replaces MeCN/H_2O as solvent. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

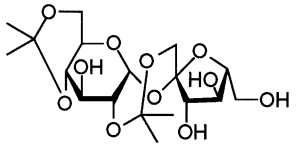
Two very interesting papers, recently, claimed the possibility of hydrolysing cyclic acetals and ketals under basic[1] or mildly alkaline[2] conditions by ceric ammonium nitrate (CAN) in an acetonitrile/water mixture. Due to the importance of ketals and acetals as alkaline-stable protective groups in carbohydrate chemistry, the possibility of cleaving them in basic or mildly alkaline conditions, where the glycoside linkage is stable, would have opened new perspectives in the protection–deprotection strategy in carbohydrate synthesis. Therefore we have undertaken an in-depth investigation on the reaction conditions in order to reproduce the results reported,[1,2] using as substrate 2,1′:4,6-di-*O*-isopropylidenesucrose **1** which contains both glycoside and ketal linkages.

2. Results and discussion

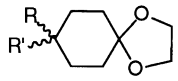
When **1** was treated with CAN in a 1:2 MeCN/H_2O mixture at 70°C according to the described conditions,[1] both the cyclic ketals and the glycosidic bond were cleaved very easily, but the solution was strongly acidic (about pH 0.2) in contrast with the claimed slightly acidic conditions.[1] In the presence of K_2CO_3, **1** was completely unaltered or the cyclic ketal opening occurred to an extent of 80% according to the mode of the carbonate addition (described later).

When **1** was dissolved in a mixture of MeCN and a buffer solution of borate/HCl (Merck) at pH 8 and treated with CAN (4%) at 60°C, according to a new procedure of the same authors,[2] the expected ketal cleavage did not occur. In order to verify whether the nature of the starting material might induce a different reaction course, the non-carbohydrate substrates **2a**, **2b** and **3**, previously used,[1] were employed as well. Since the precise procedure for K_2CO_3 addition was not reported, we used two distinct protocols, obtaining slightly different results:

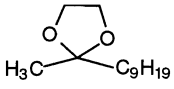
(a) addition at 70°C, under argon, of an aqueous solution of CAN to the MeCN sample solution containing the required amount of *solid* carbonate;
(b) addition at 70°C, under argon, of a *cloudy solution* of carbonate and CAN to the MeCN sample solution.



1



2a R=R'=O
2b R=H, R'=OH



3

Under the first conditions, ketal cleavage occurred to an extent of 16%, in the case of **3**, and only in trace amounts for **2a** and **2b** while for **1** the reaction proceeded to 80% with

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the opening of only the cyclic ketals. In no case did the yields change on increasing the reaction times. Under the second conditions all compounds remained completely unaltered. We suggest that the reported[1] ketal opening of **2a**, **2b** and **3** in the presence of carbonate could depend on the dissolution rate of added solid carbonate which is slower than the rate of ketal opening, thereby carbonate is unable to neutralise the acid present, due to the hydrolysis of the Ce(IV) ion, before ketal cleavage has partially occurred. This is in agreement with the fact that yields did not change with reaction time. To support this hypothesis we measured the time necessary to neutralise a 1:2 MeCN/H_2O CAN solution, whose concentration was identical to that utilised in the reactions on **2a**, **2b** and **3**, adding solid carbonate at 70°C. The neutralisation took more than 1 min, a time comparable with the rate of ketal cleavage.[1] All the above results indicated that cyclic ketal/acetal cleavage is determined mainly by protic acid environments and that under neutral or basic conditions these processes do not occur. This is supported by the fact that in no case the precipitation of cerium hydroxide, which occurs under neutral conditions,[3] was reported. Accordingly, when we worked under carefully checked neutral or basic conditions the cerium hydroxide precipitated. At this stage one of authors (E. M.) joined Markò's group in order to compare our reaction conditions with theirs. First of all the pH of the solution was measured when a catalytic amount of CAN (4%)[2] in 1:1 MeCN/H_2O was dissolved at 69°C; this value was 1.68. Under this set of conditions **3** was deprotected within 10 min, as happened when the same pH value was obtained with HNO_3 without CAN. This showed no peculiar effect of CAN suggesting that, under these conditions, in both cases there is a protic acid hydrolysis. Then it was confirmed that adding to a solid mixture of substrate **3**, K_2CO_3 and CAN (2.5 equiv.) a 1:2 MeCN/H_2O mixture at 70°C the yield of deprotected ketone ranged from 10 to 30%, both after 1 and 24 h, according to the rapidity of carbonate dissolution. On the other hand, if an aqueous solution of K_2CO_3 and CAN (2.5 equiv.) (in fact it is a suspension because a part of the Ce(IV) precipitates as hydroxide) was added to a solution of **3** in MeCN at 70°C no reaction occurred. As for the reaction with borate/HCl buffer[2] we discovered that Markò's buffer solution was more dilute than ours: using same volumes we reached pH=8, with clouding of the medium, while Markò obtained a clear solution but at pH 2. In order to see if Ce(IV) performs a Lewis acid function as well, we and Marko's group together investigated the course of reactions accomplished at equal pH but with and without CAN. To this end the pH value of the solution was increased by adding pyridine until the solution began to become cloudy due to cerium hydroxide precipitation. This happens at pH 4.4. Under these conditions **3** at 68°C with 3% of CAN in 1:1 MeCN/H_2O was deprotected to 80–85% after 1 h and completely after 2 h. Interestingly, at the same pH obtained with HNO_3 without CAN, Compound **3** was deprotected to only 10% after 3 h at 68°C. These results suggested that the role of Ce(IV) as Lewis acid works but only when the proton concentration is low. Under these conditions CAN (3%) showed a selectivity due to steric hindrance. Actually both **2a** and its reduced **2b** derivative were unaltered at pH 4.4 at 68°C. Under these conditions **1** gave quantitatively sucrose, after 1 h, showing that the ketal groups were cleaved while the glycoside linkage was unaltered. On the other hand with HNO_3 at same pH, but without CAN, **1** was unaltered after 3 h.

When this work was finished we were acquainted with another paper on the ability of CAN (1.2 equiv.) to open acetals in aqueous methanol at room temperature in the presence of excess $NaHCO_3$ or Na_2CO_3.[5] Under the described conditions we have also found that the deprotection of **2a** occurred to 85% after 30 min but the pH of the solution was strongly acid and no clouding of the solution was observed. In addition, in the presence of solid carbonate the reaction proceeded to only 32% after 10 min and this yield did not change after 30 min, suggesting that the reaction occurred only for the time necessary to dissolve a sufficient amount of carbonate to neutralise the acidity due to the Ce(IV) hydrolysis. Accordingly, when the carbonate was added with CAN as solution, the deprotection reaction did not proceed.

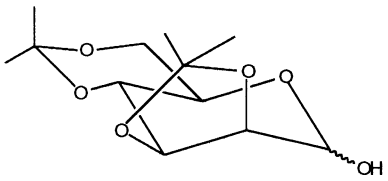
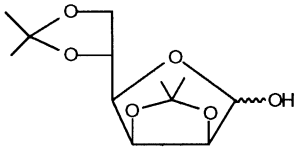
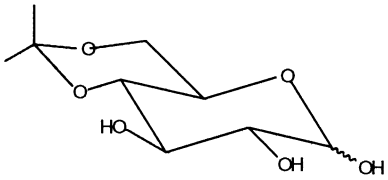
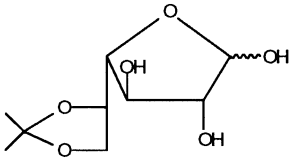
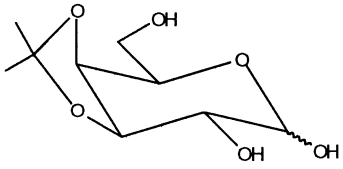
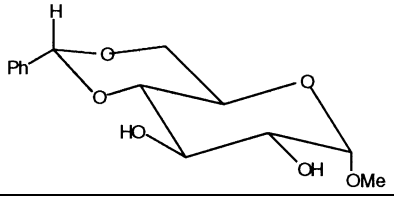
In order to evaluate the solvent effect we performed some reactions replacing MeCN with acetone or THF. Acetone gave similar yields and product distribution as MeCN whereas a slower reaction occurred in THF, due to its cation complexing ability which decreases the Lewis acidity of Ce(IV).

The use of acetone, which can improve the sample solubility, was tested on some carbohydrate acetonides. Table 1 shows the different reaction courses with and without Ce(IV), both performed at pH 4.4. From these data is confirmed the role of Lewis acid for Ce(IV) at pH 4.4 and its different reactivity with respect to the proton. In particular, whereas the opening of terminal isopropylidenes occurs to the same extent both with the Ce(IV) ion and the proton (entries 2 and 4), the cleavage of 4,6 isopropylidenes is clearly favoured by Ce(IV) (entries 1 and 3), which is also the only one able to cleave the 3,4-acetonide of galactose (entry 5) and the 4,6-benzylidene acetal (entry 6). Since in these last cases the reaction yields were rather low even for longer reaction times we thought that the concentration of Ce(IV) in solution could decrease owing to its precipitation as hydroxide. As a matter of fact the clouding of the reaction mixture increased with time. In order to confirm this hypothesis we tested the effectiveness of CAN solution at pH 4.4 with time by performing reactions with solutions, which were kept at room temperature for few hours before their use. Using a 3 h old CAN solution, whose pH was unaltered, **3** reacted to only 8% after 1 h instead of 80–85%, obtained with a freshly-prepared solution, showing a drastic decrease reactivity in agreement with the low concentration of Ce ion remained in solution. This observation allowed us to increase strongly the reaction yields by adding portions of CAN solution every 2 h (Table 1).

3. Conclusion

In conclusion, the possibility to achieve the ketal cleavage with CAN in 1:2 MeCN/H_2O or in 10% aq. methanol in the presence of carbonate is rejected. However, CAN in 1:1 MeCN/H_2O is able to cleave selectively sterically unhindered cyclic ketals under mildly acidic conditions (pH 4.4), exploiting its strong Lewis acid character. In

Table 1. Yields of reactions at pH 4.4 with CAN and without CAN (in parentheses). The yields were determined by GC-MS analysis of the acetylated reaction mixtures. All reactions were accomplished in 1:1 acetone/water mixture at 68°C

Entry	Substrate	Time (h)	2,3-Acetonide of Man*p*	Man	Glc	Gal	α-D-GlcOMe
1		1 4	82 (10) 72 (12)	0 (0) 25 (1)			
2		1 4	30 (32) 55 (55)	0 (1) 3 (4)			
3		1 4			79 – 85 (10)		
4		1 4				35 – 61 (50)	
5		1 4 5[a]				12 (0) 15 (0) 60 (0)	
6		1 4 5[a] 5[b]					10 (0) 34 (0) 93 (0) 61 (0)

[a] Adding portions of CAN (3%) every 2 h.
[b] Adding portions of CAN (1%) every 2 h.

addition, these conditions allow hydrolysis of cyclic ketals leaving glycosidic bonds unaltered and show a different reactivity from that of the proton at the same pH. Work is in progress to test the selectivity of these conditions for the deprotection of other hydroxyl protective groups.

4. Experimental

4.1. General

CAN, sucrose and **2a** were purchased from Fluka, inositol from Carlo Erba, buffer borate/hydrochloric acid from Merck, pyridine from Romil, MeCN for HPLC from Lab-Scan. All products were used without further purification. Compound **1** and the protected monosaccharides in Table 1 were prepared according to described procedures.[4,6] Compound **2b** was obtained from **2a** (300 mg) in EtOH (5 ml) by reduction with $NaBH_4$ (500 mg) under stirring for 3 h at room temperature. The reaction was quenched by adding acetic acid (500 μl), the solvent was removed by N_2 stream and the residue was treated twice with 1:9 acetic acid/methanol mixture, and then five times with only methanol. Compound **2b** was identified by GC–MS of its acetylated derivative. Compound **3** was prepared by dissolving methyl nonyl ketone (Fluka, 500 mg, 2.9 mmol) in dry DMF (Fluka, 1.5 ml). Ethylenglycol (Fluka, 245 μl, 4.4 mmol) and *p*-toluenesulfonic acid (Aldrich, 10 mg) were added. The reaction ran at 50°C overnight, under stirring. After addition of 0.25 M NH_4HCO_3, the reaction mixture was extracted with hexane, which was dried with anhydrous Na_2SO_4 and evaporated under vacuum. The product **3** was identified by the following diagnostic GLC–MS fragments: *m/z* 87 (100%), $[CH_3CO_2C_2H_4]^+$ and *m/z* 199 (17%), $[C_{10}H_{19}CO_2C_2H_4]^+$. GLC–MS spectra were measured with a Hewlett–Packard 5890 instrument.

Analysis condition: SPB-5 capillary column (SUPELCO, 30 m×0.25 mm i.d., flow rate 1 ml/min, He as carrier gas), using the following temperature programmes: for **1**: 150°C for 5 min, 150→330°C at 3°C/min, 330° for 0 min; for **2a** and **2b**: 80°C for 2 min, 80→240°C at 8°C/min, 240° for 3 min; for **3**: 150°C for 3 min, 150→280°C at 10°C/min, 280° for 10 min pH-meter (Orion) equipped with electrode by Hamilton.

4.2. Reaction of compounds 1, 2a, 2b and 3 with ceric ammonium nitrate (2.5 equiv.) in MeCN/H_2O at 70°C

4.2.1. Measure of reaction progress. The progress of reaction for **1** and **2b** was followed by GC–MS of acetylated derivative of crude reaction. After stopping the reaction with pyridine, the mixture was lyophilised and, after drying, a pyridine solution of inositol (2 mg/ml) was added, as internal standard. The acetylation was performed with acetic anhydride at room temperature under stirring overnight. After evaporation under N_2 stream, the residue was treated with $H_2O/CHCl_3$ mixture. The organic phase was injected into GC–MS. For **2a**, the reaction mixture after quenching with pyridine was extracted with $CHCl_3$, the organic phase was evaporated and dissolved in a solution of acetylated inositol in $CHCl_3$ (2 mg/ml). For **3**, the reaction mixture was cooled at room temperature and 0.25 M NH_4CO_3 solution and hexane were added. The organic phase was dried on anhydrous Na_2SO_4 and evaporated under vacuum. The solid was dissolved in $CHCl_3$ solution of inositol acetate (2 mg/ml) and analysed by GC–MS.

4.2.2. Conditions as reported.[1] Compound **1** (10 mg, 0.0237 mmol) was dissolved in MeCN (50 μl) at 70°C in argon atmosphere, and a solution of CAN (33 mg, 0.0602 mmol) in H_2O (100 μl) was added. The pH of the solution was 0.2. Then the mixture was stirred at 70°C and after 2 h the hydrolysis of **1** in glucose and fructose was complete. Compound **2a** (22 mg, 0.141 mmol) was dissolved in MeCN (0.3 ml) at 70°C under argon and a solution of CAN (195 mg, 0.356 mmol) in H_2O (0.6 ml) was added. After 30 min the ketal deprotection was complete.

For compound **2b**, the same amount and conditions of **2a** were used, obtaining the same results. Compound **3** (60 mg, 0.280 mmol) was dissolved in MeCN (0.6 ml) at 70°C, under argon, and a solution of CAN (390 mg, 0.712 mmol) in H_2O (1.2 ml) was added. The ketal deprotection was complete after 10 min.

4.2.3. Reaction conditions without ceric ammonium nitrate. All the above reaction were repeated under identical condition, but the pH was achieved by adding conc. HNO_3 and not by CAN hydrolysis. The same results as described earlier were obtained.

4.2.4. Reactions with carbonate according to our procedures

4.2.4.1. Reactions with K_2CO_3, using solid salt. Compound **1** (10 mg, 0.0237 mmol) and solid K_2CO_3 (34 mg, 0.243 mmol) were treated with MeCN (50 ml) at 70°C, in argon atmosphere, and a solution of CAN (33 mg, 0.0602 mmol) in H_2O (100 μl) was added. The reaction progress, measured by GC–MS, showed that **1** gave sucrose (80%) and starting material (20%) after 10 min. The yield did not rise on increasing the reaction time up to 24 h. Compound **2a** or **2b** (22 mg, 0.141 mmol) and solid K_2CO_3 (199 mg, 1.421 mmol) were treated at 70°C, under argon, with MeCN (0.3 ml) and a solution of CAN (195 mg, 0.356 mmol) in H_2O (0.6 ml) was added. After 1 h, the GC–MS analysis revealed only traces of deprotected product, while the main product was starting material. The distribution of products did not change after 24 h. Compound **3** (60 mg, 0.280 mmol) and solid K_2CO_3 (398 mg, 2.843 mmol) were treated at 70°C with MeCN (0.6 ml), under argon, and a solution of CAN (390 mg, 0.712 mmol) in H_2O (1.2 ml) was added. After usual work-up the yield of deprotected ketal accounted for only 16% both after 1 and 24 h, the remaining product being starting material.

4.2.4.2. Reactions with K_2CO_3, using cloudy solution of salt. Compound **1** (10 mg, 0.0237 mmol) was dissolved in MeCN (50 μl) at 70°C, and a suspension of CAN (33 mg, 0.0602 mmol) and K_2CO_3 (34 mg, 0.243 mmol in H_2O (100 μl) was added, in argon atmosphere. After 24 h, the GC–MS analysis showed only unaltered starting material. Compound **2a** or **2b** (22 mg, 0.141 mmol) was dissolved in MeCN (0.3 ml) at 70°C, under argon, and a suspension of CAN (195 mg, 0.356 mmol) and K_2CO_3 (199 mg, 1.421 mmol) in H_2O (0.6 ml) were added. After 24 h the GC–MS analysis showed only starting material. Compound **3** (60 mg, 0.280 mmol) was dissolved in MeCN (0.6 ml) at 70°C under argon, and a suspension of CAN (390 mg, 0.712 mmol) and K_2CO_3 (398 mg, 2.843 mmol) in H_2O (1.2 ml) was added. After 24 h, only starting material was present in the crude reaction mixture.

4.3. Measurements of pH variation with temperature and in presence of solid K_2CO_3

Solid CAN (3.9 g) was dissolved in H_2O (12 ml) and MeCN (6 ml). The pH measured at room temperature was 0.2. When the mixture was heated to 70°C its pH value decreased to −0.76. Adding, under this conditions, solid K_2CO_3 (3.98 g) the pH was 6.2 after 1 min and 8.42 after 4 min.

4.4. Reactions of 3 with ceric ammonium nitrate (4%) in MeCN/H_2O

To a solution of **3** (30 mg, 0.140 mmol) in 1:1 MeCN/H_2O mixture (0.9 ml), CAN (3 mg, 5.47×10^{-3} mmol) was added giving a clear solution at pH 1.68. After 10 min **3** was completely deprotected. The reaction was repeated under the same condition but the pH was achieved by adding conc. HNO_3 without using CAN. Also in this case **3** was completely deproteced after 10 min.

4.5. Reactions of 1, 2a, 2b and 3 with ceric ammonium nitrate in buffered MeCN/H_2O as decribed[2]

Compound **1** (24 mg, 0.0569 mmol) was dissolved in MeCN (0.175 ml) and in a buffer solution of borate/HCl

(0.175 ml) at pH 8. CAN (1.2 mg, 2.2×10^{-3} mmol) was added at room temperature and the reaction mixture, which became cloudy keeping its pH value at 8, was heated to 60°C, under stirring. After 24 h, a GC–MS analysis revealed the presence of only unaltered starting material. Compound **2a** or **2b** (44 mg, 0.282 mmol) was dissolved in MeCN (0.9 ml) and in a buffer solution of borate/HCl (0.9 ml) at pH 8. CAN (6 mg, 1.09×10^{-2} mmol) was added at room temperature and the reaction mixture, which became cloudy keeping its pH value at 8, was heated to 60°C, under stirring. After 24 h, a GC–MS analysis revealed the presence of only unaltered starting material. Identical procedure was employed for compound **3** (30 mg, 0.140 mmol). This was dissolved in MeCN (0.45 ml) and in the buffer solution (0.45 ml) at pH 8. CAN (3 mg, 5.47×10^{-3} mmol) was added as above, giving a turbid solution. After 24 h, only starting material was present in the crude reaction mixture.

4.6. Reaction of 2a with ceric ammonium nitrate in 10% aq. methanol[5]

Compound **2a** (16 mg, 0.1 mmol) was dissolved in 10% aq. methanol (0.2 ml). A solution of CAN (66 mg, 0.12 mmol) in 10% aq. methanol (0.8 ml) was then added dropwise under stirring. The reaction was quenched with pyridine and the mixture was diluted with water and extracted with dichloromethane.

4.6.1. Reaction of 2a with ceric ammonium nitrate and solid sodium carbonate in 10% aq. methanol.[5] Compound **2a** (16 mg, 0.1 mmol) and sodium carbonate (127 mg, 1.2 mmol) were suspended in 10% aq. methanol (0.2 ml). A solution of CAN (66 mg, 0.12 mmol) in 10% aq. methanol (0.8 ml) was then added dropwise under stirring. The reaction was quenched with pyridine and the mixture was diluted with water and extracted with dichloromethane.

4.6.2. Reaction of 2a with a solution of ceric ammonium nitrate and sodium carbonate in 10% aq. methanol.[5] Compound **2a** (16 mg, 0.1 mmol) was dissolved in 10% aq. methanol (0.2 ml). A suspension of CAN (66 mg, 0.12 mmol) and sodium carbonate (127 mg, 1.2 mmol) in 10% aq. methanol (0.8 ml) was then added dropwise under stirring. The reaction was quenched with pyridine and the mixture was diluted with water and extracted with dichloromethane.

4.7. Reaction at pH 4.4 with and without ceric ammonium nitrate (3%)

At beginning two solutions were prepared: the first, A was obtained dissolving CAN (105 mg, 0.192 mmol) in water (19 ml) and adding pyridine up to the beginning of precipitation of cerium hydroxide. Under these conditions the pH solution is 4.4. The second, B was obtained adding conc. HNO_3 to water until to achieve a solution at pH 4.4. Solutions of **1** (70 mg, 0.166 mmol), or **2a** (26 mg, 0.167 mmol), or **2b** (26 mg, 0.167 mmol) or **3** (26 mg, 0.167 mmol) in 1:1 MeCN/A (1 ml) were prepared and held with stirring at 68°C. After usual work-up, **1** gave after 1 h quantitatively sucrose, which was unaltered until 4 h. **2a** and **2b** were unreacted after 4 h. **3** was deprotected for 80–85% after 1 h and completely after 2 h. Performing the above reactions under same conditions but using solution B, that is without CAN, **1**, **2a** and **2b** gave, after 3 h, starting material, while **3** was deprotected only for 10%.

An analogous procedure, except for the use of acetone in place of acetonitrile, was followed in the deprotection of saccharidic substrates on Table 1.

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