New Oxidative Systems for Alcohols: Molecular Sieves with Chromium-(VI) Reagents [1]

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The oxidation of various kinds of alcohols, including carbohydrates and nucleosides, by molecular sieve–pyridinium chlorochromate and molecular sieve–pyridinium dichromate has been investigated. The catalytic properties of molecular sieves have been investigated using kinetic, stereochemical, and isotope-labelling experiments. It is postulated that specific sites on the sieves favour hydride-ion transfer.

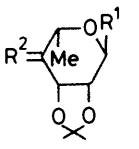
In recent years dimethylsulphoxide–dicyclocarbodiimide [2] has assumed a prominent position in ketonucleoside synthesis,[3,4] but the use of this reagent has been limited to small-scale preparations because of the side-reactions and the presence of numerous by-products. As we wanted to synthesize increasing quantities of keto-hexosyl nucleosides for biological experiments we were interested in pyridinium chlorochromate [5] (PCC) (Corey's reagent) which is known to oxidize a wide range of alcohols. Furthermore, PCC has been used for large-scale carbohydrate oxidations.[6]

Attempts to oxidize 7-(6-deoxy-2,3-*O*-isopropylidene-α-L-*manno*-hexopyranosyl)theophylline [7] (1) with PCC in dichloromethane at room temperature led to the formation of a black chromium derivative but no trace of ketonucleoside was detected by t.l.c. analysis. The precipitation of the black reduced reagent suggested that this failure was due to solvent impurities. Using the same conditions we exchanged dichloromethane for 1,2-dichloroethane, which is reputed to be more easily purified. We also investigated catalysis of the oxidation by an insoluble inorganic compound, a procedure which has proved to be useful in many reactions; in particular we looked at molecular sieves which offer, in addition, protection from moisture.

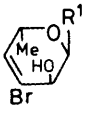
Under these conditions the reaction took place, but a large excess of PCC was necessary. In a similar way the oxidation of the nucleoside (1) by pyridinium dichromate (PDC), a reagent proposed by Corey and Schmidt [8] for oxidation in neutral media, gave the desired 4-keto-nucleoside. Furthermore, we have shown that, as described by Corey, the allylic nucleosides are easily oxidized with PDC (1.5 equiv.) at room temperature.

In order to compare the oxidation of the 7-(3-bromo-3,4,6-trideoxy-α-L-*erythro*-hex-3-enopyranosyl)theophylline [9] (2) with PDC and PCC, respectively, these two reactions were attempted at room temperature without molecular sieves present. Surprisingly the reaction with PCC did not work, although no destruction of the oxidising reagent was observed. This behaviour strongly suggested that molecular sieves could be a catalyst for PCC and PDC oxidations.

Addition of molecular sieves to the reaction mixture led to the immediate precipitation of the reduced chromium derivative, and t.l.c. analysis showed that the desired reaction took place quickly. In this manner,



(1) R^1 = theo ; R^2 = H, OH
(10) R^1 = thy ; R^2 = H, OH
(11) R^1 = thy ; R^2 = O



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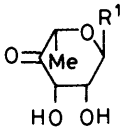

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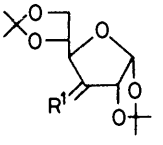

(4) R^1 = H, OH
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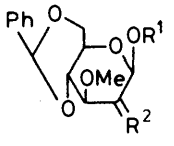
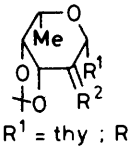
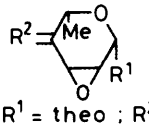


(6) R^1 = Me ; R^2 = H, OH
(7) R^1 = Me ; R^2 = O
(8) R^1 = Ph ; R^2 = H, OH
(9) R^1 = Ph ; R^2 = O



(12) R^1 = thy ; R^2 = H, OH
(13) R^1 = thy ; R^2 = O
(17) R^1 = theo ; R^2 = H, OH
(19) R^1 = theo ; R^2 = O



(14) R^1 = theo ; R^2 = H, OH
(15) R^1 = theo ; R^2 = O

theo = theophyllin-7-yl
thy = thymin-1-yl

the oxidation of the theophylline nucleoside (1) in dichloromethane † was achieved in 60 min (PCC, 3 mol

† We have found that dichloromethane can be easily purified by being left for a week on 4-Å molecular sieves (1/8 in. pellets).

equiv.; 3-Å molecular sieves, 0.5 g per mmol of alcohol) and the 4-ketohexosyl nucleoside (3) was isolated in 75% yield after deacetalation.

Using 7-(6-deoxy-2,3-*O*-isopropylidene-α-L-*manno*-hexopyranosyl)theophylline (dIMT) (1) as a model, we investigated the different factors affecting the reaction. Thus, we determined the optimal conditions for the oxidation of a wide range of alcohols, including carbohydrates and nucleosides. We also investigated the mechanism by which molecular sieves assist PCC and PDC oxidations, and have clearly shown that these zeolites favour the cleavage of the C–H bond on the alcoholic carbon. Finally, we have proposed a hypothesis to explain the action of the molecular sieves.

RESULTS AND DISCUSSION

(*a*) *Molecular Sieve–Pyridinium Chlorochromate* (*MS–PCC*).—First we investigated the effect of varying the amount of 3-Å molecular sieves on a number of identical reactions performed in dichloromethane containing PCC (3 mol equiv.) (Figure 1). These experiments showed

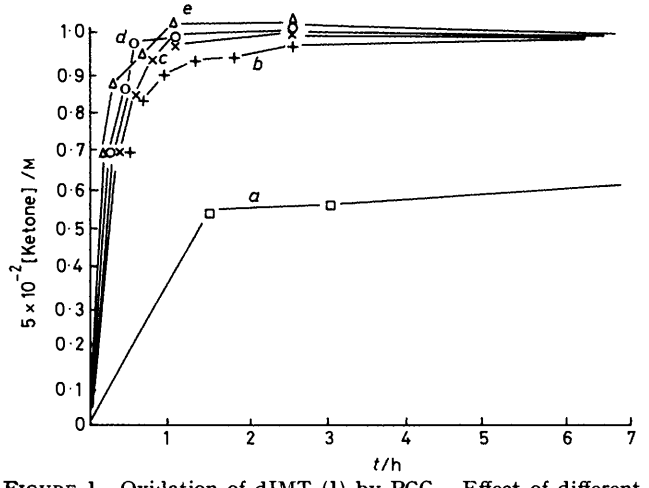


FIGURE 1 Oxidation of dIMT (1) by PCC. Effect of different amounts of 3-Å molecular sieve. [a] 0.25, [b] 0.5, [c] 1, [d] 2, and [e] 4 g

that effective oxidation required at least 0.5 g of molecular sieves per mmol of alcohol. Moreover it can be seen from Table 1 that the rate of reaction increases with the concentration of the reagents.

TABLE 1

Oxidation with MS–PCC. Effect of concentration of the alcohol [a]

10^{-1}[dIMT]/M	0.5	1	2	4
t/min	150	120	90	60

[a] PCC, 3 equiv.; 3-Å molecular sieves, 0.5 g per mmol of alcohol.

Subsequently 0.5 and 1 g per mmol of molecular sieves were generally used (2 and 4 g per mmol necessitated the use of too great a quantity of solvent).

Next we examined the effect of adding different insoluble inorganic compounds. Any dehydrated molecular sieves could have been used but we found the most effective were the 3- and 4-Å types (Figure 2). Other insoluble inorganic compounds, such as dehydrated silica gel and Celite, did not show noticeable catalysis.

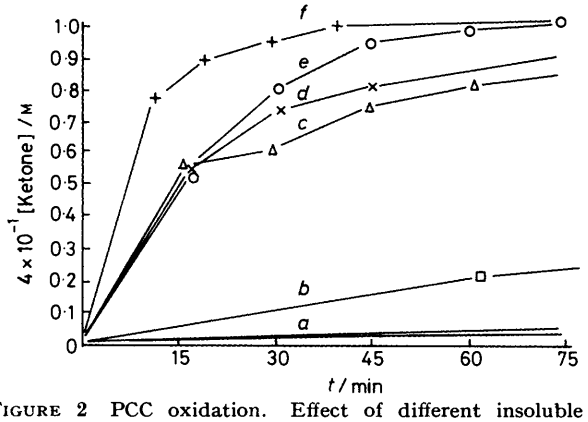


FIGURE 2 PCC oxidation. Effect of different insoluble inorganic compounds. [a] Celite, silica; [b] alumina; [c] 13-X silica; [d] 5-Å MS; [e] 3-Å MS; [f] 4-Å MS

Although alumina presented an appreciable effect at the beginning of the reaction, after a day the quantity of keto-compound obtained was no greater than that from the uncatalysed oxidation (Figure 3).

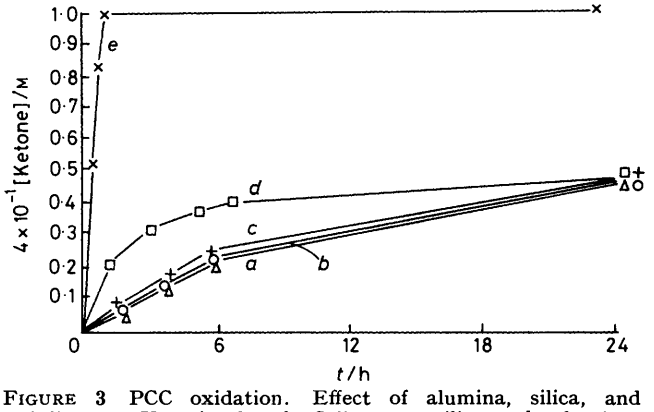


FIGURE 3 PCC oxidation. Effect of alumina, silica, and Celite. [a] Unassisted; [b] Celite; [c] silica; [d] alumina; [e] 3-Å MS

Finally, the amount of PCC required for efficient oxidation was investigated. The results from identical reactions using 3-Å molecular sieves and containing 1, 2, 3, 4, 6, and 8 mol equiv. of PCC are given in Figure 4. The use of 2 and 3 equiv. of PCC led to complete oxidation in, respectively, 120 and 60 min, whereas the reaction performed with 1 equiv. required 23 h. Virtually no difference could be detected between 3, 4, and 6 equiv. probably because of the low solubility of PCC in dichloromethane.

The results obtained above show that the optimal oxidation conditions are 2—3 mol equiv. of PCC and 3- or 4-Å molecular sieves (0.5—1 g per mmol of alcohol) in dichloromethane (2.5—5 ml per mmol).

(*b*) *Molecular Sieves–Pyridinium Dichromate* (*MS–PDC*).—Figure 5 and Table 2 clearly show that the most

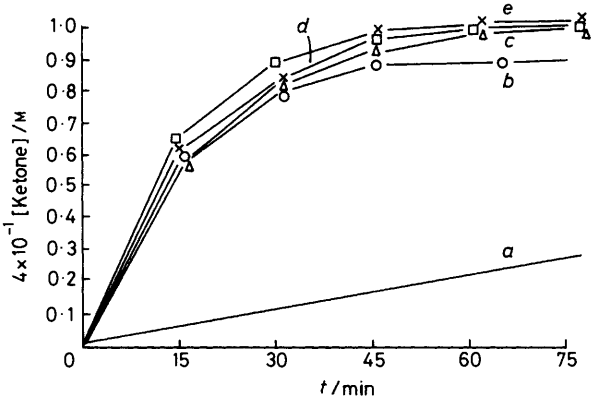


FIGURE 4 Influence of the concentration of PCC on the rate of oxidation. [a] [PCC] 0.4M; [b] [PCC] 0.8M; [c] [PCC] 1.2M; [d] [PCC] 1.6M; [e] [PCC] 2.4M

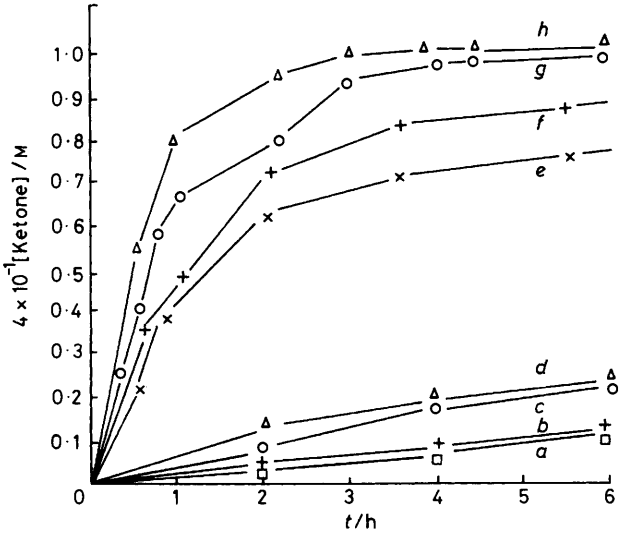


FIGURE 5 PCC oxidation. Effect of different insoluble inorganic compounds. [a] Unassisted; [b] Celite; [c] silica; [d] alumina; [e] 13-X silica; [f] 5-Å MS; [g] 3-Å MS; [h] 4-Å MS

efficient oxidation with MS–PDC was obtained when a solution of the alcohol in dichloromethane (5 ml) reacted with PDC (1—2 mol equiv.) in the presence of 3- or 4-Å molecular sieves (0.5—1 g per mmol of alcohol). Alumina, Celite, and silica gel have a very small effect which may be due to absorption of the lower valent chromium species.

TABLE 2

Oxidation with MS–PDC. Effect of the amount of PDC

[PDC]/M	0.2	0.3	0.4	0.6	0.8
t/h	Incomplete after 24 h	2	1	1	1

[dIMT], 2 × 10^{-1}M; 4-Å molecular sieves, 1 g per mmol of alcohol.

Furthermore, as Corey and Schmidt [8] have noted for PDC, we observed that the oxidation of alcohols with MS–PDC is catalysed by small quantities of pyridinium trifluoroacetate or dichloroacteic acid, but in all the cases examined the effect of these two acids was small in comparison to the sieve catalysis (Table 3).

The preparation of various aldehydes and ketones has also been examined. Using the MS–PCC procedure, benzophenone and cholestan-3-one could be prepared in 15 min, and veratraldehyde in 10 min, from the corresponding alcohols.

TABLE 3

Effect of acid on the oxidation with MS–PCC

Alcohol	Acid [a]	PDC (mol equiv.)	MS [b] (g per mmol of alcohol)	t/min
Benzhydrol	No acid	1.2	0.5	60
	$CHCl_2CO_2H$	1.2	0.5	30
	$CF_3CO_2^-$.PyH+	1.2	0.5	30
(1)	No acid	1.5	1	150
	$CHCl_2CO_2H$	1.5	1	75
	$CF_3CO_2^-$,PyH+	1.5	1	105

[a] 1 Mol equiv. [b] 3-Å Type.

Oxidation of carbohydrates with 3-Å molecular sieves and PCC was also investigated. Methyl and phenyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranos-2-uloside (7) and (9) were obtained in 180 and 90 min, and 60 and 70% yields, respectively.

Nucleosides were more quickly oxidized than carbohydrates, and generally required smaller amounts of MS–PCC. In these reactions a carbonyl function is introduced into the 2- and 4-positions of purine and pyrimidine derivatives of 6-deoxyhexopyranosyl (Table 4). The nucleosides were isolated directly in crystalline form from the crude products, without further purification, in 60–80% yield. Thus, 3- and 4-Å MS–PDC are shown to be alternatives for nucleoside and carbohydrate oxidation, particularly for fragile molecules.

Application of this method to the synthesis of 1-(6-deoxy-3,4-*O*-isopropylidene-β-L-*lyxo*-hexopyranosulosyl)-thymine (13) afforded this ketonucleoside in 70% yield, whereas it could not be isolated when dimethylsulphoxide–dicyclocarbodi-imide was used. Similarly the oxidation of the 2,3-epoxy-nucleoside (14) by PDC (1.5 mol equiv.) and 3-Å molecular sieves (19) gave the 4-ketoepoxynucleoside (15), an important intermediate for the synthesis of unsaturated and branched chain nucleosides, which could be isolated in 70% yield. The same reaction, performed with 3-Å MS–PCC, converted compound (14) into the keto-compound in only 50% yield.

Furthermore, we have ascertained that MS–PDC is of great efficiency for the oxidation of all kinds of alcohols in neutral media. Oxidation of benzhydrol and veratryl alcohol with PDC (1.2 equiv.) and 3-Å molecular sieves (0.5 g per mmol) was achieved in 60 and 30 min respectively. Oxidation of the same alcohol without sieves present required more than 10 h.

A mechanism for the PCC oxidation of benzylic alcohols has been reported [11] recently in which hydride ion transfer from the alcoholic carbon to a protonated

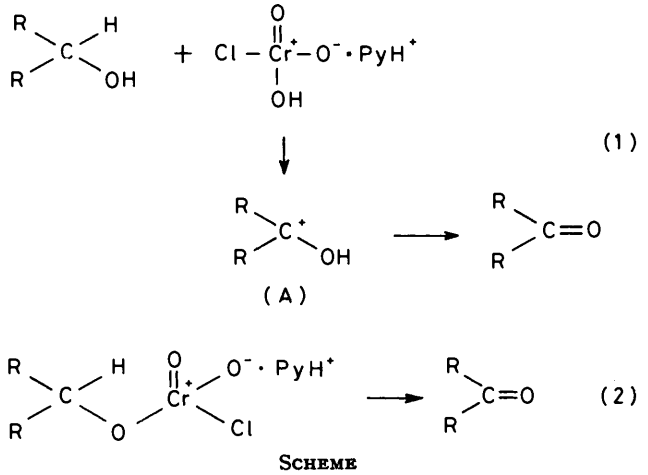
TABLE 4

Oxidation of alcohols with PCC or PDC and molecular sieves (MS) to give carbonyl compounds in dichloromethane at 25 °C

Alcohol	Amounts of Cr^{VI} reagents [a] PCC [b]	PDC [b]	MS [a] Type	Amount [c]	Time/min	Product	% Yield	M.p./°C [e]
Benzhydrol	2		3-Å	0.5	15	Benzophenone	100	45—47 [f]
Benzhydrol		1.2	3-Å	0.5	60	Benzophenone	100	
Veratryl alcohol	2		3-Å	0.5	10	Veratraldehyde	80	42—43 [g]
Veratryl alcohol		1.2	3-Å	0.5	30	Veratraldehyde	80	
Dihydrocholesterol	2		3-Å	0.5	15	Cholestan-3-one	90	128—129 [10]
Dihydrocholesterol		1.2	4-Å	1	90	Cholestan-3-one	90	
(1)	3		3-Å	0.5	60	(3)	75	140—141 [7]
(1)		1.5 [d]	3-Å	1	75	(3)	65	
(1)		1.5	3-Å	1	180	(3)	70	
(4)	4		3-Å	1	120	(5)	85	105 [h]
(6)	3		3-Å	1	180	(7)	60	172 [i]
(8)	4		3-Å	1	90	(9)	70	165—168 [i]
(8)		1.5 [d]	3-Å	1	60	(9)	50	
(10)	3		3-Å	0.5	120	(11)	60	154—156 [j]
(10)		1.5 [d]	3-Å	1	90	(11)	60	
(12)		1.5	3-Å	1	120	(13)	70	188—190
(14)	3		3-Å	0.5	90	(15)	50	188—190
(14)		1.5	3-Å	1	240	(15)	70	
(17)	4		3-Å	1	90	(19)	55	205 [k]

[a] Amounts of PCC and PDC are expressed as mmol of Cr^{VI} derivative per mmol of alcohol. Amounts of 3-Å molecular sieve are expressed as g per mmol of alcohol. Dichloromethane was dried over 4-Å molecular sieves (1/8 in. pellets) for 1 week. [b] Aldrich. [c] Sigma. [d] $CHCl_2CO_2H$ (40 μl per mmol of alcohol) also present. [e] M.p.s agreed exactly with literature values except for compound (4) for which the reference in *h* gives 111—112 °C. [f] C. Marbel and W. Sperry, *Org. Synth.*, 1932, Coll. Vol. **1**, 95. [g] F. Tieman, *Ber. Dtsch. Chem. Ges.*, 1978, **11**, 663. [h] D. C. Baker, D. Horton, and C. G. Tindall, *Carbohydr. Res.*, 1978, **67**, 491. [i] K. Antonakis and M. J. Arvor, *Bull. Soc. Chim. Fr.*, 1970, 3010. [j] J. Herscovici, A. Ollapally, and K. Antonakis, *C.R. Acad. Sci., Ser. C*, 1976, **288**, 757. [k] K. Antonakis and M. J. Arvor, *C.R. Acad. Sci., Ser. C*, 1971, **272**, 1982.

chromium(VI) species, either directly [(1) in Scheme] or after prior formation of a chromate ester [(2) in Scheme], is postulated.



SCHEME

The fact that CH cleavage was the rate-determining step of the reaction led us to investigate (Table 5) the influence of the molecular sieves on the kinetic isotope effect in the oxidations with benzhydrol–deuteriobenzhydrol (1 : 1). The reactions with an excess of the Cr^{VI} reagents present were followed by h.p.l.c. analysis. Under these conditions we observed first-order kinetics for both assisted and unassisted oxidations.

Several points arise from Table 5, as follows: (*a*) In the absence of molecular sieves the values of the kinetic isotope effect for PCC and PDC oxidations are very similar. Furthermore, acids catalyze reactions with PCC as well as those which use PDC. This observation suggests that the reported mechanism for oxidations of benzylic alcohols with PCC also applies when benzhydrol reacts with PCC or with PDC.

TABLE 5

Isotope effect for benzhydrol [a]

With PCC [b]					
Amount of 3-Å [c] molecular sieve	0	0.25	0.50	1	2
k_H/k_D (Dehydrated 3-Å sieves) [d]	2.93	1.68	1.18	1	1
k_H/k_D (5% Hydrated 3-Å sieves)	2.93	1.97	1.45	1.3	1
With PDC [e]					
Amount of 3-Å [d] molecular sieve	0	0.25	0.5	1	
k_H/k_D (Dehydrated sieves) [c]	2.77	1.66	1.13	1	

[a] [Benzhydrol], 2.5×10^{-2}M; [[α-^{2}H]benzhydrol], 2.5×10^{-2}M. [b] [PCC], 2×10^{-1}M; reaction performed in CH_2Cl_2–CH_3CN (1 : 1). [c] Expressed in g per mmol of oxidized alcohol. [d] 350 °C *in vacuo*. [e] [PDC], 10^{-1}M; reaction performed in 1,2-dichloroethane.

(*b*) The data for the oxidation of the alcohols in the presence of 3-Å molecular sieves show the decrease, and then the disappearance, of the kinetic isotope effect when the amount of sieve is increased. This suggests that the sieves work by favouring the cleavage of the CH bond from the alcoholic carbon.

(*c*) That oxidation of alcohols takes place at specific sites on the surface of the molecular sieve is suggested by the reaction with 3-Å zeolites containing 5% water. From this hypothesis it could be predicted that if the

water molecules take up a fraction of the active sites then the quantity of catalyst must be increased in order to obtain the same number of free sites as in the dry reagents. The results in Table 5 agree with these theoretical predictions.

The relative rates of the MS–PCC and MS–PDC oxidations of the epimeric nucleosides (1) and (16) and of (17) and (18) are also in agreement with these conclusions (Figure 6).

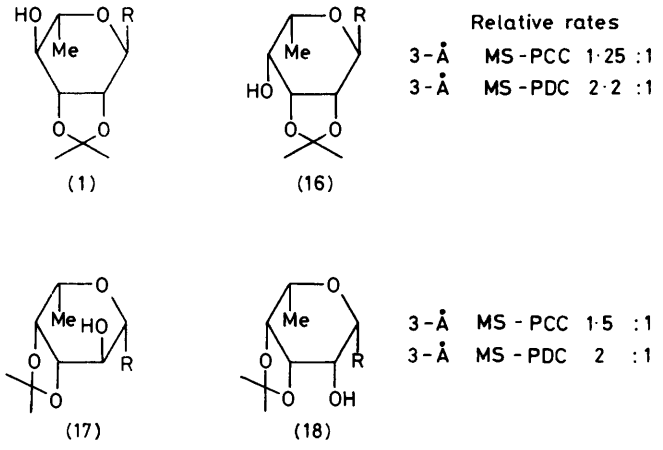


FIGURE 6 Oxidation of epimeric 6'-deoxyhexopyranosyl nucleosides

If the data in Table 5 support the assumption that the binding of the alcohol on the molecular sieve is the rate-limiting step, the values provided in Figure 6 can be explained by postulating the existence of specific sites. Moreover the molecules must be bonded to the molecular sieves by the hydroxy function. The reaction rate must therefore decrease when the OH hindrance increases, contrary to the reported results for chromic reagents.[2] If the idea of a specific site, which has previously been reported [13] in the case of zeolites, can be easily explained by the highly ordered structure, it is more difficult to understand why the molecular sieves catalyse the breaking of the CH bond from the alcoholic carbon. There are only a few examples of the utilisation of molecular sieves in organic synthesis, and then these aluminosilicates are generally only used as water or hydrochloric acid scavengers.[14] Furthermore, all the mechanistic studies in this field have been made on acidic zeolites. To our knowledge this is the first time such a phenomenon has been described for molecular sieves.

Several hypotheses can be postulated to interpret the action of the sieves: (*a*) if the alcohol is oxidized after esterification [(2) in Scheme], it is conceivable that the molecular sieves favour the correct orientation of the chromium-oxygen double bond with respect to the hydrogen which will be transferred (Figure 7); (*b*) the carbocation (A) (Scheme), postulated in the case of a direct transfer, could be stabilized by the tetracoordinate aluminium ion which forms the framework of the

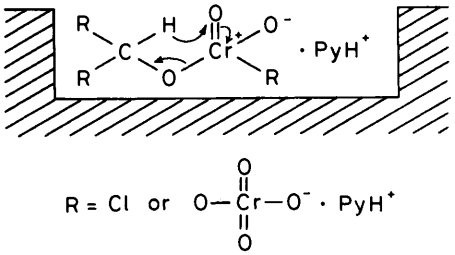


FIGURE 7 Possible mechanism for oxidation in the presence of molecular sieves

sieves; and (*c*) the electrostatic field created by the numerous positive and negative charges could labilise the CH bond and make easier the hydride transfer to the Cr^{VI} reagents.

EXPERIMENTAL

Solutions were evaporated at 40 °C under reduced pressure with a Büchi rotatory evaporator. U.v. spectra were measured with a Varian Techtron Model 635 spectrophotometer. I.r. spectra were determined for potassium bromide pellets using a Perkin-Elmer Model 137 spectrometer. N.m.r. spectra were recorded with a Varian T 60 instrument using tetramethylsilane as internal standard and decoupling was effected with a Varian T-6059 spin-decoupler using the frequency-sweep mode. Optical rotations were determined with a Roussel-Jouan ' Quick ' polarimeter.

H.p.l.c. analyses were carried out with a Dupont 830 liquid chromatograph fitted out with a 254-nm u.v. detector. The samples were introduced *via* a Rheodyne 7000 valve equipped with a 20-μl loop and chromatographed through a Zorbax-Sil column (25 % 0.46 cm), with dichloromethane as eluant for benzophenone and ethyl acetate–dichloromethane (8 : 2) for nucleosides. The chromatograms were recorded with a Varian 135 or a Linear 282 integrating recorder.

Reactions were monitored by t.l.c. on a Schleicher and Schull plastic sheet using dichloromethane or dichloromethane–ethyl acetate (1 : 1). Spots were detected by visual examination under u.v. light and by spraying with sulphuric acid (30%) and heating to 160 °C.

M.p.s are uncorrected. Elemental analyses were obtained from the laboratoire de Microanalyse du C.N.R.S.

All solvents used were commercial grade and were dried over molecular sieves (CH_3CN, 3 Å; CH_2Cl_2–$C_2H_4Cl_2$, 4 Å; 1/8 in. pellets) and used without further purification.

Pyridinium chlorochromate, pyridinium dichromate (Aldrich), and 3-Å molecular sieves (Sigma) could be used as purchased but had to be carefully protected from moisture. The 4- and 5-Å molecular sieves, 13-X silica (Merck silica gel 60), alumina (Merck) and Celite (Prolabo) were dehydrated *in vacuo* at 350 °C for 1 h.

General Procedure for Oxidation of Alcohols.—(*a*) *Molecular sieve–pyridinium chlorochromate.* Alcohol, PCC (2—4 mol equiv.), and 3-Å molecular sieves (0.5—1 g per mmol of alcohol) were placed in a round-bottomed flask. Anhydrous dichloromethane was added (2.5—5 ml per mmol of alcohol) and the suspension was vigorously stirred. When no alcohol remained the reaction mixture was worked up by addition of three volumes of diethyl ether. After decantation, the solution was filtered through a glass filter filled with 10% calcium sulphate silica gel (Silica gel G, Merck Darmstadt). The black residue was washed three times

with diethyl ether and the combined filtrates were concentrated to give the carbonyl compounds which were purified by distillation or crystallisation.

(*b*) *Molecular sieve–pyridinium dichromate.* Dichloromethane (2.5—5 ml per mmol of alcohol) was added to a round-bottomed flask containing 3- or 4-Å molecular sieves (0.5—1 g per mmol of alcohol), PDC (1—2 mol equiv.), and the alcohol. When the reaction was complete the black suspension was filtered through silica gel G and worked up as above.

Cholestan-3-one.—(*a*) 3-Å *MS–PCC.* Dihydrocholesterol (1.94 g, 5 mmol), PCC (2.15 g, 10 mmol), 3-Å molecular sieves (2.5 g), and anhydrous dichloromethane (12.5 ml) were put in a 100-ml round bottomed flask. After stirring for 15 min, t.l.c. analysis indicated that the dihydrocholesterol had disappeared. The reaction mixture was diluted with diethyl ether (40 ml). After decantation from the black solid the ethereal solution was filtered through silica gel G and the gummy residue washed with diethyl ether (3 × 15 ml). Removal of the solvent and crystallisation gave the carbonyl compound (1.75 g, 90%), m.p. 128—129 °C.[10]

(*b*) 4-Å *MS–PDC.* Dichloromethane (64 ml) was added to a round-bottomed flask containing freshly dehydrated 4-Å molecular sieves (12.88 g), dihydrocholesterol (5 g, 12.9 mmol), and PDC (5.81 g, 15.4 mmol). After stirring for 90 min the reaction was worked up as above to give pure cholestan-3-one (4.5 g, 90%), m.p. 128—129 °C.[10]

7-(6-*Deoxy*-α-L-lyxo-*pyranos*-4-*ulosyl*)*theophylline* (3).—(*a*(3-Å *MS–PCC.* 7-(6-Deoxy-2,3-*O*-isopropylidene-α-L-*manno*-hexopyranosyl)theophylline (1) (10 g, 27.3 mmol), PCC (17.6 g, 82 mmol), and dry 3-Å molecular sieves (13.6 g) were put in a 500-ml round-bottomed flask and anhydrous dichloromethane (70 ml) was added. After stirring for 1 h none of the nucleoside (1) remained and the mixture was diluted with diethyl ether (200 ml). The ethereal solution was filtered through silica gel G and the gummy residue washed with ethyl acetate–diethyl ether (3 : 1; 3 × 100 ml). Removal of the solvent followed by deacetalation[7] with 2N-hydrochloric acid gave compound (3) (7 g, 75%), isolated as the hydrate, m.p. 140—141 °C.[7]

(*b*) 3-Å *MS–PDC.* Dichloromethane (70 ml) was added to a 500-ml round-bottomed flask containing freshly dehydrated 3-Å molecular sieves (13.6 g), the nucleoside (1) (5 g, 13.6 mmol), and PDC (7.67 g, 20.4 mmol). After being stirred for 2 h the reaction was worked up as above to give compound (3) (3.29 g, 70%), isolated as the hydrate, m.p. 140—141 °C.[7]

1-(6-*Deoxy*-3,4-O-*isopropylidene*-β-L-lyxo-*hexopyranosul-osyl*)*thymine* * (13).—1-(6-Deoxy-3,4-*O*-isopropylidene-β-L-*galacto*-hexopyranosyl)thymine (12) (5 g, 15 mmol), PDC (9 g, 24 mmol), dry 3-Å molecular sieves (16 g), and dichloromethane (50 ml) were stirred together in a 250-ml round-bottomed flask.

After 2 h none of the nucleoside (12) remained and the reaction was worked up as above. Removal of the solvent and crystallisation from ethanol gave compound (13) (3.5 g, 70%), m.p. 188—190 °C, $[\alpha]_D^{20}$ −45° (*c* 0.1 in MeOH); R_F 0.68 (ethyl acetate–methanol 85 : 15); $\lambda_{max.}$ (MeOH) 265 nm (ε 12 500) (Found: C, 52.85; H, 6.2; N, 8.45. Calc. for $C_{14}H_{18}O_6N_2.0.5H_2O$: C, 52.66; H, 5.95; N, 8.77%).

7-(2,3-*Anhydro*-6-*deoxy*-β-L-lyxo-*hexopyranos*-4-*ulosyl*)-*theophylline* [10] (15).—7-(2,3-Anhydro-6-deoxy-β-L-*talo*-hexopyranosyl)theophylline (14) (6.2 g, 20 mmol), PDC (13.8 g, 36.6 mmol), 3-Å molecular sieves (20 g), and dichloromethane (50 ml) were stirred together in a 500-ml round-bottomed flask. After 4 h the suspension was diluted with diethyl ether (150 ml) then filtered through silica gel G. The pad was washed with ethyl acetate (1.5 l) and the solvent removed to give the ketonucleoside as crystalline material. Recrystallisation from ethanol yielded pure compound (15) (4.29, 70%), m.p. 188—190 °C, $[\alpha]_D^{20}$ −135° (*c* 0.1 in $CHCl_3$), R_F (ethyl acetate–methanol, 85 : 15); $\lambda_{max.}$ ($CHCl_3$) 279 nm (ε 10 910); $\nu_{max.}$ (KBr) 1 720 cm^{-1} (CO), 1 700—1 650 (theophylline CO); δ ($CDCl_3$) 8 (s), 6.6 (s), 4.3 (q, $J_{5,6}$ 7 Hz), 4.1 (d, $J_{2,3}$ 4 Hz), 3.7 (s), 3.5 (s), and 1.5 (d) (Found: C, 49.75; H, 4.8; N, 17.15. Calc. for $C_{13}H_{14}O_5N_4.0.5H_2O$: C, 49.52; H, 4.76; N, 17.77%).

The synthesis of the 7-(6-deoxy-2,3-*O*-isopropylidene-α-L-*talo*-hexopyranosyl)theophylline (16) was performed as follows: 7-(6-deoxy-2,3-*O*-isopropylidene-α-L-*manno*-hexopyranosyl)theophylline (1) (5 g, 13.66 mmol) was oxidized by the 3-Å MS–PDC procedure as described above. Work-up and removal of the solvent gave a semicrystalline compound which was dissolved immediately in methanol (100 ml). The solution was kept at 0 °C and sodium borohydride (3.6 g) was added. After 5 min the solution was diluted with water (100 ml) and the reduced product was extracted with dichloromethane (3 × 100 ml). The organic layer was evaporated to dryness and the residue crystallized from ethanol to give the *talo*-nucleoside (16) (3.75 g, 75 %), m.p. 171 °C; $\nu_{max.}$ (KBr) 3600 cm^{-1} (OH) and 1680—1640 cm^{-1} (theophylline CO); δ (CD_3SOCD_3) 8.5(s), 6.2 (d, $J_{1,2}$ 8 Hz), 4.9 (t, $J_{2,3}$ 7 Hz), 4.5 (q, $J_{3,4}$ 3.75 Hz), 4.1 (m), 3.5 (NMe), 3.3 (NMe), 1.4 (d, $J_{5,6}$ 8.5 Hz), 1.3 (s), and 1.2 (s).

Determination of Optimal Conditions for the Oxidation of 7-(6-*Deoxy*-2,3-O-*isopropylidene*-α-L-manno-*hexapyranosyl*)-*theophylline* (dIMT) (1).—(*a*) *Amount of molecular sieve.* (i) With PCC. Five reactions were set up, each containing dIMT (1) (3.66 mg, 0.1 mmol), PCC (86 mg, 0.4 mmol) in dichloromethane (2 ml), and dehydrated 4-Å molecular sieves (25, 50, 100, 200, and 400 mg). Aliquots were analyzed by h.p.l.c. and the alcohol concentration determined by internal standardization. The results are shown in Figure 1.

(ii) With PDC. Five reactions were carried out each containing dIMT (1) (146 mg, 0.4 mmol), PDC (225 mg, 0.6 mmol) in anhydrous dichloromethane (2 ml), and dehydrated 4-Å molecular sieves (0.1, 0.2, 0.4, and 0.8 g). Aliquots were removed and treated as above.

(*b*) *Effect of concentration.* Four oxidations were performed using dIMT (1) (292 mg, 0.8 mmol), PCC (516 mg, 2.4 mmol), 3-Å molecular sieves (400 mg), and anhydrous dichloromethane (2, 4, 8, and 16 ml). The data from the h.p.l.c. analyses are shown in Table 1.

(*c*) *Amount of* Cr^{VI} *reagent.* (i) With PCC. Five reactions were carried out using dIMT (1) (292 mg, 0.8 mmol), PCC (0.172, 0.344, 0.516, 0.688, and 1.032 g; 0.8, 1.6, 2.4, 3.2, and 4.8 mmol), and dehydrated 3-Å molecular sieves (400 mg) in anhydrous dichloromethane (2 ml). The results are shown in Figure 4.

(ii) With PDC. Five oxidations of dIMT (1) (146 mg, 0.4 mmol) were carried out using PDC (0.15, 0.225, 0.3, 0.45, and 0.6 g; 0.4, 0.6, 0.8, 1.2, and 1.6 mmol) and freshly dehydrated 4-Å molecular sieves (400 mg) in anhydrous dichloromethane (2 ml). Aliquots were analyzed by h.p.l.c. The values obtained are shown in Table 2.

(*d*) *Effect of different inorganic compounds.* (i) With PCC. Seven reactions were carried out with an insoluble inorganic compound (400 mg; 3, 4, and 5 Å; 13 X, SiO_2, Celite).

* Details of these syntheses will be published elsewhere.

One unassisted oxidation was also set up. Each oxidation was performed using dIMT (1) (292 mg, 0.8 mmol), PCC (516 mg, 2.4 mmol), and dichloromethane (2 ml). The results are shown in Figures 2 and 3.

(ii) With PDC. Eight oxidations were carried out in the same way as with PCC. Each reaction was set up using dIMT (1) (292 mg, 0.8 mmol), PDC (450 mg, 1.2 mmol), and dichloromethane (2 ml). The corresponding data are shown in Figure 5.

(*e*) *Investigation of the kinetic isotope effect.* (i) With PCC. Five reactions were carried out with benzhydrol (0.05 mmol), [α-^{2}H]benzhydrol (0.05 mmol), and PCC (0.4 mmol) with (25, 50, 100, and 200 mg) or without 3-Å molecular sieves in dichloromethane–acetonitrile (1 : 1; 2 ml). Aliquots were analyzed by h.p.l.c. and the concentration determined by external standardisation with a 5×10^{-2}M-benzophenone solution. The benzhydrol concentration [Bz] was calculated using the relation

$$[Bz] = [Bz]_0(1 - \alpha)$$

where $[Bz]_0$ is the initial concentration of the alcohol and α the molar fraction of the benzophenone obtained.

(ii) With PDC. Four reactions were performed using a mixture of benzhydrol (0.05 mmol)and [α-^{2}H]benzhydrol (0.05 mmol), PDC (0.02 mmol) with (25, 50, and 100 mg) or without 3-Å molecular sieves in dichloromethane (2 ml). The aliquots were analyzed as above.

The rate constants were determined graphically. Several values were ascertained by oxidation with benzhydrol or [α-^{2}H]benzhydrol. The results are shown in Table 5.

(*f*) *Oxidations of epimeric alcohols.* (i) With MS–PCC. Oxidation of dIMT (1) (36.6 mg, 0.1 mmol) was carried out using PCC (172 mg, 0.8 mmol) and dehydrated 3-Å molecular sieves (100 mg) in a mixture of dichloromethane (1.5 ml) and acetonitrile (0.5 ml) at 25 °C. Aliquots were analysed by h.p.l.c. and the alcohol concentration calculated by internal standardisation.

(ii) With MS–PDC. The reaction was carried out with compound (1) (36.6 mg, 0.1 mmol), PDC (150 mg, 0.4 mmol), and 3-Å molecular sieves (100 mg) in dichloromethane (2 ml) at 25 °C. Aliquots were treated as above. 7-(6-Deoxy-2,3-*O*-isopropylidene-α-D-*talo*-hexopyranosyl)theophylline (16), 7-(6-deoxy-3,4-*O*-isopropylidene-β-L-*galacto*-hexopyranosyl)theophylline (17), and 7-(6-deoxy-3,4-isopropylidene-β-L-*talo*-hexopyranosyl)theophylline (18) were oxidized in the same way.

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