Cleavage of Protecting Groups Catalysed by π -Acceptors[†]

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The cleavage of protecting groups is caused by the acidic adducts produced from the methanolysis of acceptors.

We have reported that the deprotection of acetals and silyl ethers was promoted by several acceptors, such as 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in aqueous MeCN.¹ Similarly, the cleavage of acetals and silyl ethers catalysed by DDQ in aqueous ethyl acetate was reported by Oku et al. and they pointed out that DDQ acted as a protic acid and/or a Lewis acid in a wet solvent.² Iranpoor et al. have reported the ring opening reaction of epoxides with alcohols catalysed by DDQ.³ Tetracyanoethylene (TCNE) was reported to catalyse similar reactions such as the alcoholysis of epoxides.⁴ Although many examples of hydrolyses of protecting groups promoted by acceptors are known, a mechanism for these reactions is still unclear. Furthermore, products formed in the reactions of acceptors with a solvent have barely been studied. In this paper, we describe the detailed results of deprotection using a variety of acceptors in MeOH. We also describe the investigation of the reactions of acceptors with MeOH.

First, we examined the cleavage of dodecyl triethylsilyl (TES) ether (1a) using 10 mol% of various acceptors at room temperature. Dry MeOH was used as a solvent in order to avoid the hydrolysis of acceptors. The results are summarized in Table 1. The deprotection proceeded more rapidly using strong acceptors possessing higher reduction potentials. In the series of quinones examined, the reaction proceeded most easily with DDQ (entry 1). The reaction occurred with polyhalogenated quinones (entries 2-5). p-Benzoquinone which has a low reduction potential did not catalyse the reaction (entry 6). Amongst the quinodimethanes 8-11, the reaction proceeded most rapidly with 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane (8, TCNQF₄). 11,11,12,12-Tetracyano-2,6-naphthoquinodimethane (9, TNAP) has less activity than 7,7,8,8-tetracyanoquinodimethane (10, TCNQ) in spite of its higher reduction potential compared to that of TCNQ (entries 8 and 9). Compound 11 required a longer reaction time than TCNO (entries 9 and 10). The activity of TCNE is almost comparable to that of DDQ and $TCNQF_4$ although the reduction potential is not so high (entries 1, 7 and 11). In the case of 2,4,7-trinitro-9-fluorenylidenemalononitrile (TNFMN, 14) the reaction did not proceed although the reduction potential is almost the same as that of p-chloranil (entries 4 and 13). The low activity of compounds 9, 11 and 14 could be attributed to the high stability of the acceptors in MeOH. Deprotection was not catalysed by 2,4,7-trinitro-9-fluorenone, 1,2,4,5-tetracyanobenzene, 9,10-dicyanoanthracene, 1,4-dicyanobenzene and 1,4-dinitrobenzene ($E_{red} = -0.43$, -0.66, -0.89, -1.60 and -0.68 V, respectively).

Next, we examined the mechanism of the acceptorcatalysed reactions. The acid concentration of the solution of representative acceptors, *i.e.*, DDQ, *p*-chloranil, TCNQ and TCNQF₄, was measured in MeOH using a pH meter under nitrogen. The medium became acidic during the reactions (For example, the pH after 1 h is 4.08, 4.71, 4.63 and 2.64 for the solution of DDQ, *p*-chloranil, TCNQ and TCNQF₄, respectively). The reactions of **1a**, carried out in the presence of sulfuric acid under identical conditions with respect to proton concentration, gave almost the same results as the acceptor-promoted reactions. Cleavage of tetrahydropyranyl (THP) ether **1b** catalysed by DDQ or TCNQF₄ was quenched by adding 4 equiv. of di-*tert*-butylpyridine⁵ (DTBP) although these acceptors reacted with DTBP slowly to give the corresponding anion radicals in MeCN when analyzed by UV–VIS spectroscopy. These facts strongly suggest that the deprotection is promoted by protons produced in the solvents.

When DDQ was treated with MeOH, 2,3-dichloro-5-cyano-6-methoxy-p-benzoquinone (18)⁶ (14%) and 2,3dichloro-5,6-dicyanohydroquinone (DDQH₂) (20%) were isolated together with a large amount of recovered DDQ after 48 h (Scheme 1). Compound 16 could not be isolated because of the easy elimination of HCN in MeOH solution. The absorption at 465 nm due to 16 was detected in the UV-VIS spectra. DDQH₂ did not catalyse the deprotection of 1b and HCN is a very weak acid $(pK_a 9.2)$. Therefore, we deduce that 16 is one of the promotors. Quinone 18 also possessed an activity for the cleavage of 1b, which was converted into the acidic complex mixture in MeOH slowly. Since the conversion of p-chloranil in MeOH was too slow, we could not isolate acidic materials. TCNQ and TCNQF₄ reacted with MeOH slowly to give adducts 21 (96 h, 33%) and 22 (48 h, 94%), respectively (Scheme 2). During the reactions, we observed the absorptions of the TCNQ anion radical⁷ and the TCNQ F_4 anion radical in the UV-VIS spectra. Compounds 21 and 22 are sufficiently acidic to cause the observed deprotection. Deprotection of 1b catalysed by adduct 22 was quenched by adding 4 equiv. of DTBP in MeOH.



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 Table 1
 Deprotonation of 1a catalysed by acceptors in MeOH^a

Entry	Acceptor		$E_{\rm red}/{\rm V}^b$	<i>t</i> /h	Yield of 1c (%)
1	DDQ	2	0.59	0.5	90
2	o-Chloranil	3	0.14	3	88
3	<i>p</i> -Chloranil	4	-0.04	3	83
4	<i>p</i> -Chloranil	5	0.01	3	95
5	<i>p</i> -Bromanil	6	0.00	3	88
6	<i>p</i> -Benzoquinone	7	-0.50	24	0
7	TCNQF4	8	0.53	0.5	84
8	TNAP	9	0.20	24	86
9	TCNQ	10	0.13	2	92
10	2,5-Me ₂ -TCNQ	11	0.02	24	92
11	TCNE	12	0.15	0.5	91
12	Fumaronitrile	13	-2.03	24	0
13	TNFMN	14	0.02	24	0

^a1a 1.0 mmol, acceptor 0.1 mmol, MeOH 10 cm³.

We propose that the reaction of DDQ with MeOH proceeds by the mechanism shown in Scheme 1.8 The first step is a nucleophilic attack of MeOH to DDQ to give adduct 16 followed by a deprotonation. Anion 17 would lose a cyanide ion to give quinone 18. An electron transfer from anion 17 to DDQ would give radical 19 and anion radical **20**, which leads to $DDQH_2$.

In Scheme 2, the formation of adducts 21 and 22 is illustrated. The addition of MeOH to TCNQ or TCNQF4 would produce 21 or 22, which is deprotonated to give anion 23. An electron transfer from 23 to TCNQ or TCNQF₄ would afford radical 24 and anion radical 25. The formation of quinodimethane anion radicals was not affected in the presence of oxygen. When the methanolysis of acceptors was performed in the presence of acrylamide, polymerization was not observed.

Formation of the anion radical was also observed in the reactions of MeONa with DDQ, TCNQ and TCNQF₄. MeONa reacted with 2 equiv. of these acceptors in MeCN to give a stable solution, which exhibited the absorptions of the corresponding anion radical of the acceptors in the UV-VIS spectra.

Interestingly, the rate of the methanolysis of acceptors was sharply increased by irradiation with a fluorescent lamp (Table 2). In the case of *p*-chloranil, we could not isolate acidic materials from the irradiated solution. However, dodecan-l-ol (1c) was obtained in 99% yield when THP ether 1b was treated with the irradiated solution for 7 h, while no reaction occurred when 1b was treated with the unirradiated



 Table 2
 The reaction of acceptors with MeOH in the dark and
 under irradiation

Entry	Acceptor	<i>t</i> /h	Yield (%) ^a
1 ^{<i>b</i>}	DDQ	48	18 14
2 ^c		10	18 13
3 ^b	p-Chloranil	158	trace ^d
4 ^c		158	trace ^e
5 ^{<i>b</i>}	TCNQ	96	21 33
6 ^{<i>c</i>}		96	21 62
7 ^b	TCNQF ₄	48	22 94
8 ^c	-	13	22 91

^alsolated yields. ^bIn the dark. ^cIrradiated by a fluorescent lamp. ^dNo reaction was observed when **1b** was treated with the unirradiated solution for 7 h. eAlcohol 1c (99%) was obtained from the reaction of 1b with the irradiated solution for 7 h.

solution. By analogy with TCNQ-mesitylene systems,⁹ the adduct formation might be explained in terms of the chemical pseudoexcitation concept proposed by Fukui et al.¹

In conclusion, the cleavage of the protecting groups is promoted by protons generated from the methanolysis of acceptors. We clarified some products derived from acceptors. However, some acceptor-catalysed reactions possess different reactivities or selectivities from those of the usual acid-catalysed ones.^{4b,11} The reason is still unclear at the present time.

Experimental

All reactions were carried out under nitrogen in the dark. Acid concentration in MeOH was measured with a pH meter, which was corrected using a scale based on a solution of hydrogen chloride in MeOH.

 α -Methoxy-p-phenylenedimalononitrile (21).—Colourless crystals, mp >250 °C (from acetone-hexane) (Found: C, 66.3; H, 3.3. $C_{13}H_8N_4O$ requires C, 66.1; H, 3.4%); ν_{max} (KBr)/cm⁻¹ 3052, 2192, 1580, 1508, 852; λ_{max} (MeOH)/nm 224 (ϵ 15000 dm³ mol⁻¹ cm⁻¹), 270 (19800), 335 (21000); δ_H (CD₃COCD₃) 3.84 (3 H, s, MeO), 6.27 [1 H, br s, CH(CN)₂, D₂O exch.], 7.99 (4 H, s, ArH).

 α -Methoxy-2,3,5,6-tetrafluoro-p-phenylenedimalononitrile (22). Colourless crystals, mp 131-134 °C (decomp) (from acetonehexane) (Found: C, 50.6; H, 1.4. C₁₃H₄N₄OF₄ requires C, 50.7; H, 1.3%); ν_{max} (KBr)/cm⁻¹ 2928, 2196, 2160, 1498; λ_{max} (MeOH)/nm 216 (ϵ 18100 dm³ mol⁻¹ cm⁻¹), 265 (7000), 332 (32000); δ_{H} (CD₃COCD₃) 3.81 (3 H, s, MeO), 6.55 [1 H, br s, CH(CN)₂, D₂O exch.]; δ_{C} (CD₃COCD₃) 18.5 (d), 57.2 (q), 65.2 (s), 110.7 (s), 111.2 (s), 143.0 (s), 143.4 (s), 148.1 (s), 148.4 (s).

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