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# Deprotection of Acetals and Silyl Ethers by DDQ. Is DDQ a Neutral Catalyst ?

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2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in wet ethyl acetate at room temperature catalytically hydrolyzed acyclic acetals effectively and selectively among ethereal functional groups such as dioxoranes, 1,3-dioxanes, oxiranes, TMS- and TBDMS ethers. The mechanism is discussed on the basis of the function of DDQ as a Lewis acid in a wet solvent.

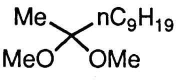
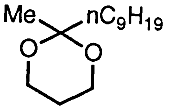
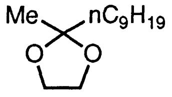
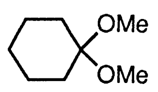
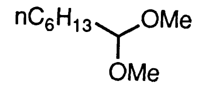
In course of investigating electron accepting character of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in combination with oxygen atom-bearing donors, we encountered a facile cleavage of dialkyl acetals in the reaction with DDQ in wet solvents. After we unveiled this fact in preliminary reports,$^{1)}$ we have been wondering and investigating the role of DDQ in the acetal cleavage reaction.

Quite recently, Tanemura and his coworkers have reported similar acetal cleavage reactions stressing that DDQ is a mild and neutral catalyst.$^{2)}$ Also reported analogously was that tetracyanobenzene cleaved acetals to give esters which was accounted to an electron-transfer mechanism.$^{3)}$ Herewith we would like to communicate to argue that DDQ is not a neutral reagent but a relatively strong Lewis acid and, in moisturized organic solvents, it increases the proton concentration to the level high enough for acetal cleavage reactions. Also included in the present report is the synthetic application of the DDQ-catalyzed hydrolysis to chemoselective cleavage among different ethereal functional groups.

While the treatment of cyclohexanone dimethyl acetal with a catalytic amount of DDQ (2.9 mol%) at room temperature for 7 h in usual reagent-grade ethyl acetate (AcOEt) produced the hydrolysis product only in a trace amount (5%), the use of wet (saturated with water) AcOEt $^{4)}$ remarkably accelerated the hydrolysis rate to give cyclohexanone in a quantitative yield (>96%) within 7 hours. Table 1 shows some examples of the hydrolysis reaction which demonstrate the effectiveness of wet AcOEt in comparison with dry solvents. Additionally, the DDQ/wet-AcOEt reagent made a selective hydrolysis feasible among different acetal groups$^{5)}$ and the order of the ease of hydrolysis among different types of acetals is consistent with that reported for protic acid-catalysis.$^{6)}$

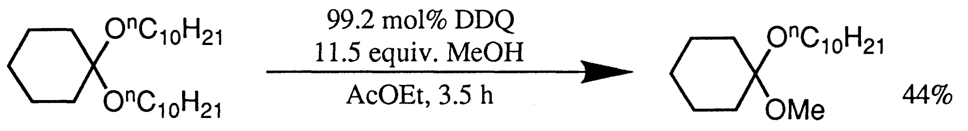
First, a trace amount of 2,3-dicyano-5,6-dichloro-1,4-hydroquinone (DDQH$_2$)$^{7)}$ which probably contaminated the DDQ we used was suspected to function as a protic acid. However, it was ruled out by the quantitative recovery of the starting acetals in the independent reaction with 3 mol % DDQH$_2$. With DDQ in wet AcOEt, intermediacy of an oxycarbenium ion or an oxonium ion intermediate was rationally evidenced by the acetal exchange reaction (Eq. 1). Alternative to the acid-catalysis mechanism is the donor-acceptor interaction$^{8)}$ which will form a charge transfer (CT) complex followed by the generation of a radical pair. However, under aerobic conditions the reaction was not disturbed, though the e.p.r. as well as UV-Vis spectroscopic

Table1. DDQ-Catalyzed Hydrolysis of Acetals in Dry or Wet Ethyl Acetate

| Acetal | Condition of AcOEt[a] | DDQ mol% | Reaction time/h[b] | Yield/% of carbonyl compound |
|---|---|---|---|---|
|  | dry | 104.7 | 2 | 100[d] |
| | dry | 8.4 | 1 | 4[d] |
| | wet | 8.4 | 1 | 100[d] |
|  | dry | 97.4 | 96 | 97[d] |
| | wet | 10.0 | 6 | 95[d] |
|  | dry | 98.2 | 96 | 2[d] |
| | wet | 13.0 | 24 | 72[d] |
|  | dry | 95.6 | 4 | 100[e] |
| | dry | 17.6 | 23 | 100[e] |
| | dry | 1.5 | 2.5[c] | 82[e] |
| | dry | 2.9 | 7 | 5[e] |
| | wet | 2.5 | 7 | 96[e] |
|  | dry | 101.5 | 96 | 44[e] |
| | wet | 11.6 | 52 | 43[e] |
| | wet | 11.6 | 144 | 99[e] |

a) wet: AcOEt was saturated with water and used. dry: AcOEt was dried over anhydrous potassium carbonate and distillated. b) Reaction temperature: 20-25 °C. c) At a reflux temperature of the solvent. d) Isolated yield. e) VPC yield.

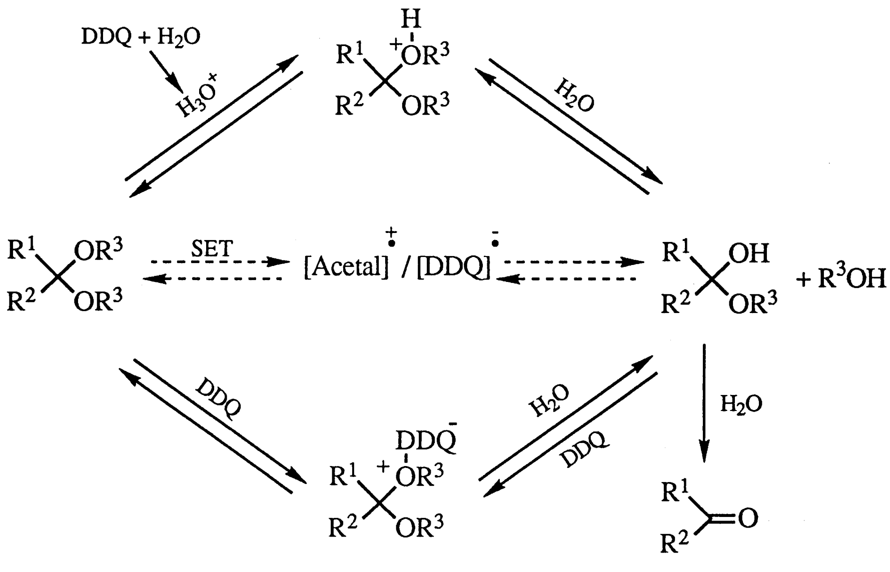
measurements on the reaction mixture did not show identifiable e.p.r. signals nor CT absorption bands either. Therefore, the donor-acceptor route has not yet obtained experimental supports so far at the present stage.



(1)

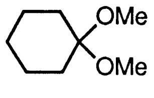
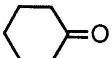
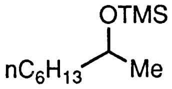
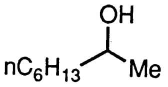
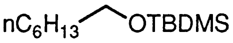
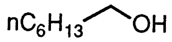
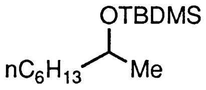
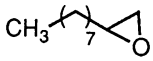
On the basis of above-mentioned evidences observed, we presumed that DDQ may form an acidic medium in wet organic solutions. Therefore, we measured the p$K_a$ value of DDQ which is sparingly soluble in water and obtained a value of 3.42 approximately.[9)] Thus, DDQ is a relatively stronger acid than $DDQH_2$ and AcOH. Therefore, as shown in Scheme 1, DDQ can act more or less as a Lewis acid in water to increase the proton concentration. Though being hardly distinguishable from the above protic route, another possible function of DDQ as a Lewis acid is the formation of oxonium ion with the ethereal oxygen atom whose concentration in equilibrium may be too low to be measured spectroscopically but the equilibrium can be rapidly shifted by the attack of water.

The DDQ/wet-AcOEt reagent, being comparably acidic to *p*-nitrobenzoic acid (PNBA),[10)] is more reactive than PNBA or AcOH in the hydrolysis of acetals and a secondary TMS ether as well. (*t*-Butyl)dimethylsilyl (TBDMS) ethers, particularly of secondary alkyl groups, resisted the reagent. The comparisons are summarized in Table 2.



Scheme 1.

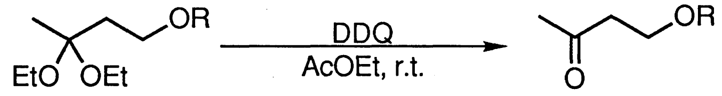
Table 2. Comparison of Acid Catalysts in the Hydrolysis of Ethereal Functional Groups in Wet Ethyl Acetate

| Substrate[a] | Acid[b] | (mol%) | Reaction time/h[c] | Product | Yield/%[d] |
|---|---|---|---|---|---|
|  | DDQ | (2.5) | 7 |  | 96[e] |
| | PNBA | (100.7) | 69 | no reaction | - |
| | AcOH | (282.4) | 85 | no reaction | - |
|  | DDQ | (11.9) | 2.5 |  | 99 |
| | PNBA | (101.2) | 46 | | 17 |
|  | DDQ | (11.6) | 2.5 |  | 0.8 |
| | DDQ | (92.4) | 26 | | 14 |
| | PNBA | (94.5) | 40 | no reaction | - |
| | AcOH | (279.0) | 85 | no reaction | - |
|  | DDQ | (10.7) | 2.5 | no reaction | - |
| | DDQ | (113.4) | 26 | no reaction | - |
| | AcOH | (284.8) | 85 | no reaction | - |
|  | DDQ | (101.7) | 20.5 | no reaction | - |

a) OTMS: trimethylsilyloxy, OTBDMS: (*t*-butyl)dimethylsilyloxy. b) PNBA: *p*-nitrobenzoic acid, AcOH: acetic acid. c) Reaction temperature: 20-25 °C. d) Isolated yield. e) VPC yield.

Synthetic application of the present reaction to some intramolecular chemoselective hydrolysis was attempted. The differences in reactivity between diethyl acetal groups and other ethereal functional groups (trimethylsilyloxy, (*t*-butyl)dimethylsilyloxy, benzyloxy, and *p*-methoxybenzyloxy group) which are incorporated together into a 1-hydroxy-3-butanone skeleton are shown explicitly in Table 3.[11] Thus, the synthetic applicability of the reagent to selective hydrolysis has been demonstrated in wet AcOEt solutions.

Table 3. Synthetic Application



| R[a] | DDQ/mol% | Reaction time/h[b] | Product yield/%[c] |
|---|---|---|---|
| TMS[d] | 10.1 | 8 | 89[e] |
| TBDMS | 8.6 | 2 | 91 |
| Bn | 12.3 | 1.5 | 95 |
| PMBn | 4.9 | 1 | 91 |

a) Bn: benzyl; PMBn: *p*-methoxybenzyl. b) Reaction temperature: 20-25 °C. c) Isolated yield. d) Reagent-grade ethyl acetate was used. e) VPC yield.

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References

1) T. Kamada, M. Kinugasa, and A. Oku, 62th National Meeting of the Chemical Society of Japan, Sapporo, September 1991, Abstr., No.2, 608; M. Kinugasa, T. Kamada, and A. Oku, 63th National Meeting of the Chemical Society of Japan, Osaka, March 1992, Abstr., No.2, 2272.

2) K. Tanemura, T. Suzuki, and T. Horaguchi, *J. Chem. Soc., Chem. Commun.*, **1992**, 979.

3) M. Mella, E. Fasani, and A. Albini, *J. Org. Chem.*, **57**, 3051 (1992).

4) At 20 °C approximately 3.0% (wt%) of water is soluble in AcOEt, "Kagakubinran," 3rd ed, ed by H. Chihara, Maruzen, Tokyo(1984), Vol. 2, p.203.

5) In comparison with dialkyl acetals, the following functional groups are practically unreactive or sparingly reactive: THP ether was hardly hydrolyzed, ethyleneglycol and 1,3-propanediol cyclic acetals were hydrolyzed at a very slow rate, ester as well as oxirane groups practically survived albeit the latter was reported to be cleaved at higher temperatures via electron transfer mechanism (see Ref. 8a) against which we argue.

6) M. S. Newmann and R. J. Harper, Jr., *J. Am. Chem. Soc.*, **80**, 6350 (1958); S. W. Smith and M. S. Newmann, *ibid.*, **90**, 1249 (1968).

7) The titrated $\mathrm{p}K_{\mathrm{a}}{}^{1}$ and $\mathrm{p}K_{\mathrm{a}}{}^{2}$ of $DDQH_2$ were approximately 4.3 and 6.5, respectively. The reported $\mathrm{p}K_{\mathrm{a}}$'s of *p*-nitrobenzoic acid and AcOH are 3.44 and 4.76, respectively.

8) a) K. Iranpoor and I. M. Baltork, *Tetrahedron Lett.*, **31**, 735 (1990); b) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *ibid.*, **23**, 3021 (1982); c) K. Horita, T. Yoshioka, T. Tanaka, and O. Yonemitsu, *Tetrahedron*, **42**, 3021 (1986).

9) The $\mathrm{p}K_{\mathrm{a}}$ of DDQ was measured in its aqueous solution (1.35 x $10^{-3}$ mol $dm^{-3}$) , using a pH meter, by the titration with aqueous NaOH (1.00 x $10^{-3}$ mol $dm^{-3}$). DDQ is slightly soluble in water whereas chloranil and TCNQ are nearly insoluble.

10) $\mathrm{p}K_{\mathrm{a}}$(PNBA) = 3.44, "Kagakubinran," 3rd ed, ed by H. Ohtaki, Maruzen, Tokyo(1984), Vol. 2, p.339.

11) Without proceeding further to the ketoalcohol, the acetal hydrolysis can be quenched at the stage of forming ketoether as the sole product.

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