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A COMMENT ON THE REACTIVITY OF METHOXYMETHYL (MOM) AND β-METHOXYETHOXYMETHYL (MEM) ESTERS.‡

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Summary: A cumulative negative inductive effect, not internal chelation of metal ions, is invoked to explain the enhanced reactivity of MEM and MOM esters.

Current interest in the protection of alcohols and carboxylic acids has led to the design of many "mixed acetal" blocking agents, archetypical of which is the widely used methoxymethyl (MOM) group.[2-5] MEM ethers represent the latest generation of such structures, and their selective hydrolysis by mild Lewis acids ($ZnBr_2$, $TiCl_4$) is thought to be facilitated by specific bidentate coordination to the ethylenedioxy chain.[6]

Two years ago the first attempt to create a highly chelated MEM ester lithium enolate was described.[7] Shortly thereafter a selective MEM ester-to-alcohol conversion with $LiHBEt_3$ in the presence of other reducible esters was keynoted in this Journal.[8] It was proposed at the time that lithium chelation by the MEM oxygens accelerated addition of hydride to the coordinated (activated) carboxyl carbonyl.[8] Work in our own laboratory now suggests that another, more fundamental feature of both MOM and MEM esters may contribute to the reported selectivity.

Our investigation was prompted by the observation that MEM esters of substituted malonates underwent rapid uncatalyzed transesterification. With no metal chelation possible, we reasoned that a cumulative negative inductive effect, exerted primarily by the MEM ester's two acetal oxygens, was responsible for the enhanced electrophilicity of its carbonyl group as compared with ordinary n-alkyl esters.[9] According to our hypothesis, MOM esters should likewise be more susceptible to nucleophilic attack, although to the best of our knowledge this has not been explicitly cited in previous reports.

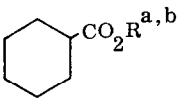
To test this rationale, a series of competitive ester saponifications was carried out using Bu_4NOH in aqueous THF. Under these conditions, where no cation complexation could be invoked, both MEM and MOM esters of cyclohexanecarboxylic acid were found to hydrolyze 5 to 6 times faster than the corresponding methyl or n-propyl esters (see Table). To put this figure in perspective with more familiar steric effects, methyl and neopentyl acetate exhibit a similar difference in saponification rate (k_{rel}=5.5).[9] This value could easily account for the selectivity noted in earlier hydride additions.[8,10]

In a related development, Schultz and Berger have shown that the fragmentation-recombination

‡Shikimate-Derived Metabolites, Part 9

of MOM ester enolates involves ketene intermediates.[3] Since kinetically generated alkyl ester enolates are stable at room temperature, this result also lends credence to the postulate that the $(ROCH_2O)$– moiety is an effective, electron withdrawing leaving group.[11,12]

TABLE

Competitive Hydrolyses of  [a,b]

	MEM	MOM
methyl	5.6	---
n-propyl	5.9	5.3

(a) Values cited are k_{rel} for column : row entries. (b) Slow addition of a standardized Bu_4NOH solution to an equimolar mixture of esters in THF at 25° was followed by extractive workup after various time intervals. Ratios of recovered esters were determined by NMR analysis; ester exchange under these conditions was negligible.

REFERENCES AND NOTES

(1) Undergraduate Research Participant, Cornell University.

(2) A. B. A. Jansen, T. J. Russell, J. Chem. Soc., 2127 (1965).

(3) A. G. Schultz, M. H. Berger, J. Org. Chem., 41, 585 (1976).

(4) F. Dardoize, M. Gaudeman, N. Goasdoue, Synthesis, 567 (1977).

(5) S. Masamune, Aldrichemica Acta, 11, 23-30 (1978); see p. 30.

(6) (a) Traces of HBr or HCl may also be responsible for MEM ether cleavage: E. J. Corey, J.-L. Gras, P. Ulrich, Tetrahedron Lett., 809 (1976); (b) See also use of the SEM group: B. H. Lipschultz, J. J. Pegram, ibid., 21, 3343 (1980).

(7) A. I. Meyers, P. J. Reider, J. Amer. Chem. Soc., 101, 2501 (1979); MOM and MEM esters displayed identical selectivity in this work.

(8) R. E. Ireland, W. J. Thompson, Tetrahedron Lett., 4705 (1979).

(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, 1959, pp. 315-318.

(10) Roddatz and Winterfeldt recently reported a high-yield MEM ester-to-aldehyde reduction with DIBAL-H; cf Angew. Chem., 93, 281 (1981). Aluminum complexation as well an an accelerated rate of reduction could contribute to the success of this process.

(11) MOM enolate fragmentation probably involves kinetic expulsion of $CH_3OCH_2O^{\ominus}$, and not concerted formation of CH_2O. For the equilibrium $CH_3O^{\ominus} + CH_2O \rightleftarrows CH_3OCH_2O^{\ominus}$ we determine $K \cong 6 \times 10^3$.

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