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MECHANISM OF THE "MICHAEL ADDITION" OF NUCLEOPHILES TO ENOL ESTERS

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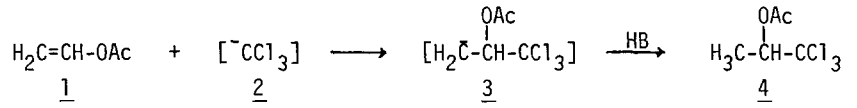
In 1961, Wagner, Kloosterziel, and van der Ven[1] reported the isolation of 1,1,1-trichloroisopropyl acetate (4) in 10% yield from the thermolysis of sodium trichloroacetate in the presence of vinyl acetate.[2] They suggested that 4 is produced simply by the addition of the intermediate trichloromethide ion (2) to vinyl acetate to form the carbanion (3) which is then protonated.



Subsequent investigators obtained substantially higher yields of 4 when the trichloromethide ion was generated by the deprotonation of chloroform with hydroxide or alkoxide.[3] Even more recently, use of this process in concert with the phase transfer concept has permitted the isolation of 4 in yields of 70-80%[4-7] [e.g., the two-phase reaction of aqueous NaOH with 1 in $CHCl_3$ in the presence of a catalytic amount of $PhCH_2\overset{+}{N}Et_3\ Cl^-$ (BTEAC)].

The reaction also has been generalized to include the enol ester analogues of 1 from other carboxylic acids[7] and from other aldehydes,[3,7] but not from ketones.[8] Other trihalomethyl anions have been substituted for 2[3,4,6,7] and in an even more remarkable extension, the list of nucleophiles has been expanded to include ethylenimine[9] and the anions from carbazoles (yields to 91%[10]) and nitriles (including $PhC(R)HCN$, Reissert compounds, and the ether derivatives of cyanohydrins, yields 50-75%[7]).

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For all of these reactions, the only mechanism which has been postulated -- though sometimes with misgivings -- is the simple addition pathway formulated in scheme A.[1,3-7]

(A) $RCH{=}CH\text{-}\overset{\overset{O}{\|}}{O}CR'$ (5) + Nu^- ⟶ $[R\bar{C}H\text{-}\underset{\underset{O}{\|}}{\overset{Nu}{|}}CH\text{-}OCR']$ (6) $\xrightarrow{HB}$ $RCH_2\text{-}\underset{\underset{O}{\|}}{\overset{Nu}{|}}CH\text{-}OCR'$ (7)

The lack of an alternative to scheme A has engendered some wrenching contortions of language. For example, these reactions have been cited as evidence of "the high electrophilicity of" the nucleophilic C=C bond in 5.[6,7] Also, to clothe scheme A in a mantle of respectability and to somehow mask the enormous energy required for the conversion of the stabilized nucleophile, Nu^-, to the destabilized, isolated carbanion (6), the process has been pronounced a "Michael addition."[7,11] This unfortunate terminology has even found its way into the review literature.[12]

We now present unambiguous evidence to support the contention that all of these reactions actually proceed by the chain transfer mechanism diagrammed in scheme B.

(B)

$RCH{=}CH\text{-}\overset{\overset{O}{\|}}{O}CR'$ (5) + :B ⟶ $RCH{=}CH\text{-}O^-$ (8) $\overset{HB}{\rightleftharpoons}$ $RCH_2\text{-}CH{=}O$ (9)

9 + Nu^- ⟶ $RCH_2\text{-}\underset{|}{\overset{Nu}{|}}CH\text{-}O^-$ (10) $\xrightarrow{5}$ $RCH_2\text{-}\underset{\underset{O}{\|}}{\overset{Nu}{|}}CH\text{-}OCR'$ (7) + $RCH{=}CH\text{-}O^-$ (8)

In this process, the enol ester (5) first acylates a base (e.g., HO^-, RO^-, Nu^-) in the medium to give a trace of the enolate (8) which is in equilibrium with the free aldehyde (9). The nucleophile then adds to the electrophilic carbonyl carbon of 9 to generate the adduct alkoxide (10) which is in equilibrium with the alcohol under most reaction conditions. Finally, acylation of 10 by the activated ester (5) yields the product (7) and liberates more enolate (8) continuing the chain.

In order to rule out mechanism A and establish scheme B as the correct reaction pathway, the following experimental evidence was obtained. First, when the phase transfer reaction of aq. NaOH, BTEAC, and 1 in chloroform was performed as described by Makosza,[4,7] a trace of 1,1,1-trichloro-2-propanol (11), a predicted intermediate from scheme B, was found. The main product (4) was also isolated in the reported yield. As anticipated, the adduct (11) also could be obtained (gc prep) by reacting 50% aq. NaOH and BTEAC (5 mol-%) with acetaldehyde in chloroform.[13] Again, according to B, 4 was isolated (12% yield) when 50% aq. NaOH was added to a stirred CH_2Cl_2 solution (no $CHCl_3$) of BTEAC, vinyl acetate (1 eq.), and 11 (1.1 eq.). Also, the simultaneous addition of

acetaldehyde in $CHCl_3$ and 50% aq. NaOH to BTEAC and p-nitrophenyl acetate in $CHCl_3$ afforded 4 in similar yield. In a parallel experiment, the nitrile (7,[7] R = H, R' = Me, Nu = PhC(Me)CN) was identified as a low yield product from the concomitant addition of acetaldehyde and aq. NaOH to a stirred benzene solution of 2-phenylpropionitrile, p-nitrophenyl acetate, and BTEAC.

Scheme A requires that the ester bond between the enol and the carboxylic acid in 5 remain intact during the "Michael addition" whereas scheme B demands cleavage of this acyl to oxygen bond. The mechanistic tests above accord with the latter alternative but more direct evidence on this point was gained in two crossover studies. In the first of these, a partial crossover experiment, a mixture of vinyl acetate (1), phenyl propionate (12[14]) and BTEAC in chloroform was treated with aq. NaOH. Reaction work-up afforded not only the normal product (4, 57%) but also the crossover product, 1,1,1-trichloroisopropyl propionate[15,16] (15%, bp 81° at 13 torr, isolated by gc prep). The yield difference is expected since 1 and 12 would not have the same acylating power toward alkoxide (10, R = H, Nu = CCl_3). In the second study, the trichloromethide reaction was performed on a 1:1 mixture of propenyl acetate (13[17]) and vinyl benzoate (14).

$$\underset{\substack{13\\(E/Z = 1/1.1)}}{MeCH{=}CH{-}OAc} + \underset{14}{H_2C{=}CH{-}OBz} \xrightarrow[\substack{BTEAC\\CHCl_3}]{\text{aq. NaOH}} \underset{\substack{15\ (R = Ac)\\17\ (R = Bz)}}{MeCH_2{-}\overset{OR}{\overset{|}{C}}H{-}CCl_3} + \underset{\substack{16\ (R = Bz)\\4\ (R = Ac)}}{CH_3{-}\overset{OR}{\overset{|}{C}}H{-}CCl_3}$$

Again the product mixture contained not only the two normal adducts, 15[3] and 16[7], expected from scheme A but also the two crossover esters, 17[15,18] (bp 161-164° at 15 torr) and 4, required by scheme B. The product ratio, 15:16:17:4 = 33:22:22:23 (obtained by distillation, gc, and nmr analysis), reflects both the differences in hydrolytic stability and acylating power between 13 (E,Z) and 14[19] and the differences in volatility between 15 and 4 compared to 16 and 17.

In summary, it is evident that the phase transfer reaction of enol esters with base and added nucleophiles constitutes a remarkably efficient one-step procedure: 1) for the *in situ* generation of aldehydes in concentrations low enough to avoid the ubiquitous self-aldol condensation,[20] 2) for the reaction of those aldehydes as classical nucleophile acceptors, and 3) for the effectively irreversible trapping by acylation of the equilibrium adducts thus formed. Some synthetic consequences of this mechanistic understanding will be explored in future papers in this series.

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References and Footnotes

1) W. M. Wagner, H. Kloosterziel, and S. van der Ven, Rec. Trav. Chim. Pays-Bas, 80, 740 (1961).

2) The normal dichlorocarbene-derived cyclopropane also was isolated in 10% yield.

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4) M. Makosza and M. Fedorynski, Rocz. Chem., 46, 533 (1972).

5) M. Makosza, A. Kacprowicz, and M. Fedorynski, Tetrahedron Letters, 2119 (1975).

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8) These react to give exclusively the dichlorocarbene-derived cyclopropanes.

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11) Possibly because of its apparent resemblance to the "real" Michael addition of trihalomethide ions to conjugated nitriles, esters, sulfones, etc.: M. Makosza and I. Gajos, Bull. Acad. Pol. Sci., 20, 33 (1972); E. V. Dehmlow, Justus Liebigs Ann. Chem., 758, 148 (1972).

12) Unfortunately, even one of us has cultivated this myth: W. P. Weber and G. W. Gokel, Phase Transfer Catalysis in Organic Synthesis, Springer-Verlag, N.Y., 1977, p. 39. Also see: M Makosza, Pure Appl. Chem., 43, 439 (1975).

13) Though related reactions are known, the adduct (11) does not seem to have been made previously by this approach. Because of the high volatility of 11, quantitative work was difficult.

14) A. Spasov, Ann. Univ. Sofia, II, Fac. Phys. Math. Livre 2, 35, 289 (1938-9), Chem. Abstr., 34, 2343 (1940).

15) New compound; spectral and analytical data, including ir, nmr, and high resolution mass spectra accord with the assigned structure.

16) Also made by the acylation of 11 with propionyl chloride.

17) E. W. Wuolijoki, Suomen Kemistilehti, B, 39(2), 36 (1966), Chem. Abstr., 64, 19400a (1966); P. Z. Bedoukian, J. Am. Chem. Soc., 66, 1325 (1944).

18) Also made by the trichloromethide reaction on propenyl benzoate.

19) Attempts also were made to avoid the problem by doing the crossover experiment on a mixture of doubly labelled and unlabelled 1, but these efforts were thwarted by the proclivity of 4 and 7 (R = H, R' = Me, Nu = PhC(Me)CN) to undergo acyl-oxygen cleavage during the mass spectrometric analysis.

20) Often, the inclusion of extra aldehyde in these reaction mixtures actually reduces the desired product yield and lowers its purity (e.g., in the treatment of aq. NaOH, BTEAC, and PhCH(Me)CN in benzene with 1).

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