Chem. Pharm. Bull.
30(7)2424—2428(1982)

Acid-catalyzed Acetal Formation from Benzoylacetone

Yoshiaki Furuya,*,[a] Yoshio Kosugi,[b] Kazuo Itoho,[c] Kazuki Yamaguchi,[a]
Toshihiro Nakashima,[a] Takashi Murayama,[a] and Yoshitaka Maeda[a]

Department of Industrial Chemistry, Faculty of Engineering, Kumamoto University,[a]
Kurokami, Kumamoto 860, Japan, Department of Synthetic Chemistry,
Faculty of Engineering, Nagoya University,[b] Chikusa-ku,
Nagoya 464, Japan, and Daiichi College of
Pharmaceutical Sciences,[c] Minami-ku,
Fukuoka 815, Japan

(Received January 7, 1982)

When mixed with methanol containing a catalytic amount of sulfuric acid and kept at 10°C for 10 h, benzoylacetone (BA) gave two products methoxylated on the side of the acetyl group (*viz.*, 3,3-dimethoxy-1-phenyl-1-butanone (AK) and 3-methoxy-1-phenyl-2-buten-1-one (A′E)) but no products methoxylated on the side of the benzoyl group (4,4-dimethoxy-4-phenyl-2-butanone (BK) and 4-methoxy-4-phenyl-3-buten-2-one (B′E)) or products methoxylated on both carbonyls. Furthermore, BA did not undergo acid-catalyzed methanolysis under our conditions.

The reason why acetal formation of the acetyl carbonyl occurs more easily than that of the benzoyl carbonyl, and the relationship of AK and A′E, which is not an intermediate in the formation of AK from BA even though AK can be formed from it, are discussed.

Keywords——kinetics of acid-catalyzed acetal formation; acetal of 1,3-diketone; benzoylacetone; 3,3-dimethoxy-1-phenyl-1-butanone; 3-methoxy-1-phenyl-2-buten-1-one; keto–enol tautomer

Compounds such as benzoylacetone that show keto–enol tautomerism are liable to be readily etherified.[1–3] Thus, benzoylacetone is easily methoxylated with methanol in the presence of a catalytic amount of mineral acid without fission between the acetyl and methylene moieties to form acetophenone (AP) and methyl acetate (MA).[4]

Little work on acetal formation of 1,3-diketones has been reported.[5] Therefore, we should like to describe the products of the title reaction and to discuss the reason why the acetyl group is subject to acetal formation. We will also discuss the relationship between 3,3-dimethoxy-1-phenyl-1-butanone (AK) and 3-methoxy-1-phenyl-2-buten-1-one (A′E) as the products of this reaction.

Experimental

Materials——Methanol was rectified; bp 64.3—65.0°C. Benzoylacetone (BA) was prepared by the reaction of acetophenone with ethyl acetate in the presence of sodium metal in ether, yield 44.6%, mp 57°C.[6] The products of BA etherification on the side of the acetyl group (A-type ether) and/or the benzoyl group (B-type ether) were obtained by the reaction of benzoylacetone with diazomethane in ether: A-type ether,[7] mp 79—82°C (lit.,[8] 79—82°C), B-type ether,[7] mp 10°C (lit.,[8] 10°C). The 4,4-dimethoxy-4-phenyl-2-butanone (BK) was prepared by the reaction of benzylideneacetone dibromide with sodium methoxide in methanol at 30—60°C[8] as a yellow oily material: yield 18%, bp 130—132.5°C (3.5—4 Torr).

Identification of the Reaction Products——A mixture of methanolic solutions of 0.1 M benzoylacetone (50 ml) and 0.05 M sulfuric acid (50 ml) was allowed to stand at 10°C for 10 h. The reaction mixture was shaken after addition of thiophene free benzene (50 ml). The mixture was then shaken again after addition of 0.6% sodium hydroxide (160 ml) and water (300 ml). The benzene layer was separated and dried on potassium carbonate. These procedures were repeated ten times, and the benzene solutions were combined. A red brown oily material was obtained when the benzene was removed under reduced pressure at 40°C. This product was directly analyzed by infrared (IR) and ^{1}H-nuclear magnetic resonance (NMR) spectrometry since the components were difficult to separate completely even by distillation at 2 mmHg.

IR and ^{1}H-NMR spectra were recorded on a JASCO A-702 spectrometer and a JEOL JNM-MH-100 spectrometer with tetramethylsilane (TMS) as an internal standard, respectively.

IR (neat) cm^{-1}: 1680 and 1660 (str. bands of benzoyl carbonyl), 1446 (def. band of methylene), 1283 and 1265 (str. and def. bands of benzoyl carbonyl), 1200, 1180 and 1045 (*anti-sym.* str. bands of ether linkage), 860 (def. band of vinyl group). ^{1}H-NMR (CCl$_4$), δ: 1.36 (3H, s, $C\underline{H}_3$), 2.10 (2H, s, $C\underline{H}_2$), 2.35 (3H, s, $C\underline{H}_3$), 3.17 (6H, s, $OC\underline{H}_3$), 3.64 (3H, s, $OC\underline{H}_3$), 6.03 (1H, s, $C{=}C\underline{H}$), 7.30 and 7.81 (5H, m, $C_6\underline{H}_5CO$).

Taking into account these results and the starting materials, it is considered that A′E and AK are the only products of the title reaction, and BE and BK are not formed. This is confirmed by the plots shown in Fig. 3. Furthermore, the acid-catalyzed methanolysis of BA to form AP and MA[4] does not take place, since actual data points deviate from the calibration curve of the reaction.

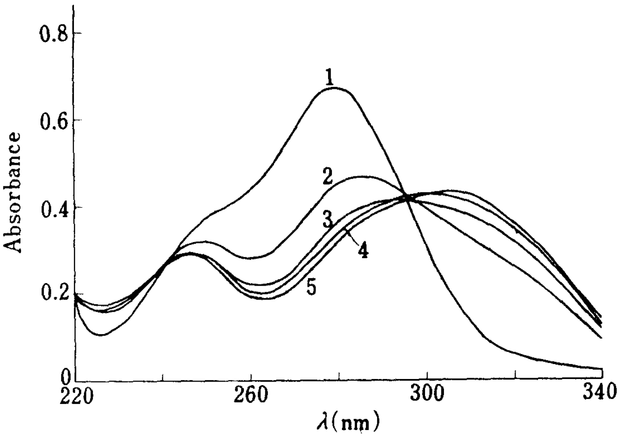


Fig. 1. UV Absorption Curves of Five Reaction Mixtures containing A′E and AK

Total concn. for UV measurement, 4×10^{-5} M; for reaction, 0.05 M.
Concn. of sulfuric acid: for UV measurement, 4×10^{-5} M; for reaction, 0.05 M.
Reaction time: 1, 0 h; 2, 1 h; 3, 2 h, 4, 3 h; 5,5 h.

Chemical Analysis of Double Bonds——An excess of *ca.* 0.5 M methanolic solution of bromine which had been allowed to stand for more than four days was added to a methanolic sample solution (0—0.06 M A′E), and the whole was magnetically stirred in a stoppered flask for 5 min at 20°C. Iodine liberated by adding an aqueous solution of potassium iodide was titrated with 0.02 M aqueous solution of sodium thiosulfate. The bromine value of benzylideneacetone (as a model) thus obtained was within 1% of the expected value.

Preparation of Ternary Diagram of BA, AK and A′E——Ultraviolet (UV) spectra were recorded on a Hitachi Perkin-Elmer 139 spectrophotometer. Aliquots (2 ml each) pipetted from the reaction mixture at appropriate time intervals were diluted with methanol to a 4×10^{-5} M total concentration of A′E and AK. From five UV absorption curves thus obtained, those of A′E and AK were obtained by the use of Eq. (2) with the least-squares method.[9] Concentrations of A′E for each curve were estimated by the bromine addition method mentioned above.

$$C_{AK} + C_{A'E} = 4\times10^{-5} \qquad (1)$$

$$\kappa^{\lambda}_{AK}C_{AK} + \kappa^{\lambda}_{AK'E}C_{A'E} = A^{\lambda} \qquad (2)$$

Here, A^{λ} is the absorbance of a mixed solution of A′E and AK, and κ^{λ}_{AK} and $\kappa^{\lambda}_{A'E}$ are the molecular extinction coefficients of AK and A′E, respectively, at λ nm. The UV absorption curves of A′E and AK were obtained by repeating this procedure at appropriate intervals of wavelength over the whole UV range (Fig. 2). By

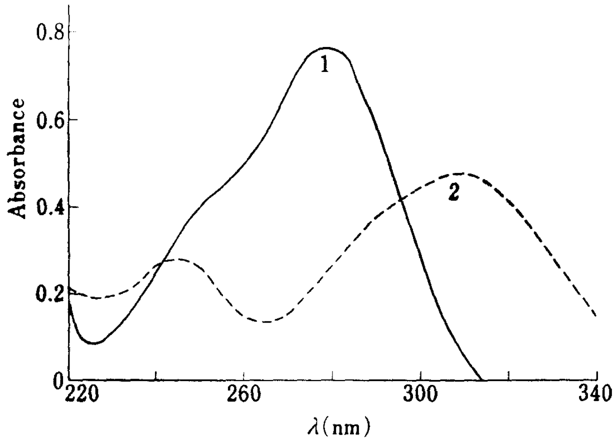


Fig. 2. UV Absorption Curves of A′E and AK
s ures containing A′E
a 0.05 M Sulfuric Acid

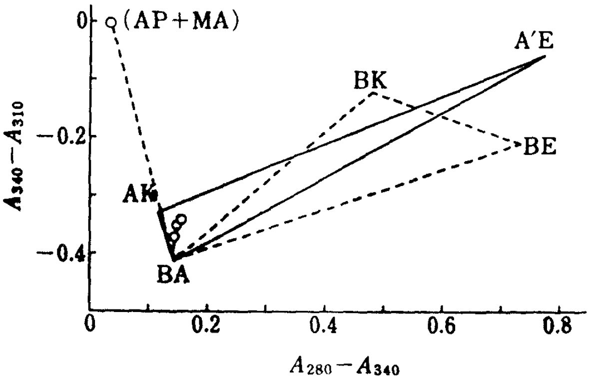


Fig. 3. Calibration Curves of the Ternary System BA–A′E–AK and/or BA–BE–BK and of Methanolysis for BA

Total concn. for UV measurement, 4×10^{-5} M; for iodometry, 0.05 M.

plotting the differences of absorbance, (A_{280}—A_{340}) *vs.* (A_{340}—A_{310}), the positions of 100% AE and AK were obtained. The points of 100% BA and BE can be obtained from the UV absorption curve in the same way. The conversion curve of each component can be obtained from the former diagram.

Typical Run for Rate Measurements——A 0.1 M methanolic solution of BA (15 ml) was mixed with a 0.1 M methanolic solution of sulfuric acid (15 ml), after both solutions had attained temperature equilibrium. Aliquots (1 ml each) were pipetted out at suitable intervals of time and diluted with methanol to a 4×10^{-5} M total concentration of BA, AK and A′E. The formed concentrations of AK and A′E and the remaining concentration of BA were obtained from the ternary diagram.

Results and Discussion

The plots of (A_{280}—A_{340}) *vs.* (A_{340}—A_{310}) of the actual reaction deviate from the calibration curve of acid-catalyzed methanolysis as shown in Fig. 3. Therefore, it is clear that the methanolysis of benzoylacetone to form acetophenone and methyl acetate[4] does not take place under our reaction conditions.

As IR and ^{1}H-NMR spectra revealed that the reaction products are a mixture of A′E and AK, this reaction should be a simultaneous reversible one containing an equilibrium point among three compounds. Methanol is present in large excess in this system. The acid-catalyzed reaction, which gives A′E and AK simultaneously, is a reversible one and can be written as follows:

$$\underset{\{(a-y)-x\}}{\mathrm{BA}} + \mathrm{MeOH} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{x}{\mathrm{AK}} + \mathrm{H_2O} \tag{3}$$

$$\underset{\{(a-x)-y\}}{\mathrm{BA}} + \mathrm{MeOH} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \underset{y}{\mathrm{A'E}} + \mathrm{H_2O} \tag{4}$$

From Eq. (3), the reversible pseudo-first order rate equation was obtained.

$$\mathrm{d}x/\mathrm{d}t = k_1(A-x)k_{-1}x \tag{5}$$

Here, A is (a—y) and is a variable function. At the equilibrium stage,

$$k_1(A-x_e) = k_{-1}x_e, \tag{6}$$

where x_e is x at the equilibrium stage. From Eqs. (5) and (6), the following equations were obtained.

$$k_1t = (x_e/A)\ln\{x_e/(x_e-x)\} \tag{7}$$

$$k_{-1}t = \{(A-x_e)/A\}\ln\{x_e/(x_e-x)\} \tag{8}$$

Treating Eq. (4) similarly, the rate constants of the forward and reverse reactions of A′E formation from BA are obtained,

$$k_2t = (y_e/B)\ln\{y_e/(y_e-y)\} \tag{9}$$

$$k_{-2}t = \{(B-y_e)/B\}\ln\{y_e/(y_e-y)\} \tag{10}$$

Here, B is a function, (a—x), and y_e is y at the equilibrium stage.

Then, the reaction forming AK from A′E can be expressed as follows:

$$\underset{(b-c-z)}{\mathrm{A'E}} + \mathrm{MeOH} \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} \underset{(c+z)}{\mathrm{AK}} \tag{11}$$

The rate constants, k_3 and k_{-3}, are given by,

$$k_3t = \{(c+z_e)/b\}\ln\{z_e/(z_e-z)\} \tag{12}$$

$$k_{-3}t = \{(b-c-z_e)/b\}\ln\{z_e/(z_e-z)\} \tag{13}$$

The rate data are listed in Table I. If AK is formed only *via* A'E from BA, the constant, k_1, should be equal to or smaller than the value of k_3. The value of k_1 is, however, larger than that of k_3 under the same reaction conditions, as is shown in Table I. This also suggests that A'E is not an intermediate in the title reaction, but a by-product, and both reactions are reversible ones.

Table I. Rate Constants for the Formation of 3,3-Dimethoxy-1-phenyl-1-butanone (AK) and/or 3-Methoxy-1-phenyl-2-buten-1-one (A'E) from Benzoylacetone in the Presence of 0.05 M Sulfuric Acid at 10°C

10^4k_1 s^{-1}	10^4k_{-1} s^{-1}	10^4k_2 s^{-1}	10^4k_{-2} s^{-1}	10^4k_3 s^{-1}	10^4k_{-3} s^{-1}
5.73	2.57	0.68	2.64	2.79	0.31

Initial concn. of BA: 0.05 M.

Next we wish to discuss the reason why acetyl carbonyl is methoxylated only under acid-catalyzed conditions such as those of the title reaction. It has been reported that BA molecules enolize nearly quantitatively on the side of the benzoyl group, and most of them form a six-membered ring by hydrogen bonding to the acetyl oxygen atom.[10] That is to say, a carbonyl group is present only on the side of the acetyl group. As acetal formation is one of the characteristic reactions of the carbonyl group, it is natural that only the acetyl side ismethoxy lated.

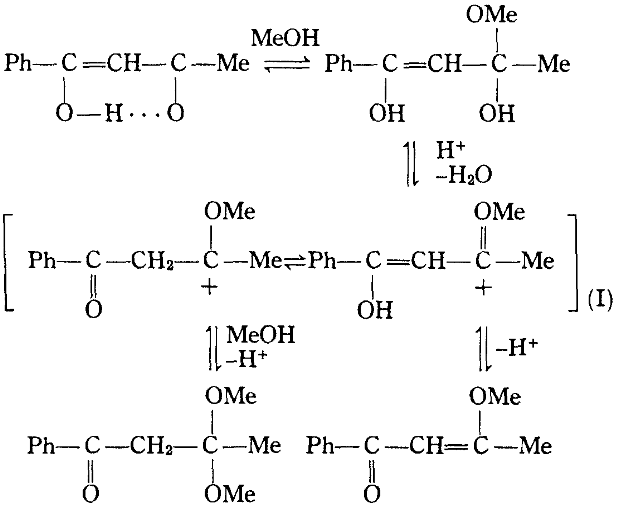


Chart 1

The relationship between A'E and AK is shown in Chart 1. The carbonium ion of the keto-enol tautomer, (I), was assumed to be involved. When it is considered that A'E and AK are formed reversibly by deprotonation from the hydroxyl group of the enol and from methanol attached to the carbonium carbon of the keto form respectively, the fact that AK is formed reversibly from A'E, which is not an intermediate of AK formation from BA, may be interpreted satisfactorily.

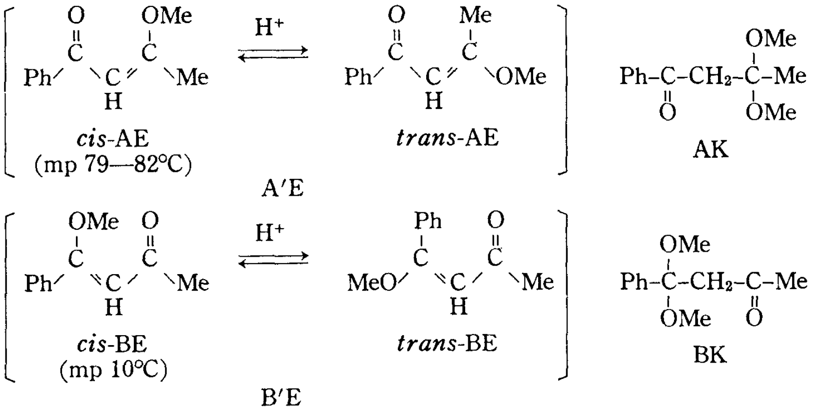
Acknowledgement The authors are indebted to Messrs. Hiromi Ozaki, Tsuyoshi Kotoh and Yoshiyuki Ikejiri for their assistance in performing these experiments.

References and Notes

1) Y. Furuya, D. Morikawa, and K. Itoho, *Bull. Chem. Soc. Jpn.*, **40**, 1425 (1967).
2) Y. Furuya, I. Urasaki, K. Itoho, and S. Miyazaki, *Bull. Chem. Soc. Jpn.*, **42**, 1769 (1969).

3) Y. Furuya, I. Urasaki, K. Itoho, and A. Takashima, *Bull. Chem. Soc. Jpn.*, **42**, 1922 (1969).
4) H. Adkins, W. Kutz, and D. Coffman, *J. Am. Chem. Soc.*, **52**, 3212 (1930).
5) For example, G. Büchi, D. Minster, and J.C.F. Young, *J. Am. Chem. Soc.*, **93**, 4319 (1971).
6) L. Claisen, *Ann.*, **291**, 51 (1896).

7) Constitutional formulae of the ethers and the acetals and their relationship.[8]



A′E: a mixture of *cis*- and *trans*-AE in equilibrium, an oily mixture.
B′E: a mixture of *cis*- and *trans*-BE in equilibrium, an oily mixture.

8) B. Eistert and E. Merkel, *Chem. Ber.*, **86**, 895 (1953).
9) Y. Furuya, Y. Kosugi, K. Itoho, H. Ozaki, and M. Hirano, *Yakugaku Zasshi*, **101**, 791 (1981).
10) J.U. Lowe, Jr., and L.N. Ferguson, *J. Org. Chem.*, **30**, 3001 (1965).