CROATICA CHEMICA ACTA CCACCA 57 (3) 331—337 (1984)

YU ISSN 0011-1643
UDC 347,546
CCA-1448 Original Scientific Paper

Solvolysis Rate of 3-Methyl-2-(3-pentynyl)-2-cyclohexenyl *p*-Nitrobenzoate. A Model System for π-Participation of the CC Triple Bond

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Received December 19, 1983

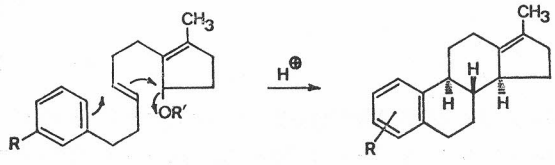
The synthesis of 3-methyl-2-(3-pentynyl)-2-cyclohexenyl *p*-nitrobenzoate is described. This ester solvolyzes in 97% CF_3CH_2OH at 25 °C without π-participation of the CC triple bond, showing solvolysis rate retardation in comparison with the saturated analog. This result is explained by electron-withdrawing inductive effect of the CC triple bond. The log k values of alkanyl- (*4*), alkenyl- (*5, 6*), and alkynyl-substituted (*10*) esters show good linear correlation with the pK_a values of the corresponding carboxylic acids.

INTRODUCTION

Cationic polyene cyclizations were extensively investigated during the last two decades and biomimetic syntheses of various terpene- and steroid-like compounds were developed[1]. However, the question of mechanism of these reactions is still open to debate. It is not certain whether two or more rings are formed in a concerted manner or whether the polycyclization is a stepwise process proceeding through one or more partially cyclized intermediates. According to Johnson,[1a] at present time the balance is somewhat in favor of the former, while some cogent arguments in favor of the latter have been presented by van Tamelen.[2] There are very few examples where either the concerted[3,4] or the stepwise[5] nature of these reactions has been unequivocally demonstrated.

Allylic cations have been extensively used as initiators in biomimetic olefinic polycyclizations.[1a] Thus acid catalyzed heterolysis of the C—OR' bond in *1* leads to estrone derivative *2*. Since the rate of formation of *2* from *1* depends[3] upon the nature of the substituent R, it appears that this reaction proceeds by way of extended π-participation, i.e. the formation

of both new rings is concerted with the breaking of the C—OR' bond. In this particular case an allyl cation is not formed in the rate determining step as a discrete intermediate.



1 2

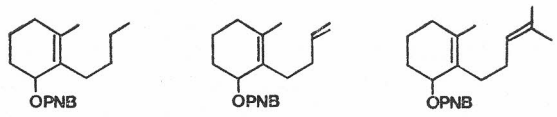
This remarkable observation led us to an investigation of possible π-participation in the model system *3* which resembles *1* in that the cyclization initiator is a potential endocyclic allyl cation. This resemblance appears clearly if formula *1* is drawn as in *1a*.

3 1a

a, R = D, R' = H
b, R = CD_3, R' = CH_3

R'' = $-CH_2CH_2$

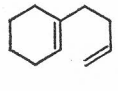
Acid catalyzed cyclization of *3* yielded products with an even distribution of the deuterium label between the two allylic positions.[6] It was concluded that here cyclization occurs after the rate determining formation of an allylic cation intermediate. In continuation of this work, we recently reported[7] on rates and α-deuterium kinetic isotope effects (KIE) in solvolyses of *p*-nitrobenzoates *4*—*6*.



4 5 6

The rates of *5* and *6* were reduced with respect to that of the reference compound *4* both in 80% *v/v* aqueous ethanol and in 97% *w/w* aqueous 2,2,2-trifluoroethanol although extensive cyclization occured in most cases. In accordance with these results secondary α-deuterium KIE measured with *5* and *6* were very similar in magnitude to those obtained with *4* and near the maximum value. Thus both, relative rates and KIE, unambiguously prove that π-electrons of the alkenylic side chain do not participate in the rate determining step of the investigated solvolytic reactions and that resonance-stabilized allylic cations are formed as first intermediates.

It seemed puzzling that no simple π-participation occurs in cationic reactions of *3*, *5* and *6* while extended π-participation is observed in an analogous reaction with *1*. The behavior of 2-alkenylcyclohex-2-enyl derivatives seems even more peculiar in view of the fact that acid catalyzed cyclization of *7*[8] and epoxide ring opening with *8*[2] as well as the solvolysis od *9*[9] all occur with π-participation.



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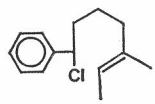

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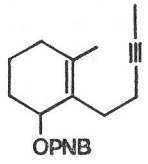
Therefore further investigation of cationic reactions with substrates related to *3*, *5* and *6* seemed warranted. Herewith we report solvolysis rate of 3-methyl-2-(3-pentynyl)-2-cyclohexenyl *p*-nitrobenzoate *10*.



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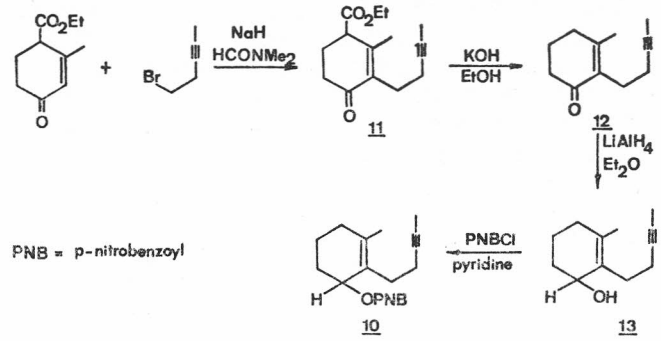
Substituted acetylenic groups have been used as terminators in biomimetic olefinic polycyclizations so as to form directly the five-membered D ring of steroid precursors.[1a,b,10,11] It was observed that the stereoselectivity of the C/D ring junction was less pronounced with acetylenic than with the corresponding olefinic terminators.[10,11] Smaller steric requirements of the former relative to the latter group was mentioned as a possible explanation of this observation. Another factor which was considered is a difference in the angle of attack on the sp^1 vs. sp^2 carbon by the cationic center.[11,12] These observations led us to the belief that *10* might behave differently upon solvolysis than the olefinic counterparts *3*, *5* and *6*. It also seemed reasonable to consider the possibility of π-participation with *10* since it was shown that the tendency of the triple bond to participate slightly exceeded that of the double bond in solvolyses of 6-heptyn-2-yl and 6-octyn-2-yl tosylates and their olefinic analogues.[13] It was also shown that triple and double bonds show a similar nucleophilic activity towards vinyl cations.[14] The nucleophilicity of a CC triple bond towards external electrophiles may be as high as or higher than that of a double bond. In these reactions relative rates of pairs of equally substituted olefins and acetylenes, k_o/k_a, have been reported to range from 10^8 to 10^{-2}, depending mainly on the nature of the electrophilic reagent but also on the structure of the unsaturated substrates and, in some cases, on the solvent.[15]

RESULTS AND DISCUSSION

The ester *10* was synthesized by appropriate modifications[7] of standard procedures,[16,17] according to Scheme I.



Scheme I.

Ester *10* was solvolyzed in 97% *w/w* aqueous 2,2,2-trifluoroethanol (TFE) at 25.00 ± 0.05 °C. The clear first-order kinetic behavior was observed and the following rate constant was determined (the uncertainty is the standard deviation of the mean):

$$k = (7.27 \pm 0.02) \times 10^{-4}\ s^{-1}$$

In Figure 1 the rate constants of solvolysis of esters *4*—*6*,[7] and *10* are compared with the pK_a values of carboxylic acids *14*,[18] *15*,[19] *16*,[19] and *17*.[20]

R—CH_2CO_2H
14, R = CH_2CH_3
15, R = CH = CH_2
16, R = CH = CMe_2
17, R = C ≡ C—CH_3

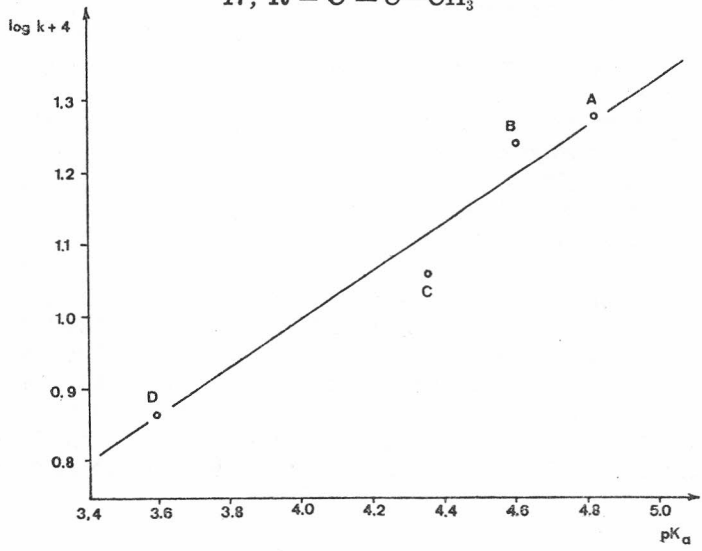
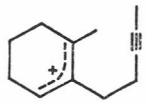


Figure 1. Plot of log *k* values for solvolysis of esters *4* (A), *5* (C), *6* (B) and *10* (D) in 97% *w/w* CF_3CH_2OH at 25 °C against ionization constants of acids *14* (A), *15* (C), *16* (B) and *17* (D).

Our result shows that the solvolysis of ester *10* is slower than the solvolysis of 2-butyl-substituted ester *4*, and also than the solvolysis of 2-alkenylic esters *5* and *6*. This result can be explained in general by electron-withdrawing inductive effect of a CC triple bond in ester *10*, which is even stronger than inductive effects of alkenylic bonds in side chain of esters *5* and *6*. These inductive effects of 2-alkenyl and 2-alkynyl substituents in esters *5*, *6* and *10* can be compared with the inductive influence of the same substituents on pK_a values of carboxylic acids *15*—*17* (Figure 1.). The plot (log $k + 4$) vs. pK_a shows satisfactory linear correlation (the correlation coefficient is 0.977).



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The obtained rate constant of ester *10* is in keeping with the proposed stepwise mechanism of solvolysis, according to which the π-participation is not revealed in this reaction, and the resonance-stabilized allylic cation *18* is the first formed intermediate.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer 167 spectrometer. ^1H NMR spectra were recorded on a Varian T-60 instrument. All commercial reagents were ACS reagent grade.

3-Methyl-2-(3-pentynyl)-2-cyclohexen-1-one (12)

Ethyl 2-methyl-4-keto-2-cyclohexenecarboxylate[21] (3.72 g; 20.41 mmol) was added dropwise to a cold (0 °C) suspension of NaH (490 mg; 20.42 mmol) in 17 ml of *N,N*-dimethylformamide. The resulting mixture was stirred and heated (60 °C) in nitrogen atmosphere over a 12-h period. The mixture was then cooled to 0 °C, 5-bromo-2-pentyne[22] (3.00 g; 20.41 mmol) was added and the resulting mixture was stirred and heated (90 °C) in nitrogen atmosphere over a 12-h period. The reaction mixture was then diluted with water and extracted with diethyl ether (3 × 20 ml). The combined etheral layers were dried with anhydrous Na_2SO_4 and the solvent was removed on a Büchi rotary evaporator to give the crude alkylated ketoester *11* (5.13 g) which was used in further synthesis without additional purfication.

Alkylated ketoester *11* (5.13 g) was added to a solution of KOH (2.14 g; 38.1 mmol) in anhydrous ethanol (15 ml). Reaction mixture was stirred and refluxed in nitrogen atmosphere over a 20-h period. After evaporation of solvent, the residual dark oil was diluted with water and extracted with diethyl ether (3 × 20 ml). The combined etheral layers were dried with anhydrous Na_2SO_4 and the solvent was removed on a Büchi rotary evaporator. The residual crude ketone was purified by column chromatography on silica gel, using mixture benzene--diethyl ether 8 : 2 as the eluent. This procedure gave ketone *12* (1.32 g; 36.7%) which was homogenous on thin-layer chromatography. IR (neat, NaCl) : 6.01 μm (C=O). ^1H—NMR (CCl_4, internal Me_4Si) δ 1.74 (3H, s, C ≡ C—CH_3), 1.70 (3H, s, C=C—CH_3).

3-Methyl-2-(3-pentynyl)-2-cyclohexen-1-ol (13)

The solution of ketone *12* (163 mg; 0.925 mmol) in anhydrous diethyl-ether (3 ml) was added dropwise to the suspension of $LiAlH_4$ (185 mg; 4.87 mmol) in anhydrous diethyl ether (8 ml). The reaction mixture was stirred 2 h at room temperature. After that, 3 ml of water was added, etheral layer was separated and the residual slurry was extracted with diethyl ether (3 × 10 ml). The combined etheral layers were dried with anhydrous Na_2SO_4 and ether was evaporated to give alcohol *13* (154 mg; 93.4%) which was homogenous on thin-layer chromatography. IR (neat, NaCl): 2.98 μm (O—H). ^{1}H—NMR (CCl_4, internal Me_4Si) δ 3.93 (1H, br.s., O—C—H), 3.06 (1H, br.s., OH), 1.71 (3H, s, C ≡ C—CH_3), 1.65 (3H, s, C = C—CH_3), 0.60—2.43 (10 H, absorption of residual protons).

3-Methyl-2-(3-pentynyl)-2-cyclohexen-1-yl p-*nitrobenzoate* (10)

Solution of alcohol *13* (126 mg; 0.707 mmol) and *p*-nitrobenzoyl chloride (550 mg; 2.96 mmol) in anhydrous pyridine (8 ml) was stirred for 3 days at room temperature. The mixture was then poured on ice and extracted with pentane (5 × 10 ml). The combined pentane extracts were dried with anhydrous Na_2SO_4, solvent was evaporated and the residual crude product was purified on a silica gel column using mixture pentane-benzene 9 : 1 as the eluent. The yellow oily crystals of ester *10* were obtained (207 mg; 89.5%). This product was homogenous on a thin-layer chromatography. IR (neat, NaCl): 5.81 (CO—O—C), 6.21 (C=C), 6.52 and 7.41 (NO_2), 9.03 (C—O) and 13.79 μm (Ar—H). ^{1}H—NMR (CCl_4, internal Me_4Si) δ 8.14 (4H, s, $C_6H_4NO_2$-p), 5.56 (1H, br.s., O—C—H), 1.79 (3H, s, C ≡ C—CH_3), 1.68 (3H, s, C=C—CH_3), 0.70—2.45 (10 H, absorption of residual protons).

Kinetic Measurements

The titrimetric rates were obtained using the automatic potentiometric titration method by means of a Radiometer, Copenhagen, automatic titrator TTT2 with autoburette ABU11 and titrigraph SBR3. The substrate concentration was 6—7 mg in 15 ml of solvent. The solution for titration was 0.02 M NaOH in 97% TFE. Seven solvolyses of ester *10* were performed and the rate constant was calculated using a nonlinear least-square sum-fitting program.

Acknowledgment. — We are grateful to Professor Michael Hanack from the University of Tübingen for a gift of 3-pentyn-1-ol.

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SAŽETAK

Brzina solvolize 3-metil-2-(3-pentinil)-2-cikloheksenil-*p*-nitrobenzoata. Modelni sistem za π-participaciju trostruke veze CC

M. Ladika, S. Borčić i D. E. Sunko

Opisana je sinteza 3-metil-2-(3-pentinil)-2-cikloheksenil-*p*-nitrobenzoata. Taj ester solvolizira u 97%-tnom CF_3CH_2OH pri 25 °C bez π-participacije trostruke veze CC i pokazuje usporenje solvolize u usporedbi sa zasićenim analogom. Taj rezultat objašnjen je elektron-izvlačećim induktivnim efektom trostruke veze CC. Pokazalo se da su vrijednosti log k za alkanil- (*4*), alkenil- (*5,6*) i alkinil-supstituirane (*10*) estere u dobrom linearnom odnosu s pK_a-vrijednostima odgovarajućih karboksilnih kiselina.