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Preliminary Communication

Allylic Cations in Solvolysis. A Case of Non-Participation

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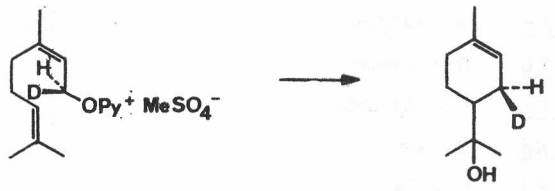
The rate constants and secondary deuterium isotope effects are measured in the solvolysis of various allylic p-nitrobenzoates. The obtained results are explained by differences in inductive effects of various groups in the side-chain. These results are in keeping with the stepwise mechanism according to which neighboring group π- and n-participation is not revealed in the studied solvolytic reactions.

The question of mechanism of stereospecific cationic polyene cyclizations, whether enyzmatic or biomimetic, is still open to debate. There has been very little direct evidence obtained till now for deciding between the »stepwise« and the »synchronous« mechanism, but according to Johnson, »at the present time the balance is somewhat in favor of the latter«.[1]

The especially interesting question is the concertedness of biomimetic cyclizations of allylic substrates, where the possible stepwise mechanism should include the highly stabilized allylic cation. A concerted mechanism offers an attractive rationale for the complete inversion of configuration at chiral centre in the cyclization of optically active, specifically deuterated neryl derivative (I).[2] It was also shown[3] that cationic cyclizations are concerted if the allylic cation is sufficiently destabilized, for example, by fluorinated substituents.



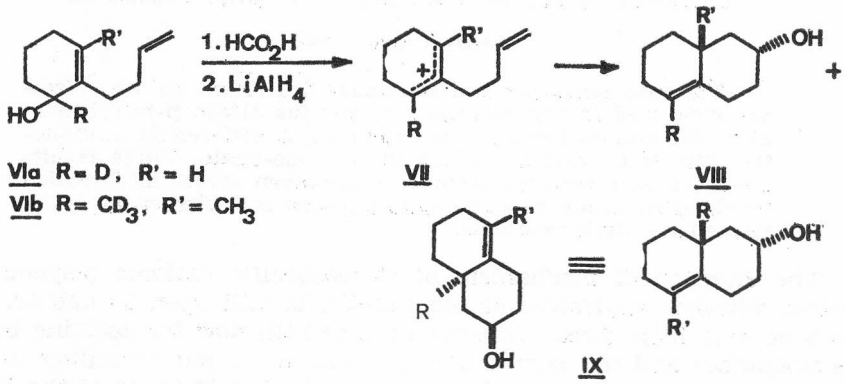
I II

On the other hand, Johnson proposed[4] the stepwise mechanism of the cyclization of 2-butenyl-Δ^2-cyclohexenol (III), where the allylic cation (IV) should be the reaction intermediate.

III IV V

However, this cyclization could also be considered[4] as a concerted process which gives the same stereoisomer V.

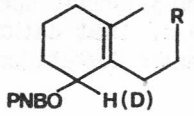
Our previous results[5] proved that in the intramolecular cationic π-cyclization reactions of deuterium-labeled 2-butenyl-Δ^2-cyclohexenol derivatives (VI), the resonance-stabilized allylic cation (VII) is the first formed intermediate, resulting in a mixture of equal parts of isomeric products VIII and IX.

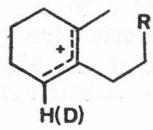


VIa R = D, R' = H
VIb R = CD_3, R' = CH_3

VII VIII IX

In this work we studied the solvolysis of various esters Xa — Xe under the mild, non-acidic conditions, in order to investigate the possible effect of π- and n-participation of the side chain on the kinetic data.





XI

Xa R = CH_2CH_3
Xb R = $CH{=}CH_2$
Xc R = $CH{=}CMe_2$
Xd R = OMe
Xe R = SMe

PNB = p-nitrobenzoyl

The required esters Xa — Xe were obtained from the corresponding alcohols, which were prepared in a straight-forward manner.[6,7] Solvolyses of esters Xa — Xe were accomplished in 80% v/v aqueous EtOH at 50 °C

and 97% w/w aqueous 2,2,2-trifluoroethanol at 25 °C. Results are summarized in Table I.[8]

TABLE I

Relative Rate Constants and Deuterium Isotope Effects in the Solvolysis of Δ^2-Cyclohexenyl p-Nitrobenzoates

Compd.	80% EtOH; 50 °C		97% TFE; 25 °C	
	k_{rel}[a]	k_H/k_D[b]	k_{rel}[a]	k_H/k_D[b]
Xa	1.000[c]	1.19±0.02	1.000[d]	1.190±0.008
Xb	0.847	1.19±0.01	0.607	1.204±0.005
Xc	0.833	1.17±0.01	0.925	1.218±0.006
Xd	0.792	1.18±0.01	0.126	1.218±0.009
Xe	0.711		0.499	

[a]The values correspond to undeuterated compounds.
[b]Uncertainties are standard errors.
[c]$k = (2.94 \pm 0.04) \times 10^{-4} s^{-1}$
[d]$k = (1.879 \pm 0.006) \times 10^{-3} s^{-1}$

The obtained differences in reaction rate constants (Table I) of the compounds Xa — Xe are small, showing that the structural changes in the chain substituted at C-2 centre of such allylic substrates do not have a large influence on the rate of ionization in the rate-determining step.[9] In the series of substrates Xa — Xe, ester Xa with the butyl substituent at C-2 shows the largest rate of solvolysis in both solvents (80% EtOH and 97% TFE). The retarding effect of various substituents at C-2 in the solvolysis of esters Xb — Xe shows that π-electrons of the alkenylic chains in esters Xb and Xc, as well as n-electrons of oxygen and sulfur in the side-chain of esters Xd and Xe do not observably participate in the rate-determining step of the investigated solvolytic reactions. This retarding effect can be explained in general by differences in inductive effects of various groups in the chain.

The rates of solvolysis of esters Xb and Xc are reduced in relation to the solvolysis of ester Xa by the π-electron withdrawal inductive effect of alkenylic groups at C-2. In the case of esters Xd and Xe with the methoxy and methylthio groups in the side chain at C-2, the solvolysis rates are even more decreased relative to the solvolysis of ester Xa, due to the large electron-withdrawal inductive effects of oxygen and sulfur.[10] The extent of the rate-retardation in the solvolysis of esters Xb — Xe depends on the solvent. Solvolyses of these esters in 97% TFE include the formation of the corresponding cations XI, due to the large ionization power and low nucleophilicity of this solvent.[11] Substituents at C-2 have influence on the stability and rate of formation of these cations. Solvolyses of esters Xb — Xe in 80% EtOH involve the stronger participation of solvent in the rate-determining step[12] compared with the solvolyses in 97% TFE, resulting in lower percentage of bicyclic products[8] and smaller extent of rate-retardations.

The obtained normal values of secondary α-deuterium isotope effects[13] for esters Xa — Xd (1.17—1.19 in 80% EtOH and 1.19—1.22 in 97% TFE) are also in keeping with the proposed mechanism, according to which neighboring group n- and π-participation is not revealed in these solvolytic reactions.

The reported results should also be discussed in terms of quasi-aromaticity and Hückel's $(4n + 2)e^-$ rule. This discussion will be published in a full paper.

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SAŽETAK

Alilni kationi u solvolizi. Primjer izostanka participacije

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Izmjerene su brzine reakcija i sekundarni deuterijski izotopni efekti pri solvolizi niza alilnih *p*-nitrobenzoata. Dobiveni rezultati objašnjeni su razlikama u induktivnim efektima skupina u postraničnom lancu. Ti su rezultati u skladu sa stupnjevitim mehanizmom prema kojemu u proučavanima solvolitičkim reakcijama ne dolazi do π- ili n-participacije susjedne skupine.

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Novel Syntheses of Thiazolo[3,2-a]pyrimidin-7-ones

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The silver acetate-iodine oxidation of 1-allyl-2-thiouracil (I) in refluxing acetic acid proceeded to 2-methyl-7H-thiazolo-[3,2-a]pyrimidin-7-one (II) *via* a series of intramolecular transformations.

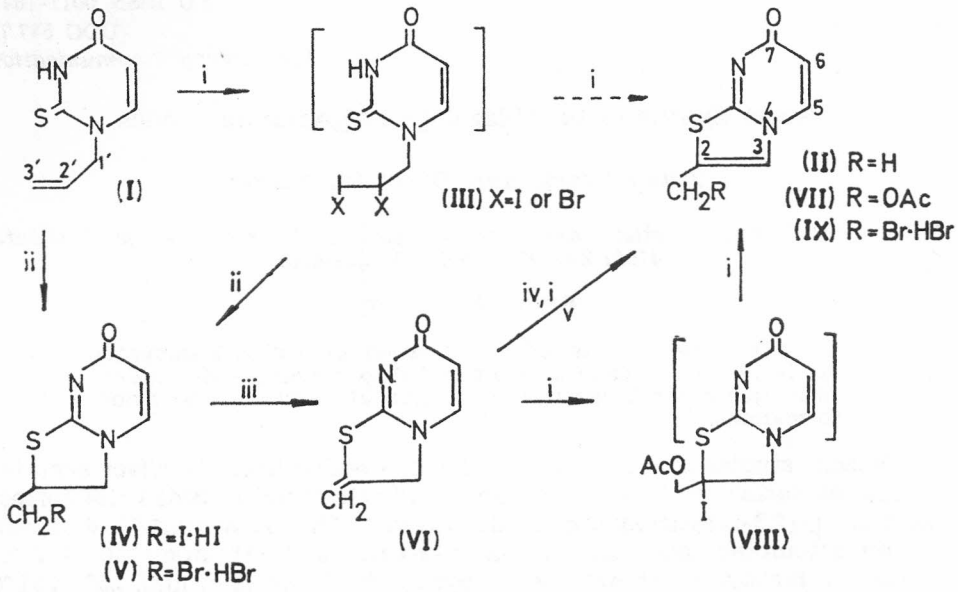
Recent studies in our laboratory have revealed that the silver acetate--iodine oxidation[1] of 1-allyluracil and 1-allylthymine[2] afforded the corresponding 1-(2,3-dihydroxypropyl) derivatives. This is strikingly different for an attempted oxidation of 1-allyl-2-thiouracil (I), m.p. 136—137 °C, yielding 2-methyl-7H-thiazolo[3,2-a]pyrimidin-7-one (II), m.p. 250—251 °C (73%), C(3)-proton at δ 6.96(s) and C(2)-methyl resonances at δ 2.34(s) with secondary splitting (J 1.2 Hz). The thio-analogue I was prepared from 2-thiouracil by silyl method in reaction with allyl bromide and acetonitrile as solvent.[3] The synthesis of II appeared to proceed *via* thiazolo-ring formation, and then by a dehydroiodination and double bond migration. To understand better the structural requirements for this intramolecular transformation, we examined the chemistry of the possible intermediates.

The iodination of 1-allyl-2-thiouracil (I) in methylene chloride gave 2-iodomethyl-2,3-dihydro-7H-thiazolo[3,2-a]pyrimidine-7-one, hydroiodide (IV), m.p. 186—187 °C (79%), most likely by an internal nucleophilic attack of the C(2) thioxo group[4] at the C(2') rather than at the C(3') position of the intermediary 2',3'-iodonium ion. For the comparative experiments the bromination of 1-allyl-2-thiouracil (I) in methylene chloride afforded 2-bromomethyl-2,3-dihydro-7H-thiazolo-[3,2-a]pyrimidin-7-one, hydrobromide (V), m.p. 215—216 °C, in nearly quantitative yield. The ^{1}H-NMR spectra of IV and V are in good accordance with those of the analogous structures in uracil[5] and thymine[6] series.

The availability of the bicyclic 2-halomethyl compounds IV and V made feasible the synthesis of 2-methylene-3H,7H-thiazolo[3,2-a]pyrimidine-7-one (VI) up to 69% yields, using bases (KOH—EtOH or NaOMe—MeOH) as reagents. The ^{1}H-NMR spectrum evidenced the structure of thus isolated intermediate VI, m.p. 271—273 °C, by the characteristic triplets with allylic coupling (J 2.1 Hz) at δ 5.38 and 4.93 attributed to

the C(2)-methylene protons, as well as by the triplet at δ 4.28 (J 2.1 Hz) for the C(3)-protons.

The isomerization of the intermediary 2-methylene compound VI to



Reagents: *i*, AgOAc-I_2-99% HOAc; *ii*, I_2- or Br_2-CH_2Cl_2; *iii*, 0.1 mol dm^{-3} KOH--EtOH or 0.1 mol dm^{-3} NaOMe-MeOH; *iv*, AgOAc-HBr-HOAc; *v*, Br_2-CH_2Cl_2.

the more stable and fully aromatic 2-methyl isomer II was successfully achieved (in 75% yield) by a treatment with equimolar amounts of hydrobromic acid and silver acetate[7] in refluxing acetic acid. It is interesting that the addition of hydrobromic acid was decisive for the isomerization of VI into II. The conversion of 2-methylene compound VI into 2-acetoxymethyl-7H-thiazolo[3,2-a]pyrimidin-7-one (VII), m.p. 193—195 °C (64%), with silver acetate-iodine, however, in refluxing acetic acid indicated the intermediacy of 2-iodo-2-acetoxymethyl product (VIII) in good accordance with the Woodward's oxidation procedure.[1] It is worth noting that the bromination of the 2-methylene compound VI in methylene chloride afforded 2-bromomethyl-7H-thiazolo-[3,2-a]pyrimidin-7-one, hydrobromide (IX), m.p. 259—262 °C (92%). The ^{1}H-NMR spectra of VII, and IX showed the characteristics of the aromatic thiazolo[3,2-a]pyrimidin--7-ones causing marked downfield shifts of the respective C(3) protons resonances to δ 7.46(s) and 7.85(s).

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SAŽETAK

Nova sinteza tiazolo[3,2-a]pirimidin-7-ona

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Oksidacijom 1-alil-2-tiouracila (I) sa srebro-acetat-jodom u kipućoj octenoj kiselini dobije se 2-metil-7H-tiazolo[3,2a]-pirimidin-7-on (II) nizom intramolekularnih pretvorba.