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INTRAMOLECULAR CYCLIC ETHER FORMATION VERSUS β-FRAGMENTATION IN THE REACTION OF SATURATED ALIPHATIC ALCOHOLS WITH LEAD TETRAACETATE[1]

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Abstract—In the reaction of lead tetraacetate with saturated aliphatic alcohols containing an alkyl chain long enough to participate in the cyclization process, it was found that intramolecular tetrahydrofuran formation decreases and β-fragmentation increases in the order: primary alcohol—secondary alcohol—tertiary alcohol, and also in the order: β-unsubstituted alcohol—β-monomethyl substituted alcohol—β,β-dimethyl substituted alcohol. These results are discussed in terms of structural factors (steric and polar effects) which control the rate of the two competing homolytic processes in the intermediate alkoxy radicals, i.e. 1,5-hydrogen transfer from the δ-carbon to the hydroxyl oxygen leading to cyclic ether products and cleavage of the αC—βC bond leading to fragmentation products.

INTRAMOLECULAR cyclization involving hydrogen abstraction from a δ-carbon (and much less readily from a ε-carbon) with formation of a C—O bond (Scheme 1) and fragmentation involving bond cleavage between the α-carbinol carbon and β-carbon (Scheme 1) are two (of more) reactions which may occur when monohydric alcohols (I) are treated with lead tetraacetate in refluxing benzene;[2–5] both these processes, according to evidence available so far,[2a, 3–8] proceed, in the first stages, by homolytic decomposition of the initially formed alkoxy–lead(IV)-acetate (II)† and *via* a common transition state with alkoxy radical character (III) and/or a more or less fully developed alkoxy radical (IV), which subsequently collapses either to cyclic ether products (in the majority of cases to tetrahydrofurans VII) or β-fragmentation products, i.e. an aldehyde or ketone VI and a carbon radical fragment V (this latter fragment affording usually an acetate VIII or/and an olefin IX),[2–8, 10–12]‡ and quite frequently to both,[2–8, 10, 12, 13] in dependence on structural features of the substrate.

Although factors which control the rates of these two processes have been discussed in the case of geometrically more or less fixed reacting centers (particularly in lead tetraacetate reactions of steroid alcohols and cycloalkanols),[2, 5, 7, 8, 10–13] they have

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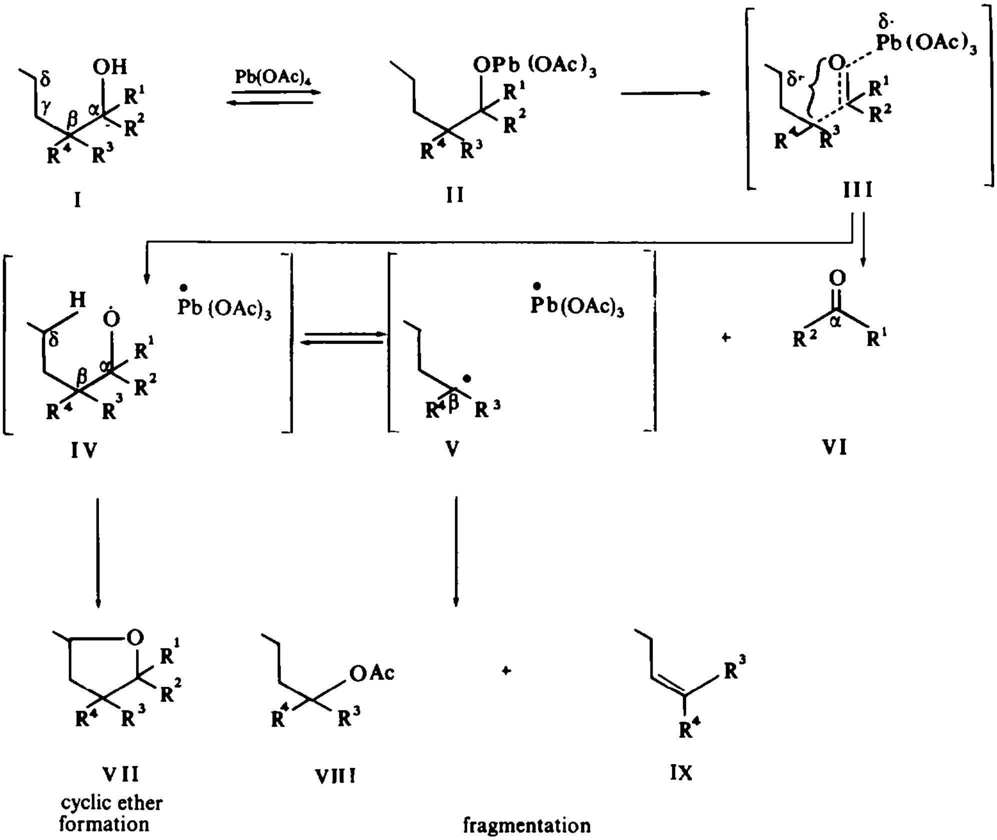
† If, similarly to lead(IV)-acylates (e.g. lead 4$^{\oplus}$-tetraacetate), alkoxy-lead(IV)-acetates [such as II or of the more genelar type $(RO)_nPb(OAc)_{4-n}$] are predominantly ionic with a salt-like character,[8, 9] then the term "homolytic decomposition" means an one-electron transfer from the alkoxide anion ($RO^{\ominus}$) to $Pb4^{\oplus}$.

‡ Other fragmentation products derived from the carbon radical (V) have also been reported, such as saturated,[10] dimeric[5] and cyclic compounds.[13]



SCHEME 1

not been investigated in much detail in reactions of lead tetraacetate with saturated open-chain hydroxyl-containing flexible systems.[2–6, 14] For that reason we have now studied the action of lead tetraacetate on various β-unbranched and β-branched primary, secondary and tertiary alkanols (I), with the purpose of determining the influence of structure on the outcome of the competition between intramolecular cyclic ether formation and β-fragmentation.

Oxidations were performed in refluxing benzene, by using a 1·1–1·5:1 molar ratio of lead tetraacetate to alcohol (until complete consumption of the oxidant). Yields of reaction products are based on gas-chromatographic analyses.

In order to compare similar systems and to eliminate errors due to statistical possibilities, the carbinols used as substrates (I) had only one alkyl-group which could participate in intramolecular cyclization; this alkyl-rest had always a straight chain of four C-atoms, so that in the formation of tetrahydrofuran ethers a C—H bond of the δ-methylene group was involved (this group being more reactive than a δ-methyl group[3]), whereas the formation of 6-membered tetrahydropyran ethers, which is usually much less favoured than tetrahydrofuran formation,[3, 15] was negligible, since it necessitated attack on a C—H bond of the considerably less reactive terminal ε-methyl group.[3, 15] The other substitutents on the α-carbinol carbon (I, R^1 and R^2)

or/and on the β-carbon of the longer (four carbon) alkyl-chain (I, R^3 and R^4), when present, were always Me-groups.

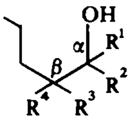
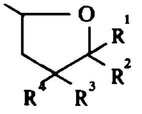
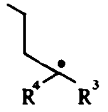
The results are presented in Table 1. In addition to the cyclization and fragmentation products shown in the Table, primary and secondary alcohols gave always the corresponding aldehydes (and also further oxidation products, such as α-acetoxy aldehydes, acids, etc.) and ketones (and α-acetoxy ketones) in 3–12% yield (which are preferentially formed by heterolytic decomposition of the alkoxy–lead(IV)-acetate II and only to a minor extent from the alkoxy radical IV),[3, 4, 6–8, 15–17] and in all experiments starting alcohol, the corresponding acetate and formate were isolated in yields ranging from 10–46%, 10–24% and 1–4%, respectively.

From runs 1, 2 and 3, and 4, 6 and 7, respectively, it is evident that as one increases the number of alkyl substituents on the α-carbinol carbon, i.e. as one goes from the primary (I, $R^1 = R^2 = H$) to the secondary (I, $R^1 = CH_3$, $R^2 = H$) and to the tertiary (I, $R^1 = R^2 = CH_3$) aliphatic alcohol, and although the longer alkyl carbon radical fragment (V) formed by homolytic cleavage of the αC—βC bond does not change, intramolecular ether formation (VII) decreases and the amount of β-fragmentation (reflected in the yield of the acetate VIII) increases. This change in the ratio of cyclization to fragmentation in favour of the latter process may be due, in part, to the facts (a) that the introduction of one and two methyl substituents on the α-carbinol carbon atom should retard sterically to a certain extent the alkoxy radical (IV) of attaining a conformation in which the attacking hydroxylic oxygen and the δ-C—H bond being attacked are close enough for hydrogen transfer from δ-carbon to oxygen through a cyclic six-membered transition state,[2a, 3, 5] and (b) that these same methyl groups (R^1 and R^2), by their electron releasing (+I) inductive effect, will increase electron density on the oxygen of the alkoxy radical (IV), thus diminishing its "electrophilic" properties as hydrogen abstracting agent;[3] these two factors should, therefore, slow down intramolecular cyclic ether formation (VII) in the order: primary alcohol—secondary alcohol—tertiary alcohol. On the other hand, the ease of β-fragmentation is enhanced by the introduction of one and two methyl groups (R^1 and R^2) on the α-carbinol carbon, because the stability of the carbonyl fragment (VI) increases in the order: formaldehyde (from primary alkyl–carbinol) < acetaldehyde (from secondary alkyl–methyl–carbinol) < acetone (from tertiary alkyl–dimethyl–carbinol).

It should be noted that tertiary alcohols (runs 3 and 7) react very slowly with lead tetraacetate and that a considerable amount of unchanged starting alcohol was recovered after the reaction (over 40%). This is probably due to the fact that crowding around the hydroxyl group hinders the approach of lead tetraacetate to the distance necessary for the formation of the initial product, i.e. alkoxy–lead(IV)-acetate (II).

If one keeps structural features on the α-carbinol carbon unchanged and increases branching on the β-carbon atom by introducing methyl substituents on the four carbon atom alkyl rest of the starting carbinol (I, R^1 and R^2 = H or Me, R^3 or R^3 and R^4 = Me), then again one observes (runs 1, 4 and 5, and 2, 6 and 8, respectively) a decrease in cyclic ether formation (VII) and an increase in the yield of β-fragmentation products (V, i.e. its acetate VIII) as one goes from the β-unbranched (I, $R^3 = R^4 = H$) to the β-monomethyl-substituted (I, $R^3 = Me$, $R^4 = H$) and to the β,β-dimethyl-substituted alcohol (I, $R^3 = R^4 = Me$). This situation may be rationalized, on one hand, by assuming that steric hindrance to intramolecular 1,5-hydrogen transfer (leading to tetrahydrofurans) increases in the same order and therefore

TABLE 1. CYCLIZATION AND β-FRAGMENTATION PRODUCTS IN THE REACTION OF LEAD TETRAACETATE WITH β-UNBRANCHED, β-MONO-METHYL AND β,β-DIMETHYL SUBSTITUTED PRIMARY, SECONDARY AND TERTIARY SATURATED ALIPHATIC ALCOHOLS (IN BENZENE AT 80°)

Run	Alcohol	Products[a] (yields in %)[b]	
		Cyclization	Fragmentation[c]
	 I	 VII	 V
1	$R^1 = R^2 = H; R^3 = R^4 = H$ (primary; β-unbranched)	43–45	0
2	$R^1 = CH_3; R^2 = H; R^3 = R^4 = H$ (secondary; β-unbranched)	41[d]	~1[e]
3	$R^1 = R^2 = CH_3; R^3 = R^4 = H$ (tertiary; β-unbranched)	10[f]	7[g,h] (+0·4)[i]
4	$R^1 = R^2 = H; R^3 = CH_3, R^4 = H$ (primary; β-monobranched)	36[j]	10
5	$R^1 = R^2 = H; R^3 = R^4 = CH_3$ (primary; β,β-dibranched)	17	19
6	$R^1 = CH_3, R^2 = H; R^3 = CH_3, R^4 = H$[k] (secondary; β-monobranched)	21[l]	13[m]
7	$R^1 = R^2 = CH_3; R^3 = CH_3; R^4 = H$ (tertiary; β-monobranched)	4	16[n,o]
8	$R^1 = CH_3, R^2 = H; R^3 = R^4 = CH_3$ (secondary; β,β-dibranched)	6	22

[a] See Scheme 1.

[b] Yields calculated from gas-chromatographic analyses and based on the total amount of alcohol introduced in the reaction mixture.

[c] When not otherwise stated the yield of β-fragmentation was based on the acetate (VIII, Scheme 1) corresponding to the initially formed carbon alkyl radical (V).

[d] Mixture of *cis*- and *trans*-2,5-dimethyltetrahydrofurans, in a ratio of 40:60.[3,18]

[e] Mixture of 1-butyl acetate and 2-butyl acetate.[3]

[f] For the same $Pb(OAc)_4$ reaction Greene *et al.* have reported a 3% yield of 2,2,5-trimethyltetrahydrofuran (VII).[19]

[g] Consisting of 1-butyl acetate, 2-butyl acetate and a mixture of 1- and 2-butylbenzene, in yields of 2·5, 2·5 and 2%, respectively.

[h] About 45% of unreacted starting alcohol and 20% of the corresponding acetate were isolated.

[i] This yield corresponds to another fragmentation product, i.e butyl methyl ketone, resulting from β-scission of a methyl radical.

[j] Mixture of *cis*- and *trans*-2,4-dimethyltetrahydrofurans (the ratio of these geometrical isomers was 60:40, but the configurations were not assigned).

[k] Probably mixture of both diastereoisomers.

[l] Mixture of all four possible *cis-trans* isomers (configurations not assigned).

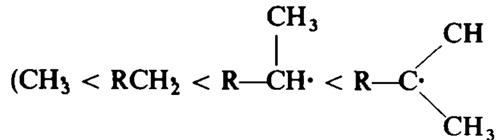
[m] Consisting of about 10% of 2-pentyl acetate and 3% of the dimeric product, 4,5-didimethylene

[n] Consisting of about 12% of 2-pentyl acetate, 2% of the dimeric product, i.e. 4,5-dimethyloctane, and 2% of 2-pentylbenzene.

[o] About 40% of unreacted starting alcohol and 18% of the corresponding acetate were isolated from the reaction mixture.

retards somewhat cyclic ether formation (but this steric interference, according to models, should not be very serious); however, on the other hand, it appears that in this case increase in the ease of β-fragmentation is the predominant factor which determines the ratio of cyclic ether products to β-cleavage products, this increase being controlled by the stability of the carbon alkyl radical fragment (V), which, as is well known, follows the order: primary < secondary < tertiary.[19–22] [*]

In the case of secondary (I, R^1 = Me) and tertiary carbinols (I, $R^1 = R^2$ = Me) with an unbranched butyl chain (runs 2 and 3, respectively) two competitive β-fragmentation reactions may occur, one between the α-carbinol carbon and the butyl carbon affording a primary $CH_3CH_2CH_2CH_2\cdot$ radical and acetaldehyde (from the secondary alcohol) or acetone (from the tertiary alcohol), and the other between the α-carbinol carbon and the Me carbon giving rise to a Me radical ($CH_3\cdot$) and valeraldehyde (from the secondary alcohol) or butyl methyl ketone (from the tertiary alcohol). In the case of the secondary alcohol (run 2) fragmentation with formation of a methyl radical was not observed (probably because of the relative instability of the aldehyde fragment and lesser relief of steric strain), but in the case of the tertiary alcohol (run 3) such a bond cleavage between the α-carbinol carbon and the Me β-carbon was found to occur, although to a much smaller extent (0·4% yield) than the β-fragmentation involving the generation of the 1-butyl radical (7% yield).

The results reported above for the ease of β-fragmentation in the lead tetraacetate reaction of saturated aliphatic alcohols parallel those obtained previously by other authors for the β-fission of alkoxy radicals generated by various methods, i.e. the rate of β-fragmentation increases, in the first place, with increasing stability of the carbon alkyl radical fragment (V)  $(CH_3 < RCH_2 < R\text{—}\overset{\overset{CH_3}{|}}{C}H\cdot < R\text{—}\overset{CH}{\underset{CH_3}{C}}\cdot)$, but the stability of the carbonyl fragment (VI) is also of considerable importance.[19–24] [†] However, the ratio of 1,5-hydrogen transfer (leading to tetrahydrofurans VII in the case of the lead tetraacetate reaction) to β-fragmentation in the intermediate alkoxy radical (of type IV) appears to be somewhat dependent on the way by and on the conditions under which this radical is generated and further converted to products, and may differ from one type of reaction to another.[19,22,23] [‡]

It should be noted that the isolation of 4,5-dimethyloctane in runs 6 and 7 (which is

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[*] Possibly relief of steric compression which results from cleavage of the αC—βC bond has also some influence on the ease of the β-fragmentation process, particularly in the case of heavily α- and β-substituted carbinols (e.g. run 8).

[†] Mosher *et al.*[25] have shown that in the lead tetraacetate reaction of t-butylmethylcarbinol, $(CH_3)_3C\text{—}CHOH\text{—}CH_3$ (an alcohol which cannot give cyclic tetrahydrofuran-type ether products from the corresponding alkoxy radical), β-fragmentation may occur to a considerable extent, in dependence on reaction conditions; however, it is difficult to compare the results of these authors with our data, because their experiments were not carried out in benzene (but in acetic acid, acetic acid–acetone, and in nitrobenzene) and the product yields are based on reacted alcohol (except in one case, the amounts of recovered alcohol are not stated).

[‡] Our results are also in general agreement with those obtained in the lead tetraacetate reactions of various steroid and other cyclic alcohols.[2,5,7,8,10–13,26,27]

the dimerization product of the secondary alkyl radical V),* represents further support for the β-fragmentation process indeed proceeding through a transition state with alkoxy radical character (III) or/and an alkoxy radical of type IV.†

EXPERIMENTAL

B.ps are uncorrected. Gas chromatography: Perkin–Elmer instrument, Model 116-E, equipped with a thermistor detector; the columns (2 m × 4 mm, 8 m × 8 mm) consisted of 1,2,3-tris(2-cyano-ethoxy)-propane adsorbed on Chromosorb P (40%), polyethylene glycol 1500 adsorbed on Celite (25–30%) or Apiezon L adsorbed on Celite (30–40%); the temp of the columns (80–110°), the sensitivity of the detector and the press and the flow rate of the carrier gas (dry H_2) were adjusted according to the fractions which were analysed. IR spectra: Perkin–Elmer Infracord, Models 137B and 337. NMR spectra: Varian A-60A spectrometer.

The preparation of lead tetraacetate, drying of the reagents and the lead tetraacetate oxidations in benzene were carried out as described previously.[3] The reactions were performed under reflux at 80°, usually using 0·1 mole of alcohol, 0·11–0·15 mole of $Pb(OAc)_4$, 0·11–0·15 mole of and $CaCO_3$, and 130–150 ml dry benzene. The neutral products from the benzene–ether extract (neutral part),[3] upon separation by distillation and gas chromatography, were characterized and identified on the basis of their elemental analyses (when necessary) and physical properties (characteristic bands in the IR and NMR spectra, retention times, mass spectra, refractive indices), which were compared, when possible, with those of authentic compounds synthesized by independent routes. These products were in most cases already reported and described in the literature. The acid components (further oxidation products of aldehydes) were isolated from the $NaHCO_3$-washings (acid part),[3] upon acidification and ether extraction. The yields of products were calculated from gas-chromatograms (planimetrically) and are based on the total amount of starting alcohol (used and recovered, i.e. introduced into the mixture before the reaction). All the starting alcohols were known compounds, either available commercially or prepared by conventional procedures.

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* A similar dimeric product resulting from β-fragmentation with ring opening was isolated in the lead tetraacetate reaction of cyclobutanol.[5]

† In the case of β,β-dimethyl-substituted alcohols (runs 5 and 8) similar dimerization products could not be detected, possibly because the initially formed carbon alkyl radical fragment (V) is tertiary and therefore is further oxidized at a much faster rate to the corresponding carbonium ion than a primary or secondary alkyl radical.[3]

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