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NUCLEOPHILIC CHARACTER OF ALKYL RADICALS GENERATED IN REDOX PROCESSES—I

REACTIVITY OF THE 5-(METHOXYCARBONYL)-PENTYL RADICAL TOWARDS CONJUGATED OLEFINS

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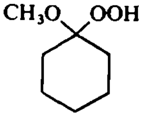
Abstract—New syntheses of polyfunctional long-chain compounds were performed by alternating free radical additions of 5-(methoxycarbonyl)-pentyl radical to pairs of conjugated olefins. Copolymerization was avoided by a metal salt redox system, which selectively oxidizes the radicals involved. Quantitative data of relative reactivities towards α-methylstyrene, acrylic acid, methyl acrylate, acrylonitrile and maleic anhydride emphasize the nucleophilic character of the 5-(methoxycarbonyl)-pentyl radical. Theoretical and synthetic aspects are discussed.

IN A preliminary communication[1] we have briefly reported new synthetic possibilities connected with the nucleophilic character of alkyl radicals generated in redox processes. Two reactions are especially significant: the alternating addition to conjugated olefins and the alkylation of protonated heteroaromatic bases, in which orientation and reactivity are particularly indicative of the influence of the polar character of the alkyl radicals.

A readily available alkyl radical is the 5-(methoxycarbonyl)-pentyl radical (R·), which is also useful for synthetic purposes of practical interest:[2] it is obtained by reduction with Fe^{2+} or Cu^{+} salts of 1-methoxy-cyclohexylhydroperoxide (from cyclohexanone and hydrogen peroxide in methanol)[3].



$$+ \mathrm{Fe}^{2} \rightarrow \mathrm{CH_3OCO{-}(CH_2)_4{-}CH_2\cdot} + \mathrm{FeOH}^{2}+ \qquad \text{(a)}$$

I

The addition of the radical I to conjugated olefins in the presence of metal salts redox systems was studied by Minisci *et al.*[4] and by Kochi and Rust,[5] who reported that this radical exhibits electrophilic properties in that it adds relatively slowly to olefins possessing electron-withdrawing groups, such as acrylonitrile, in comparison with butadiene or styrene. Our results qualitatively indicated an opposite sequence of reactivity, that is higher reactivity with olefins conjugated with strongly electron-withdrawing groups according to the nucleophilic character of the alkyl radical. Both our own and Kochi and Rust's methods were indirect, based on the total yields of adduct products by adding the 5-(methoxycarbonyl)-pentyl radical to the respective olefin in the presence of a redox system under standard conditions. The validity of the method was based on the fact that there is an alternative route by which the radical I can also react, i.e. its oxidation by the metal salt. This method, qualitatively valid, was not rigorous from a quantative point of view, especially since it was not always possible to avoid formation of telomers with olefins conjugated with strongly electron-withdrawing groups. In the belief of the correctness of our results, we have

$$I + M^{2+} \rightarrow \text{products} + M^{+} \qquad M^{+} = Cu^{+} \text{ or } Fe^{2+}$$

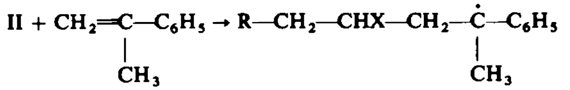
accomplished new reactions, which combine a synthetic interest with the possibility of a more rigorous determination of the affinity of the radical I towards conjugated olefins. In this, the first paper, we report the results obtained when the radical I is generated in the presence of two conjugated olefins, one of which is always α-methylstyrene and the other one is in turn acrylic acid, methyl acrylate, acrylonitrile and maleic anhydride.

The theoretical aspects which underlie these new reactions are the following: (1) The radical I, owing to its nucleophilic character and according to our previous views,[4] is more reactive towards olefins conjugated with strongly electron-withdrawing groups (COOH, $COOCH_3$, CN) than with α-methylstyrene, so that it adds to the former olefins preferentially:

$$R\cdot + CH_2{=}CH{-}X \rightarrow R{-}CH_2{-}\dot{C}H{-}X \qquad X = COOH, COOCH_3, CN \qquad \text{(b)}$$

II

(2) The polar character of the new carbon free radical II is greatly modified by the neighbouring electron-withdrawing groups: further addition takes place exclusively on the α-methylstyrene:

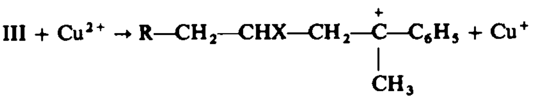


$$II + CH_2{=}\underset{CH_3}{\underset{|}{C}}{-}C_6H_5 \rightarrow R{-}CH_2{-}CHX{-}CH_2{-}\underset{CH_3}{\underset{|}{\dot{C}}}{-}C_6H_5 \qquad \text{(c)}$$

III

This interaction is one of the elementary steps characteristic of the well known alternating effect in radical copolymerizations.

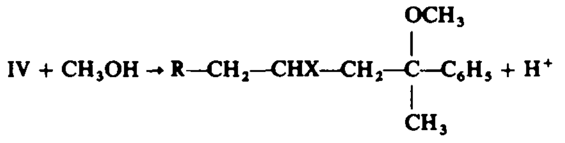
(3) The easy oxidation by Cu^{2+} of the radicals I, II and III follows the sequence III > I > II and can be roughly correlated with the respective ionization potentials.[7] Thus, at low Cu^{2+} concentrations, the radical II is practically unoxidized, I only to a small extent, and III is quantitatively oxidized:



$$III + Cu^{2+} \rightarrow R{-}CH_2{-}CHX{-}CH_2{-}\underset{CH_3}{\underset{|}{\overset{+}{C}}}{-}C_6H_5 + Cu^{+} \qquad \text{(d)}$$

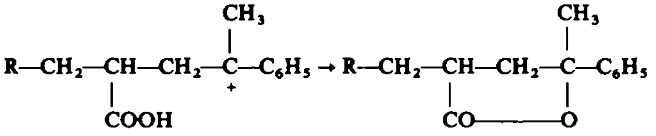
IV

The reaction product arises from inter or intra-molecular interaction of the benzylic cation with the nucleophilic species present in solution:



$$IV + CH_3OH \rightarrow R{-}CH_2{-}CHX{-}CH_2{-}\underset{\displaystyle CH_3}{\overset{\displaystyle OCH_3}{C}}{-}C_6H_5 + H^+$$

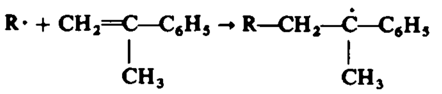
V



$$R{-}CH_2{-}\underset{\displaystyle COOH}{CH}{-}CH_2{-}\underset{+}{\overset{\displaystyle CH_3}{C}}{-}C_6H_5 \rightarrow R{-}CH_2{-}\underset{\displaystyle CO}{CH}{-}CH_2{-}\underset{\displaystyle O}{\overset{\displaystyle CH_3}{C}}{-}C_6H_5$$

VI

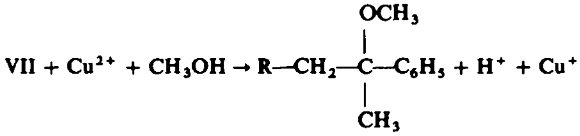
The possibility of obtaining quantitative determinations of the affinity of the radical I to conjugated olefins is due to the fact that this radical also adds although to a smaller extent to α-methylstyrene:



$$R\cdot + CH_2{=}\underset{\displaystyle CH_3}{C}{-}C_6H_5 \rightarrow R{-}CH_2{-}\underset{\displaystyle CH_3}{\dot{C}}{-}C_6H_5 \qquad (e)$$

VII

and the resulting radical is quantitatively oxidized by Cu^{2+}



$$VII + Cu^{2+} + CH_3OH \rightarrow R{-}CH_2{-}\underset{\displaystyle CH_3}{\overset{\displaystyle OCH_3}{C}}{-}C_6H_5 + H^+ + Cu^+$$

VIII

The amount of VIII in some cases is very small, but it can be increased by increasing the concentration of α-methylstyrene. The V or VI to VIII ratios give the relative reactivities of the radical I towards the pair of olefins. The reaction medium must be homogeneous and an excess of olefins must be used in order to minimize the error for the changes of concentration during the reaction course.

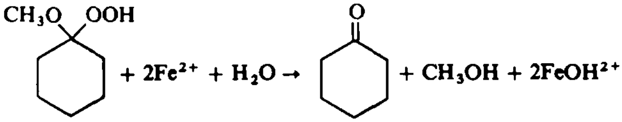
RESULTS

The choice of α-methylstyrene instead of styrene was due to the fact that the oxidation of the benzylic radical arising from the former is cleaner: a lower ionization potential and steric factors contribute to this behaviour. The reaction with styrene is still interesting from a synthetic point of view, since the results are analogous, but it is less suitable for quantitative determinations because some telomers are always formed. The reaction is carried out by adding a methanolic ferrous sulphate solution to the solution of the peroxide, the pair of olefins and cupric sulphate in methanol.

The cupric salt is effective in catalytic amount: the cuprous salt formed according to (d) is continuously oxidized by the ferric salt formed in (a):

$$Cu^{+} + Fe^{3+} \rightarrow Cu^{2+} + Fe^{2+} \qquad (f)$$

The required amount of ferrous salt according to (a), (b), (c), (d) and (f) should be catalytic: it is a redox chain in which the ferrous salt is consumed in (a) and regenerated in (f). Actually more than the catalytic amount of ferrous sulphate is consumed, since the hydroperoxide is not isolated as a pure compound, but a methanolic solution of cyclohexanone and hydrogen peroxide is used; moreover some reduction of hydroperoxide to cyclohexanone takes place:



In practice an excess of ferrous sulphate is always used to avoid the presence of traces of peroxide at the end of the reaction. An excess of olefins is also used: 8 moles/mole of peroxide; this excess is limited by the solubility of the α-methylstyrene in methanol.

The reaction products, analysed by GLC are: two racemates of V or VI, VIII and a small amount of oxidation product of the radical I, mainly methyl-5-hexenoate.

$$I + Cu^{2+} \rightarrow CH_3OCO{-}(CH_2)_3{-}CH{=}CH_2 + Cu^{+} + H^{+} \qquad (g)$$

The yield, based on hydrogen peroxide, of V or VI is connected with the reactivity of the olefins: it is high (75%) with maleic anhydride, the most reactive olefin, and then gradually decreases with the decreasing reactivity of the olefins, owing to the side reactions (e) and (g). Experiments at different olefin concentrations were carried out to verify the quantitative data or to find the best conditions for synthetic purposes. The results with acrylonitrile and α-methylstyrene, at three different concentrations, are summarized in Table 1. In this case, in V, X = CN; both racemates are formed.

TABLE 1

Molar ratio Acrylonitrile:α-methylstyrene	% VIII	% V	Relative reactivity
3:1	2·5	97·5	10·8
1:1	7	93	11·1
1:3	18·8	81·2	10·8

The results with acrylic acid and α-methylstyrene are shown in Table 2: in this case only the intramolecular process takes place yielding the γ-lactone VI.

TABLE 2

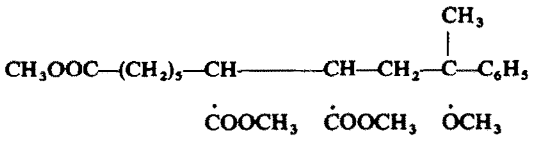
Molar ratio Acrylic acid : α-methylstyrene	% VIII	% VI	Relative reactivity
3:1	13	87	1·9
1:1	27	73	2·4
1:3	54·9	45·1	2·1

The results with methyl acrylate and α-methylstyrene are reported in Table 3; in this case the intramolecular process is in competition with the intermolecular one and both V and VI, in which $X = COOCH_3$, are formed.

TABLE 3

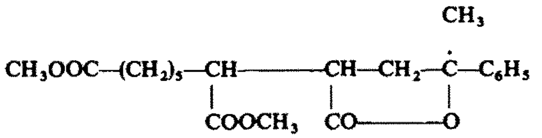
Molar ratio Methyl acrylate : α-methylstyrene	% VIII	% V + VI	Relative reactivity
1:1	12·8	87·2	5·6
1:3	32	68	5·3

In Table 4 the results with maleic anhydride and α-methylstyrene are presented. Only the 1:3 ratio was investigated, since higher ratios lead to very small amounts of VIII and consequently to higher analytical errors, whereas still lower ratios do not work in homogeneous medium. Obviously in this case the products are not V or VI but IX and X:



$$CH_3OOC{-}(CH_2)_5{-}\underset{COOCH_3}{CH}{-}\underset{COOCH_3}{CH}{-}CH_2{-}\overset{CH_3}{\underset{OCH_3}{C}}{-}C_6H_5$$

IX



$$CH_3OOC{-}(CH_2)_5{-}\underset{COOCH_3}{CH}{-}\underset{CO}{CH}{-}CH_2{-}\overset{CH_3}{\underset{O}{C}}{-}C_6H_5$$

X

TABLE 4

Molar ratio Maleic anhydride : α-methylstyrene	% VIII	% IX	% X	Relative reactivity
1:3	9·2	88·3	2·5	19·3

In Table 5 the relative reactivities of the different olefins are summarized.

TABLE 5. RELATIVE REACTIVITY OF THE OLEFINS TOWARDS I

α-Methylstyrene	1
Acrylic acid	2·15 ± 0·25
Methyl acrylate	5·4 + 0·2
Acrylonitrile	11 ± 0·2
Maleic anhydride	19·3

DISCUSSION

The results reported in the above Tables clearly point out that the four olefins conjugated with electron-withdrawing groups are all more reactive than α-methylstyrene. Initial concentration of the two olefins being equal, the product of alternating addition always prevails; moreover, at suitable olefin ratios, the formation of VIII can be minimized: this is interesting from a synthetic point of view, since the preparation of a series of new product can be performed from trivial starting materials.

Resonance stabilization, steric and polar effects usually contribute to the overall reactivity in the radical addition to unsaturated systems. In the case in point, we think that steric effects do not affect the reactivity sequence we observe with the radical I. Although it is difficult to clearly separate resonance stabilization effects from polar ones, it can be maintained that the resonance energy of the α-cyano- or α-carboxyalkyl radicals II cannot be as high as that of the benzylic radical arising from α-methylstyrene. Consequently the nucleophilic character of I does determine the reactivity sequence. Additionally for a correlation of the observed data with the polar characteristics of the substituents on the olefins, it would be necessary to separate the resonance stabilization from the merely polar effects. In Table 6, however, relative reactivities are compared with some polar characteristics of the substituents, that is the σ_p and σ_p^+ constants, the parameters e of the "Q–e scheme" and the α constants of the "Patterns of Free Radical Reactivity" concerning the radical copolymerization.

TABLE 6

Substituent	$\sigma_p{}^9$	$\sigma_p^{+\,10}$	e^{11a}	α^{11b}	Relative reactivity
—COOH	+0·406	+0·421	0·77	−3·0	2·1
—COOCH$_3$	+0·385	+0·489	0·60	−3·0	5·4
—CN	+0·660	+0·659	1·20	−3·0	11
Maleic anhydride			2·25	−4·5	19·3

The σ_p^+ values give the best agreement, i.e. the same sequence as the relative reactivities. On the whole it is clear however that the reactivity increases with the increasing electron-withdrawing power of the substituents on the olefins.

Another aspect pointed out by these new syntheses is the different oxidation rate of the radicals I, II and III: it can be roughly correlated with the ionization potentials of the radicals in the gas phase.[6] Thus, ionization potentials of the α-cyanoethyl, ethyl and benzyl radicals are 9·76, 8·78[7] and 7·76[8] eV respectively. Similar radicals are involved, e.g. in the reaction with acrylonitrile and the oxidation rate increases with decreasing ionization potentials. This correlation can be only approximate chiefly because the oxidation mechanism of carbon radicals of different structure can hardly be the same in every case. Thus, while the formation of ethers V and lactone VI can be explained by oxidation of the radical III to the corresponding cation by simple electron-transfer, the oxidation of the radical II, observed[6] to some extent, with X = CN, cannot occur by an equally simple mechanism. Complexation phenomena between radicals and metal salts, or formation of real organometallic compounds may play an important part. Steric effects may also possibly contribute to the quantitative oxidation of radical III (besides its low ionization potential, certainly lower than for the benzylic one), they decrease the addition rate of the tertiary radical to olefins, while affecting to a lesser degree the oxidation by the copper salt.

A further interesting aspect of these syntheses is the intramolecular reactivity, observed when X is a carboxy- or carboxymethyl-group, leading to γ-lactones. The intramolecular reactivity is completely selective in the case of acrylic acid: this selectivity, even in such a nucleophilic solvent as methanol, may be expressed by the statement that the intramolecular COOH has a very high effective concentration. Also striking is the fact that in the case of methyl acrylate the intramolecular nucleophilic attack on the benzylic cation competes with the intermolecular process. Actually it is not surprising that γ-lactone is formed by the interaction of a carboxyl group with a benzylic cation, however, it is unusual that the same interaction takes place with a carbomethoxy group. On the other hand both the results in the relative reactivities and the recovery of the excess methyl acrylate would exclude its partial saponification and therefore again the intervention of the acrylic acid in the formation of the lactone.

Analogous results have been achieved by using butadiene or isoprene instead of α-methylstyrene and different redox sources of alkyl radicals, such as oxaziridines and ferrous salts, acylperoxides and cuprous salts, alkanoic acids and lead tetraacetate, thus noticeably enlarging the synthetic possibilities. The quantitative results of these processes will be published in future papers.

EXPERIMENTAL

General procedure

Ten g of 34% hydrogen peroxide was added to 19·6 g cyclohexanone while maintaining the temperature below 40°. After 1 hr at room temperature the mixture was dissolved in 150 ml of methanol containing 20 ml of concentrated sulfuric acid. The solution was cooled at 0° and the pair of olefins (in the ratios indicated in Tables 1–4; 8 moles of olefins: 1 mole of hydrogen peroxide) and 5 g cupric sulfate pentahydrate in 150 ml of methanol were added. A solution of 28 g of ferrous sulfate heptahydrate in 100 ml of methanol was added dropwise with stirring and nitrogen flushing at 0° over a period of 40 min. The solution was then stirred for an additional 30 min and poured into water; the aqueous solution was extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate solution and dried over sodium sulfate. After removal of the solvent and the excess of the olefins and cyclohexanone, the residue was directly analysed by GLC, except in the case of maleic anhydride. In this case the ethereal solution was not washed with sodium bicarbonate, but, after removal of the solvent, the esterification of a sample of the residue was completed with diazomethane before GLC. Yields of the crude mixture V or VI + VIII, based on the hydrogen peroxide, were in the range 50–80%.

Quantitative GLC

Instrument: Carlo Erba Fractovap Model G/V, equipped with a flame ionization detector and a 2 m × 0·4 cm i.d. Pyrex column, packed with silanized Chrom. W. 60/80 mesh and 1% SE-30 silicon grease as the stationary phase. Column temperature: 190°. Carrier gas: helium at a flow rate of 25 ml/min.

Preparative GLC

Instrument: Varian Aerograph Model 90 P with a thermoconductivity detector. 5 ft × ¼ in i.d. column, packed with Chrom. W-DMCS 60/80 mesh and 20% SE-30 silicon grease as the stationary phase. Column temperature: 220°. Carrier gas: helium at a flow rate of 60 ml/min.

Products

The compound VIII was prepared in an experiment in which the sole olefin was α-methylstyrene. It was a colourless mobile oil, b.p. 106–108°/1 mm. (Found: C, 73·12; H, 9·36. $C_{17}H_{26}O_3$ requires: C, 73·34; H, 9·41.) Saponification equiv.: 279 mol. wt.: 278 (mass spectrum). Formula wt.: 278.

Reaction with acrylonitrile (*Table* 1)

Three products were present and isolated by preparative GLC. The product with lowest retention time was VIII (identical retention time, IR and mass spectra). The other two, Va and Vb, have the same elementary composition (Va, Found: C, 72·13; H, 8·84; N, 4·56. Vb, Found: C, 72·28; H, 8·71; N, 4·32. $C_{20}H_{29}O_3N$ requires: C, 72·47; H, 8·82; N, 4·23).

IR and mass spectra of Va and Vb were substantially identical. IR peaks at 2250 cm^{-1} (CN), 1735 cm^{-1} ($COOCH_3$). MS: Molecular ion, M_{331} (formula wt. 331). Significative ions were: 316 (M—CH_3), 300 (M—OCH_3), 135 (C_6H_5—$\overset{+}{C}(CH_3)$—OCH_3) and 105 (benzoyl ion). The pure samples were used to check the quantitative response of GLC.

Reaction with acrylic acid (*Table* 2)

VI and VIII were present and were isolated by preparative GLC. VI (Found: C, 71·36; H, 8·43. $C_{19}H_{26}O_4$ requires: C, 71·67; H, 8·23). IR peaks at 1780 cm^{-1} (γ-lactone), 1735 cm^{-1} ($COOCH_3$). MS: *m/e* (%): 318(1), 303(10), 300(3), 271(10), 105(100). 318 is the molecular ion; 303 (M—CH_3); 300 (M—H_2O); 271 (303 —CH_3OH). Base peak at *m/e* 105 corresponded to benzoyl ion. The corresponding acid–lactone, obtained from alkaline hydrolysis melted at 83–84° (ethyl acetate). (Found: C, 71·29; H, 7·95. $C_{18}H_{24}O_4$ requires: C, 71·02; H, 7·95). Acid equiv.: found at 20°, 304; at 100°, 150. calc.: 304 and 152.

Reaction with methyl acrylate (*Table* 3)

The chromatogram shows the presence of VIII and several products which were not separated but calculated as a whole. IR, mass spectra and saponification equiv. of these last products indicate a mixture of V in which X = $COOCH_3$, and VI. The same acid–lactone, m.p. 83–84°, obtained with acrylic acid, was qualitatively isolated from the saponified mixture.

Reaction with maleic anhydride (*Table* 4)

VIII, IX (a mixture of various isomers) and X were isolated by preparative GLC. The various isomers of structure IX were not separated by GLC. The mixture was directly analysed. (Found: C, 65·15; H, 8·26. $C_{23}H_{34}O_7$ requires: C, 65·38; H, 8·11). Significant mass peaks at 358 (M—2CH_3OH), 326 (M—3CH_3OH), 135 (C_6H_5—$\overset{+}{C}(CH_3)OCH_3$) and 105 (benzoyl ion). The saponification of the isomer mixture of structure IX yields a mixture of tricarboxylic acids. Acid equiv.: Found: 130; calc.: 127. A pure isomer, m.p. 181°, was isolated by crystallization from methanol. (Found: C, 63·49; H, 7·49. $C_{20}H_{28}O_7$ requires: C, 63·14; H, 7·42). Acid equiv.: Found: 129; calc.: 128. X was present in very small amounts and was characterized by the IR spectrum (1780 cm^{-1}, γ-lactone).

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