146. *The Inhibiting Effect of Chain-lengthening on Aldehyde Reactivity in the Perkin Reaction.*

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The lower aliphatic ethers of *o*-, *m*-, and *p*-hydroxybenzaldehyde undergo the Perkin reaction readily. As the chain-length of the alkyl group increases the yield of substituted cinnamic acid at first remains constant, then decreases abruptly at the point at which the end of the chain can reach the carbonyl group. This exemplifies the " rule of six."

NEWMAN[1] formulated a " rule of six " to correlate the abrupt change in reactions and properties which occurs in many carbonyl compounds with increase in chain length. The sixth atom from the carbonyl-oxygen interacts in an unspecified fashion with the carbonyl group owing to chain-coiling. Examples in ascending homologous series are the sudden increase in strength at butyric acid,[2, 3] variation in esterification and hydrolysis rates of fatty acids and their esters,[4] changes in optical rotation,[5] and movement of reaction sites in aliphatic ketones.[6] The Perkin reaction of lower aliphatic aldehydes with sodium *p*-nitrophenylacetate and acetic anhydride[7] succeeds only with lower members:[8] the inertness of the higher homologues is a further example of the rule of six. Coiling is also responsible for the inertness of citral *b*, but reactivity of citral *a*. Inertness was also found in the reaction of 2-phenyloxazol-5-one with higher aldehydes.[8] Some examples of failure of aromatic aldehydes to give the Perkin reaction are reported below.

The double bond in citral stiffens the molecule. Other molecules can be more effectively stiffened by the introduction of a benzene ring, whose *ortho*-, *meta*-, and *para*-positions can be used to secure different rigid lengths. Various alkoxybenzaldehydes have been subjected to the normal Perkin reaction, results being given in the table together with others already known.

	Yield (%) of the cinnamic acid from $RO{\cdot}C_6H_4{\cdot}CHO$		
R	*ortho*	*meta*	*para*
Me	44[a]	39[a]	30[c] 20[a]
Et	43	Reacts readily[b]	36[d]
Pr^n	3·2	12	40[d]
Bu^n	0·22	7·6	35 40[d]

	Yield (%) of the cinnamic acid from $RO{\cdot}C_6H_4{\cdot}CHO$		
R	*ortho*	*meta*	*para*
C_5H_{11}	0·16	2·1	0·1
C_6H_{13}	—	0	Trace
$C_{16}H_{33}$	—	—	Trace[d]
5-Nitro-2-pentyloxy	16	—	—

[a] Lock and Bayer, *Ber.*, 1939, **72**, 1064. [b] Werner, *Ber.*, 1895, **28**, 1997. [c] Posner, *J. prakt. Chem.*, 1910, **82**, 425. [d] Stoermer and Wodarg, *Ber.*, 1928, **61**, 2323.

In the *meta*-series the yield decreases with chain-length to zero at $R = C_6H_{13}$. The *m*-propoxy-compound is the first to be affected. In it the side-chain does not quite reach to the van der Waals touching distance from the carbonyl group, as indicated by Catalin models. *m*-Propoxybenzaldehyde may be compared to *n*-butyraldehyde which is the shortest aliphatic aldehyde to show a decrease in yield in a Perkin–Oglialoro reaction.[8] It has a " six number "[1] of 3. Newman's notation cannot, however, be used in partly rigid molecules, but the effect is the same, namely, a reduction in reactivity when the end of the chain can approach the reactive group.

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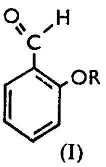
[1] Newman, " Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 206.
[2] Dippy, *J.*, 1938, 1222.
[3] Bennett and Mosses, *J.*, 1930, 2364.
[4] Newman, *J. Amer. Chem. Soc.*, 1950, **72**, 4783.
[5] Smith and McReynolds, *ibid.*, 1939, **61**, 1963.
[6] Alexander, " Principles of Ionic Organic Reactions," Wiley, New York, 1950, p. 128.
[7] Häffcke and Becker, *J. Org. Chem.*, 1951, **16**, 863.
[8] Crawford and Little, preceding papers.

In the *para*-series Stoermer and Wodarg[9] observed without comment that, whereas the lower members up to butoxy react readily to give the cinnamic acids, *p*-cetyloxybenzaldehyde gives a negligible yield. Repetition with the inclusion of some intermediate members confirms this. *p*-Pentyloxybenzaldehyde is found to be the lowest member in which a decrease of yield occurs. *p*-Hexyloxybenzaldehyde gives only a trace of product. Hence in the *para*-series the decrease in yield takes place at a higher point than in the *meta*-series, showing that the effect is not due to some inherent property of a particular chain length. It begins at that chain-length (C_5) which is almost long enough to impinge on the carbonyl group if the chain follows the shortest path that its valency angles will allow. The formyl group is assumed to remain always coplanar with the ring. In *p*-hexyloxybenzaldehyde, which is practically non-reactive, the side chain can readily reach the formyl group. The fall in yield is much sharper in this series.

In the *ortho*-series, as might be expected, complications arise. In *o*-methoxybenzaldehyde the methyl group is already in close proximity to the formyl group yet reaction takes place readily, as also with the *o*-ethoxy-compound. It is with *o*-propoxybenzaldehyde that falling off first takes place. This becomes reasonable if one assumes that in *o*-substituted benzaldehydes the formyl group occupies the reversed planar position (I) (or, much less likely, a non-planar position) owing to steric repulsion by the *ortho*-substituent. The carbonyl group can then be reached readily by an *o*-butoxy-group, almost by an *o*-propoxy-group, but not by an *o*-ethoxy-group. Yields are in keeping with this.



(I)

In all three series yields fall off appreciably as soon as the chain is long enough to reach almost to the van der Waals radius of the carbonyl oxygen atom. It is difficult to see how the chain is held in this position, especially at the temperature of the reaction ($\sim$160°) since the force holding it there is not strong enough even to twist the formyl group in *o*-ethoxybenzaldehyde out of the plane of the ring. For fatty acids Dippy[2] suggested a hydrogen bond O • • • H but this would be extremely weak. It is more likely that the side chain interferes sterically with an intermediate state such as a transition complex or the hydroxy-intermediate. There is no evidence whether the side-chain interferes with the stability or with the reactivity of the intermediate.

o-Pentyloxybenzaldehyde gives only a 0·16% yield in the Perkin reaction. Its 5-nitro-derivative gives a 16% yield which, however, is much less than that from *m*-nitrobenzaldehyde; thus reactivity is restored by activation.[8]

In Dippy's curve[2] illustrating the strengths of fatty acids, in addition to the marked increase between propionic and butyric acid, there is a sharp fall between octanoic and nonanoic acid which he did not explain (see also ref. 5). A scale model shows that in nonanoic acid the chain can continue past the C=O group until the end methyl group reaches the carboxylic hydroxyl group, a result which might perhaps affect the acid strength.

EXPERIMENTAL

Preparation of Aldehydes.—The hydroxybenzaldehyde (1 mol.), alkyl bromide (2 mol.), and potassium hydroxide (0·4 mol.) were refluxed in ethanol or, for higher alkyl bromides, *cyclo*hexanone, for 24 hr. The cold product, in ether, was extracted with potassium hydroxide solution. The ether layer, when washed, dried, and distilled under reduced pressure, gave the aldehyde. Apart from the following, which are new, the aldehydes had b. p.s in agreement with those given in the literature: *o*-Pentyloxybenzaldehyde, b. p. 167°/15 mm. [*semicarbazone*, needles (from aqueous alcohol), m. p. 178° (Found: C, 62·7; H, 7·5; N, 16·8. $C_{13}H_{19}O_2N_3$ requires C, 62·6; H, 7·7; N, 16·9%)]; with fuming nitric acid at $<10°$ it gave *5-nitro-2-pentyloxybenzaldehyde*, yellow plates (from aqueous alcohol), m. p. 44° (Found: C, 60·7; H, 6·1; N, 6·1. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·4; N, 5·9%) [*semicarbazone*, yellow needles, m. p. 221° (Found: C, 53·8; H, 6·1. $C_{13}H_{18}O_4N_4$ requires C, 53·1; H, 6·2%)]. *m*-Pentyloxybenzaldehyde, b. p. 156°/10 mm. [*semicarbazone*, needles (from aqueous alcohol), m. p. 166° (Found: C, 63·6; H, 8·0; N, 16·4. $C_{13}H_{19}O_2N_3$ requires C, 62·6; H, 7·7; N, 16·9%)].

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[9] Stoermer and Wodarg, *Ber.*, 1928, **61**, 2323.

Perkin Reaction.—The aldehyde (1 mol.), acetic anhydride (2 mol.), and sodium acetate (0·6 mol.) were heated at 160—180° for 8 hr. The acid formed was isolated in the usual way, recrystallised from aqueous acetic acid, dried, and weighed. Yields are given in the Table. Among them the following are new: o-*Butoxy-*, needles, m. p. 96° (Found: C, 71·0; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), o-*pentyloxy-*, needles, m. p. 85° (Found: C, 71·9; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%), *5-nitro-2-pentyloxy-*, needles, m. p. 145° (Found: C, 61·0; H, 6·1; N, 5·0. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%), m-*propoxy-*, plates, m. p. 135·5° (Found: C, 69·0; H, 6·2. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%), m-*butoxy-*, needles, m. p. 91·5° (Found: C, 70·7; H, 7·4%), and m-*pentyloxy-cinnamic acid*, plates, m. p. 75° (Found: C, 71·4; H, 7·7%).

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