THE METHOXYL GROUP

L. A. WILES

Chemistry Department, Royal Military College of Science, Shrivenham, Swindon, Wiltshire, England

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CONTENTS

I. Introduction

The methoxyl (—OCH_3) group is one of the commonest substituents found in natural products. It is present in most classes of alkaloids, in anthraquinones, and in flavones and related compounds. Many mould metabolic compounds and a few antibiotics (e.g., chloromycetin, erythromycin, and carbomycin) contain the methoxyl group. The structure of lignin, although still obscure, is

known to be based in great part upon phenolic units related to the methoxy compounds vanillin and syringaldehyde. Much progress has been made in the study of the biogenesis of the methyl group when it is attached to carbon, nitrogen, and sulfur, but less is known of the origins of the methoxyl group (85).

It has been shown recently that the methoxyl groups of green plant products can arise from methionine, $CH_3S(CH_2)_2CH(NH_2)COOH$, or from formate, and that the latter is the less efficient methyl donor (78, 79, 106).

It is noteworthy that the group has played a minor part in terpene and steroid chemistry, and that no vitamin—and only one carotenoid (rhodoviolascin)—is a methyl ether. Methylated carbohydrates are extremely rare in nature, but methylation as a means of protecting hydroxyl groups has been particularly useful in elucidating their structures. This protective function undoubtedly plays an important part in natural syntheses.

Some polymethoxy compounds have powerful physiological properties. Striking examples are the following: colchicine, which by its profound effect on cell division has acquired high importance in biological studies; reserpine, a valuable alkaloid in the treatment of high blood pressure and neurotic conditions; mescaline, which if eaten produces strange hallucinations; and papaverine and its analogs, which are valuable as antispasmodics.

The methoxyl group is an electron donor in many reactions, and the feature of its opposing inductive and mesomeric effects has been of great use in studying reaction mechanisms.

These various aspects of the methoxyl group have resulted in a diverse and scattered volume of knowledge. This review describes the properties of the group and, in particular, the manner in which as an ether linkage to an aromatic ring it can influence the chemical behavior of a molecule. Much that is written here will also apply to the ethoxyl group and to the lower alkoxyl homologs.

Methods of methylation and of methoxylation are not considered, and demethylation has been covered in a recent review on the cleavage of ethers (76).

II. The Electronic Effects of the Methoxyl Group

A. THE INDUCTIVE EFFECT

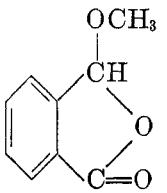
Since oxygen is more electronegative than carbon the covalency electrons in the carbon–oxygen link are permanently displaced towards the oxygen. Experimental evidence in support of this statement is the fact that methoxyacetic acid ($pK_a = 3.5$) is a stronger acid than acetic acid ($pK_a = 4.7$), and that *m*-methoxybenzoic acid ($pK_a = 4.1$) is stronger than benzoic acid ($pK_a = 4.2$). In the terminology of Ingold (171) this inductive effect of methoxyl is represented by the symbol $-I$.

The effect of the alkyl group is noteworthy. Although methyl attached to carbon is inductively a $+I$ group, methoxyacetic acid is a stronger acid than glycolic acid ($pK_a = 3.8$), so that methyl joined to oxygen is apparently oppositely polarizable and becomes a $-I$ group. The effect may, however, be due to the solvent. The hydroxyl group of glycolic acid can form a hydrogen bond

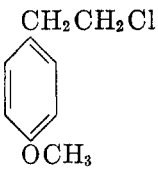
with the solvent. This will decrease the electron-repelling effect of the hydroxyl group and hence the strength of the acid. Interaction of the methoxyl group of methoxyacetic acid with the solvent is less likely.

Some comparative inductive relations are: $-F > -OCH_3 > -N(CH_3)_2 > -C(CH_3)_2$; $-OCH_3 > -SCH_3 > -SeCH_3$; $=O > -OCH_3$.

The inductive action is propagated along a chain of atoms, through space or solvent, and the effect diminishes rapidly with the distance from the source. For the methoxyl group it is sufficiently marked to affect the acid strength of *m*-methoxybenzoic acid, and to increase the infrared carbonyl stretching frequency of 3-methoxyphthalide (I) (149). Even more striking is its influence in increasing the velocity of reaction of β-(*p*-methoxyphenyl)ethyl chloride (II) with potassium iodide in acetone solution (18).



I



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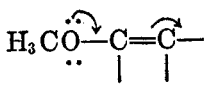
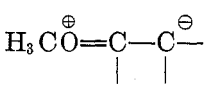
B. THE MESOMERIC EFFECT

An unshared pair of electrons on an oxygen atom may enter into some degree of conjugation with an unsaturated system, as in



This permanent electron displacement ($+M$) is the mesomeric effect. The order of electron release along the same Mendeléeff period is $-N(CH_3)_2 > -OCH_3 > -F$, while in the same group the relationship is $-OCH_3 > -SCH_3 > -SeCH_3$.

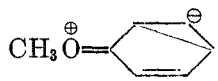
The mesomeric influence will vary according to the system to which it is attached, being called into play to a greater or less extent as the system is more or less capable of extended conjugation and consequent resonance stabilization. At the demand of a reagent the partial electromeric displacements of the mesomeric state are augmented, so that the group is then more closely represented as



This polarizability is termed the electromeric effect (E), the combined electron displacements, $M + E$, being the tautomeric (T) effect. The permanent nature of mesomerism is shown by the difference in dipole moment between dimethyl ether (1.31 D) and anisole (1.16 D).

The $+T$ effect of methoxyl is largely one of polarizability, and it operates

more powerfully at a para than at an ortho position (211); moreover at the ortho position steric effects may hamper conjugation with the nucleus. Direct transmission of the mesomeric effect to the meta position is unlikely, as it would involve the formation of high-energy structures such as III. It was sug-



III

gested that such meta-bonding explained the enhanced reactivity of *m*-methoxystyrene in its copolymerization with styrene (229), but there is no increase of the rate in the solvolysis of *m*-methoxybenzyltosylate (188) in which the same carbonium ion is involved in the transition state, and it is possible that the increased reactivity of *m*-methoxystyrene may be due to attack on the ring by the growing polymer ion. This would give a higher methoxyl content for the polymer and thus an apparent higher reactivity if the polymer were of low molecular weight (228). Support for this view is that anisole is a good molecular terminating agent (114).

C. THE COMBINED INDUCTIVE AND MESOMERIC EFFECTS

The permanent inductive and mesomeric displacements of the methoxyl group are in opposite directions ($-I$, $+M$) and in conjugated systems the $+M$ effect predominates. Where conjugation is not possible the inductive action is the more influential, as exemplified above. The infrared spectra of methyl esters (154) show a diminution of the ionic character of the carbonyl group—an effect which is explained if the inductive effect of the methoxyl group exceeds the mesomeric effect. Occasionally the results of a reaction suggest that the inductive effect has outweighed the mesomeric effect. For example, in the decomposition of diazotized *o*- and *p*-anisidines by cupric chloride in neutral and acid solutions there is a substantial replacement of the $-N_2X$ group by —Cl, indicating that a $-I$ effect is predominant and has appreciably increased

TABLE 1

Conjugation energy of a number of methoxyl and thiomethyl compounds

Compound	Conjugation Energy
	kcal./mole
Anisole	3–4*
Thioanisole	1–2*
1,4-Dimethoxynaphthalene (V)	1.2†‡
1,4-Di(methylthio)naphthalene	0.6†§
1,5-Dimethoxynaphthalene (VI)	3†‡
1,5-Di(methylthio)naphthalene	0.9†§
1,4-Di-*tert*-butyl-2,5-dimethoxybenzene (VII)	0.6†‡
1,4-Dimethoxy-2,5-dichlorobenzene	1.2†‡¶

* Uncorrected for the compression energy of the C_{aryl}—O bond.

† The value is for a single methoxyl (or thiomethyl) group and may be underestimated by 1 kcal./mole.

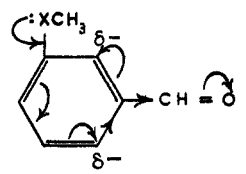
‡ For the compression energy of the C_{aryl}—O bond 2.2 kcal./mole may be added.

§ For the compression energy of the C_{aryl}—S bond 0.8 kcal./mole may be added.

¶ The values for the corresponding dibromo and diiodo compounds are the same.

the positivity of the diazonium group (160). The formation of an oxonium salt would produce such a result.

From the meta position there may be superimposed upon the $-I$ effect a second-order influence due to the inductive relay of charges arising from the $+M$ displacement (IV). Baker, Barrett, and Tweed (28) examined the cyanohydrin equilibrium with substituted benzaldehydes. The $+M$ effect will stabilize the aldehyde more, with respect to benzaldehyde, than the cyanohydrin with respect to the benzaldehyde cyanohydrin. In the meta position the substituents $—XCH_3$ (X = O, S, or Se) all destabilized the aldehyde relative to the cyanohydrin in the order O > S > Se. This order is the reverse of their $-I$ effects. The second-order $+M$ release, although not operative to produce an overall electron donation from the meta position, completely reverses the order of their weak $-I$ effects. The second-order effect is referred to again later (pages 348, 364).

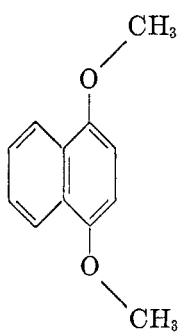


IV

D. CONJUGATION WITH AN AROMATIC NUCLEUS AND THE ORTHO EFFECT

Electric dipole moments, x-ray crystal structures, and ultraviolet spectra have given information on the bonding of the methoxyl group with an aromatic ring.

Lumbroso (205) has calculated the conjugation energy of a number of methoxyl compounds from dipole moment data. These are given in table 1 together with the values for corresponding thiomethyl compounds. The conjugation energy for anisole is in reasonable agreement with the value of 5.2 kcal./mole. for the ethoxyl group in phenetole (271). The figure of ca. 11 kcal./mole for anisole, given by Wheland (289) from the heat of combustion, is too high.



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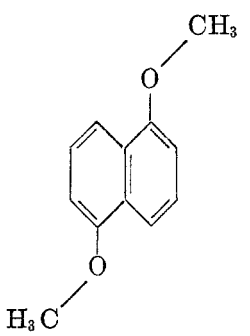
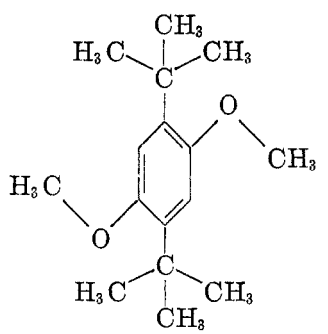


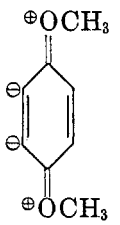
VI



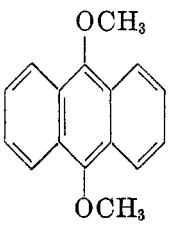
VII

The bulky *tert*-butyl groups in VII sterically hinder the methoxyl groups, and the conjugation energy is greatly reduced. The hindrance in the corre-

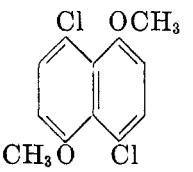
sponding halogen compounds is less. When two methoxyl groups are para to each other there is a diminution in their conjugation with the nucleus, a result to be expected since conjugation will result in negative charges on neighboring carbon atoms (VIII). The difference between the observed and calculated dipole moments of 1,2-dimethoxybenzene (93, 218) supports the same view for two ortho-situated groups. With methoxyl groups meta to each other there is excellent agreement between the measured and calculated values (185).



VIII



IX

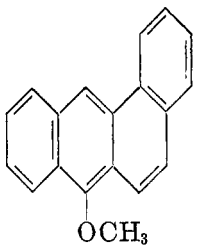


X

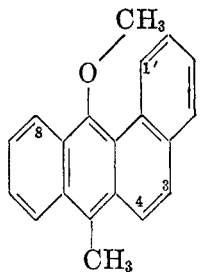
Everard and Sutton (118) have shown that the dipole moments of 1,4- and 1,5-dimethoxynaphthalene are 2.09 D and 0.67 D, respectively, while that of the analogous 1,4-dimethoxybenzene is 1.73 D. These differences are attributed to restriction of free rotation about the C_{aryl}—O bond by conjugation of the methoxyl groups with the nucleus. Moreover, molecular models of the naphthalene compounds indicate that the likely configurations (V, VI) have the methoxyl groups lying *trans* to the peri-hydrogen atoms because of steric interaction between these atoms and the methyl groups. If there are two peri-hydrogen atoms, as in 9,10-dimethoxyanthracene (IX), the methyl groups project roughly at right angles to the plane of the ring (119), while in 4,8-dichloro-1,5-dimethoxynaphthalene (X) the interference between the peri-substituents is so great that the oxygen atoms may not lie in the plane of the rings (118).

The x-ray crystal structure of 1,4-dimethoxybenzene (144) shows clearly that the methoxyl groups are conjugated with the ring. The C_{aryl}—O bond is short (1.36 Å.). It therefore has considerable double-bond character, and the methyl carbon atoms are likely to lie in the plane of the ring. The resonance energy of the compound, based on a heat of combustion determined many years ago by Stohmann, Rodatz, and Herzberg (269), is 65 kcal./mole, a value which gives a conjugation energy for the methoxyl groups of about 25 kcal./mole. This value is far higher than those quoted above, and it is perhaps significant that a number of the heats of combustion determined by Stohmann have required revision (41).

The ultraviolet spectra of 10-methoxy- and of 9-methoxy-10-methyl-1,2-benzanthracene (XI, XII) (182) have marked differences from the spectra of the corresponding hydroxyl compounds, with the inference that the methoxyl groups are sterically hindered. Molecular models reveal that whatever the orientation of the 9-methoxy group, it touches the hydrogen atoms in the 8- and 1′-positions.



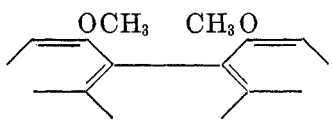
XI



XII

Burawoy and Chamberlain (71) have studied the ultraviolet absorption spectra of ortho-substituted phenols and their methyl ethers. With a single ortho substituent the benzenoid and conjugation bands are displaced on methylation to slightly shorter wavelengths and their intensities are diminished. In these compounds the methyl group is able to turn away from the substituent and evade steric interaction. If both ortho positions are occupied there is a reduction in conjugation and the bands are displaced by 70–100 Å. to much shorter wavelengths and their intensity is lowered by 70–80 per cent.

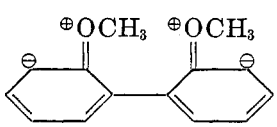
An interesting structural case is provided by 16,17-dimethoxydibenzanthrone (XIII). The ultraviolet spectrum compared with that of the parent compound



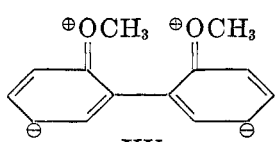
XIII

has a considerable decrease in the intensity of the absorption around 600–700 mμ and a large bathochromic shift of the maximum absorption (231). A scale drawing shows that the methoxyl groups interfere with each other. If they were twisted out of the plane of the rings to avoid this interference, the spectrum of the dimethoxy compound would be similar to that of the parent hydrocarbon. It is possible that this polynuclear compound undergoes a slight adjustment of bond angles so that the whole system can remain planar.

As a criterion of coplanarity the results of ultraviolet absorption spectra must, however, be used with reserve. The ultraviolet spectra of biphenyl compounds in which the rings are locked in a non-coplanar position show that the two nuclei are still conjugated (42). Introduction of methoxyl groups into the 2,2′-positions of these compounds reduces this conjugation, though it cannot seriously alter the shape of the molecules concerned. The diminution in double-bond character of the link between the rings is attributed to structures such as XIV and XV.

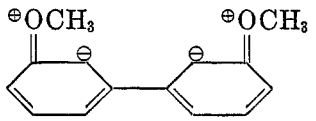


XIV

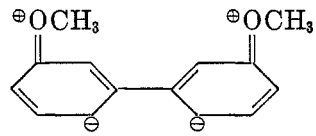


XV

A similar non-steric reduction of conjugation has been observed in 3,3′-dimethoxybiphenyl (296) and is likely from XVI and XVII.

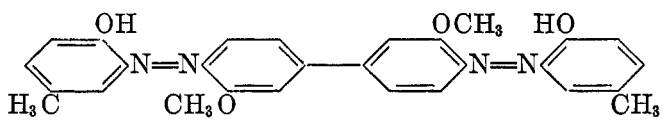


XVI



XVII

On the other hand there are a number of dyes of high tinctorial value prepared from *o*-dianisidine (e.g., XVIII) which owe their greater absorption properties to the increased coplanarity in the molecule over that of dyes derived from an unsubstituted benzidine.

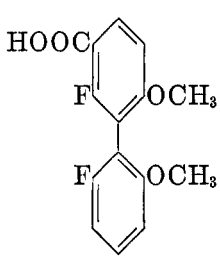


XVIII

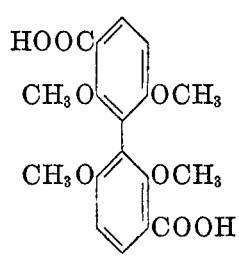
From dipole moment and absorption spectra measurements it is concluded that the methyl group in 2-methoxytropone lies at a considerable angle to the plane of the ring, and the conjugation between the methoxyl group and the ring is weak (198).

Other instances in which ultraviolet spectra show the hindrance of a methoxyl group are 1-methoxynaphthalene (175), 1,1′-dimethoxy-2,2′-binaphthyl (112), various methoxyphenoxybenzoic acids (278), and methoxyacridones (65).

The methoxyl group has played an important role in the study of optically active biphenyls (143). Fluorine and methoxyl, with the smallest space requirements, are the least effective in restricting rotation, and compounds such as XIX and XX are unresolvable.

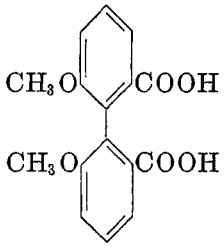


XIX

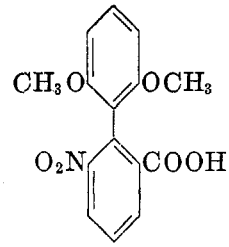


XX

With ortho substituents of increasing bulk the compound XXI is resolvable but racemizes readily, while compound XXII shows greater optical stability.



XXI



XXII

However, the sizes of the substituents are not the sole determining factor of the rates of racemization (1). Tentative explanations, such as variable interannular conjugation (80) and increased nuclear electron density (17, 90), have been made.

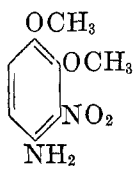
Chemical results of the steric inhibition of conjugation of a methoxyl group have been observed in a few instances. The steric effects of many ortho substituents have been compared on a quantitative basis for *o*-benzoates from published rates of esterification and hydrolysis. Of the groups considered the effect of methoxyl is least (272).

Anisole, 2-methylanisole, and 2,6-dimethylanisole undergo bromination at relative rates of 1:8.3:0.2. The increased rate of bromination of 2-methylanisole is due to the inductive action of the methyl group, and 2,6-dimethylanisole might therefore be expected to undergo bromination even more readily. Its low reactivity is due to curtailment of the conjugation between the methoxyl group and the ring (291).

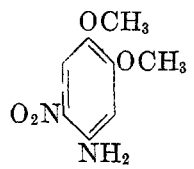
As is to be expected, substitution ortho to methoxyl may be impossible if the incoming group is bulky. Thus, the *tert*-butylation of 2-methoxyphenol gives no substitution in the 3-position, in spite of the equal directing powers of the hydroxyl and methoxyl groups in this compound (251).

Iodine chloride iodinates anisole rapidly in acetic acid solution, giving *p*-iodoanisole together with about 20 per cent of the chloro compound. With methyl *p*-tolyl ether the relative amount of iodination is lowered to 50 per cent by steric hindrance to the entry of the large iodine atom into the ortho position (199).

An unusual rearrangement which is dependent, in part, on the steric influence of a methoxyl group is the migration of the nitro group of 4-amino-3-nitroveratrole (XXIII) to 4-amino-5-nitroveratrole (XXIV) when heated with an acetic acid–phosphoric acid mixture (134, 233).



XXIII



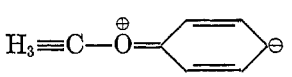
XXIV

The effect of methoxyl and of other groups as a meso substituent (9,10-positions) on the rate of addition of osmium tetroxide to the 3,4-double bond of 1,2-benzanthracene (XII) has been studied (23). While some groups, e.g., methyl and acetoxyl, profoundly alter the rate, the methoxyl group has no activating influence since it is not coplanar with the ring system (182).

A comparison of the metal complexes of dimethylglyoxime with those of its *O*-methyl ether shows that the Cd(II) and Ni(II) chelates of the ether are less stable than those of dimethylglyoxime, while there is no complex formation with Pb(II) (86). These results may be caused by steric hindrance between the methoxyl group and the metal atom.

E. HYPERCONJUGATION

It is of some interest to speculate on the possibility of the hyperconjugation of the alkyl portion of the methoxyl group. A methyl group attached directly to an unsaturated group (as in toluene) or to another methyl group (as in ethane) is able to induce double-bond character into the intervening single bond by delocalizing its electrons. The methyl group is separated by the carbon–oxygen bond from the partially unsaturated O—C_{aryl} bond, and therefore the H_3C—O bond should be shortened. In support of this, x-ray studies on 1,4-dimethoxybenzene (144) show that the carbon–oxygen bond has a length of 1.35 Å. However, caution is necessary in using physical data as evidence for hyperconjugation (27). Any such action would be so small in relation to the large conjugation of the unshared pair on the oxygen atom that it would be difficult to detect. In the para-substituted benzaldehyde–cyanohydrin equilibria a *p*-methoxyl group has a relative stabilizing effect on the free aldehyde of ca. 1355 cal./mole in spite of its small destabilizing $-I$ effect (28), whereas for *p*-methyl the value is only ca. 400 cal./mole, a value which includes its stabilizing $+I$ effect (31). The energy contribution of conjugated divalent oxygen is therefore at least four to five times as great as that due to hyperconjugation of a similarly placed methyl group. Moreover oxygen in the canonical structure (XXV) has all its orbitals filled; hence any overlap of the electron orbitals of the hydrogen and carbon atoms must be exceedingly small.



XXV

X-ray investigation of other methoxyl compounds will be of interest. The unusual nuclear reduction products obtained from *o*-methoxy aryl ethers by the action of sodium and liquid ammonia (page 360) have been accounted for by cyclic hyperconjugation.

III. Protonation of the Methoxyl Group

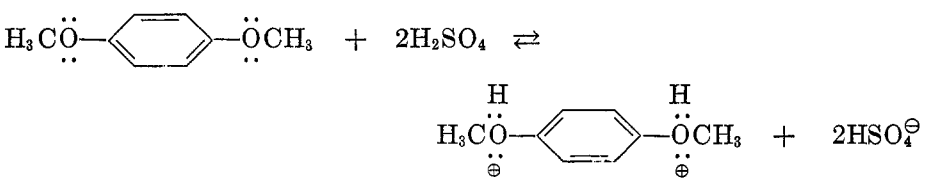
A. SALT FORMATION AND THE INTERMOLECULAR HYDROGEN BOND

The unshared electrons on the oxygen atom indicate that an unconjugated methoxyl group should be markedly basic. The monohydrobromide and mono-

hydrochloride of dimethyl ether have been isolated as compounds with low melting and boiling points. The hydrobromide, for example, melts at −13°C. and boils at 3–5°C. The question whether these compounds are true oxonium salts or whether the interaction is more appropriately considered as hydrogen bonding has been reviewed (76, page 620), with the conclusion that the solids are substantially oxonium salts, while in the vapor the complexes are hydrogen-bonded.

Aliphatic ethers in strong acids are largely in solution as their conjugate acids, and in 100 per cent sulfuric acid they are completely ionized. The basic strength of the group is considerably diminished when it activates an aromatic nucleus or another basic group in the molecule. The basic strengths of a number of different types of ethers have been compared from the rate of self-etherification of benzhydrol under acid catalysis (238). The rate of etherification is lowered, since the added ether competes with the benzhydrol for the catalyst, and from this the relative basic strengths are butyl ethers > alkyl benzyl ethers > alkyl phenyl ethers.

Strongly acid media are needed to investigate the protonation of the methoxyl group, and the use of sulfuric acid is often complicated by rapid sulfonation of the nucleus. Bradley (56) found that 1,4-dimethoxybenzene at 10°C. gave initially a van't Hoff *i* factor of 3. This value is attributed to diprotonation.



Little work has been done on the protonation of the methoxyl group in other strong acids, but it does occur with 1,3,5-trimethoxybenzene in perchloric acid. The free base in water shows no characteristic absorption between 250 and 400 mμ. In 48.51 per cent perchloric acid peaks occur at 252 and 347 mμ. In 60 per cent acid the spectrum changes rapidly with time, and finally it is identical with that of the trihydroxy compound in the same medium (72).

The spectrum of anisole in 70 per cent perchloric acid presents the interesting feature that the presumed conjugate acid has a lower λ_{max} than the free base. This may be due to a decrease in conjugation between the functional group, $CH_3—\overset{H}{\underset{\oplus}{O}}—$, and the ring (258).

The infrared absorption spectrum of hydrogen chloride in a carbon tetrachloride solution of anisole has a displacement of the fundamental band at 2849 cm.$^{-1}$ to a slightly smaller value (77). In similar experiments with ether and hydrogen chloride the band is shifted to 2415 cm.$^{-1}$, a result which shows the weakness of the intermolecular bond formed by anisole.

The protonation of the methoxyl group is often not apparent when it is conjugated with other basic groups present in the molecule. Wiles and Baughan

(294) could find no evidence for the protonation of the group in any methoxyanthraquinone in sulfuric acid solution, though it is in *p*-methoxyacetophenone and in *p*-methoxybenzoic acid (56).

In common with other alkoxyl groups the acid hydrolysis of a methyl ester and of a phenol methyl ether is initiated by the protonation of the group —OR (142; 172, page 767).

The *O*-methyl ethers of aldoximes are sufficiently basic to form salts: $RCH{=}NOCH_3 \cdot HX$ (237). Doubts were at one time cast on this observation because of the possibility of salt formation at the nitrogen (58), but more recently the hydrochloride and the perchlorate of *O*-methylanisaldoxime and other analogous salts have been isolated (59).

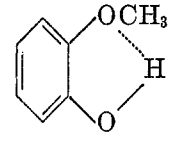
B. INTRAMOLECULAR HYDROGEN-BOND FORMATION

The basic character of the methoxyl group is further demonstrated by the ability of the oxygen to hold a proton in a chelate ring by electrostatic attraction. The experimental evidence is derived largely from infrared and ultraviolet spectroscopy and from dipole moments. Measurements of boiling point, density, viscosity, surface tension, and molar latent heat have also been used, since intermolecular association by hydrogen bonding increases these quantities, while the formation of a chelate ring opposes association and diminishes the values.

The existence of a ring in the linkages $O{-}H\cdots O(CH_3)$ and $N{-}H\cdots O(CH_3)$ is well established, and it is possible that $C{-}H\cdots O(CH_3)$ may also exist.

$O{-}H\cdots O(CH_3)$: The *o*-methoxy derivatives of phenol, benzaldehyde, and benzoic acid all show intramolecular hydrogen bonding to form five- or six-membered rings.

The infrared spectrum of *o*-methoxyphenol (guaiacol) has been examined by several workers (209, 299). A single peak at ca. 6930 cm.$^{-1}$ corresponds to the form shown in formula XXVI.

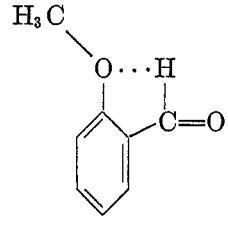


XXVI

The area of absorption, however, is about half that observed with phenol at ca. 7000 cm.$^{-1}$, a fact which suggests that many of the molecules are intramolecularly bonded. Intermolecular association would be possible with the other molecules but might be too weak to give definite absorption in the 7000 cm.$^{-1}$ region. The calculated dipole moment for the configuration shown in formula XXVI is 2.45 D, and the observed moment is 2.41 D (93). The viscosity of *o*-methoxyphenol is less than that of phenol but greater than that of the dimethoxybenzenes in spite of the differences in molecular weight, facts which support the joint existence of inter- and intramolecular bonds. Moreover the density, viscosity, surface tension, and latent heat of *o*-methoxyphenol are

lower than of its *m*- and *p*-isomers, which have values for these properties which are closely similar (130, 208). The rheochor–temperature curves show that *p*-methoxyphenol rapidly breaks down to simpler molecules, whereas the ortho compound is almost monomeric from 140°C. upwards.

The evidence for an intramolecular hydrogen bond in *o*-methoxybenzaldehyde rests largely upon interpretations of dipole moments (93, 206). The large moment, determined experimentally as 4.20 D and calculated as 4.1 D, indicates

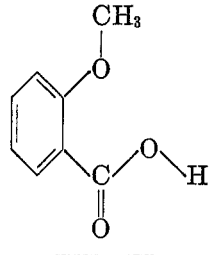


XXVII

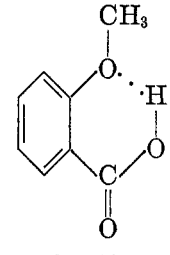
a configuration (XXVII) stabilized by resonance and a weak CH···O bond. The observed molar refraction of *o*-methoxybenzaldehyde is only 0.1 cc. higher than the value calculated from the refractions of anisole, benzaldehyde, and benzene, and again shows the weakness of the bond (93).

The α and β crystalline modifications of *o*-methoxybenzaldehyde (236) are considered to be the inter- and intramolecular hydrogen-bonded forms, respectively (279).

The existence of the intramolecular bond in *o*-methoxybenzoic acid is well authenticated. The infrared spectrum in carbon tetrachloride solution has two sharp monomeric O—H stretching bands at 3530 cm.$^{-1}$ and 3362 cm.$^{-1}$ (128, 214). These correspond to the free and internally bridged hydroxyl groups in equilibrium (XXVIII, XXIX).



XXVIII



XXIX

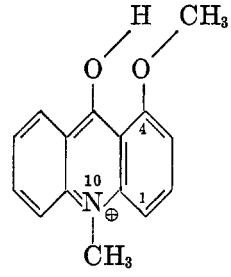
From the relative intensities of these absorption bands at three different temperatures the energy of the bond has been calculated as 3.3 ± 0.5 kcal./mole., a value in close agreement with that determined for the association equilibrium by the distribution in benzene solution (100).

There is little experimental evidence for the O—H···O(CH_3) linkage in more complex aromatic systems, but the infrared spectrum of 1-hydroxy-8-methoxynaphthalene shows a hydroxyl band at 3436 cm.$^{-1}$, which is a shift of the hy-

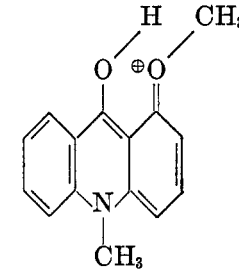
droxyl stretching frequency to a lower value and is attributed to the hydrogen bridge (169).

The bonding O—H···O(CH_3) has frequently been postulated, and a number of illustrations are given.

It is well established that a methoxyl group situated in the position peri to a carbonyl group is more readily cleaved than methoxyl elsewhere in the molecule. The following hypothesis accounts for the ready demethylation of the 4-methoxy group in 10-methylacridones (92, 170) and can be extended to the demethylation of other *o*-methoxyketones. The initial step in the cleavage of ethers is the addition of a proton, and this is most likely to occur at the carbonyl group (XXX).

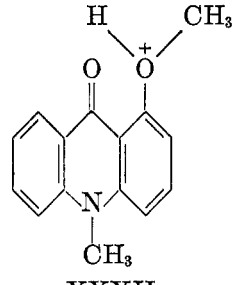


XXX

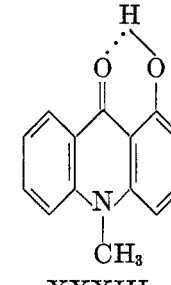


XXXI

If a 4-methoxy group is present, the proton addition product will be stabilized by hydrogen bonding (XXXI, XXXII). This increase in stability will lower the activation energy necessary for the addition of a proton compared with that required when the methoxyl group is located elsewhere. Moreover the addition of a second proton for the demethylation of a 1-, 2- or 3-methoxy group will be rendered more difficult by a general inductive deactivation brought about by the protonation of the carbonyl group. If now a methyl group is lost from the 4-position the molecule will increase in stability, since it becomes neutral and a stronger hydrogen bond is formed (XXXIII).



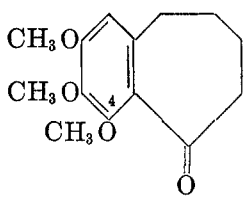
XXXII



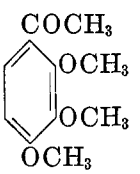
XXXIII

Interesting observations on the effect of a second methoxyl group adjacent to that readily cleaved have recently been made. In polymethoxybenzosuberones (e.g., XXXIV) the 4-methoxy group is very readily demethylated by hydrobromic acid in acetic acid at room temperature (137), but under these very

mild conditions only when there is a 3-methoxy group (168). The work has been extended to methoxyacetophenones. The 2-methoxy group again is only cleaved in high yield when there is a 3-methoxy group. With 2,3,4-trimethoxyacetophenone (XXXV) the product is 2,3-dihydroxy-4-methoxyacetophenone (166); it seems that this compound has been erroneously described as 2,4-dihydroxy-3-methoxyacetophenone (34). A similar preferential cleavage is the conversion of 2,3,4,6-tetramethoxyacetophenone to 2-hydroxy-3,4,6-trimethoxyacetophenone and not to the isomeric 2-hydroxy-4,5,6-trimethoxyacetophenone (37).

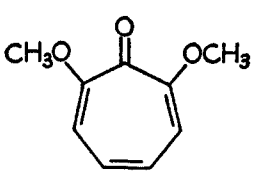


XXXIV

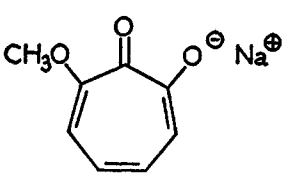


XXXV

It may be noted that only one ether group in 2,7-dimethoxytropolone (XXXVI) is hydrolyzed in *alkaline* solution. The resulting tropolone (XXXVII) will exist as the ion in solution, and the remaining methoxyl group will have the usual resistance of a phenolic ether to alkaline cleavage.

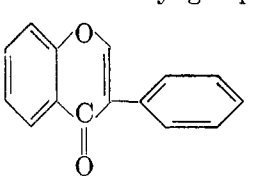


XXXVI

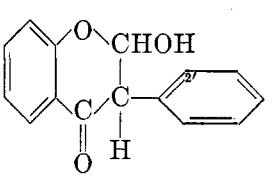


XXXVII

The synthesis of isoflavone (XXXVIII) and its derivatives from *o*-hydroxyphenylbenzyl ketones has been postulated as proceeding through the hydroxyisoflavone (XXXIX) as an intermediate. This has been substantiated by Whalley (286, 287), who has isolated a number of 2-hydroxy-2′-methoxyisoflavones and attributes their particular stability to hydrogen bonding between the hydroxyl and methoxyl groups.



XXXVIII

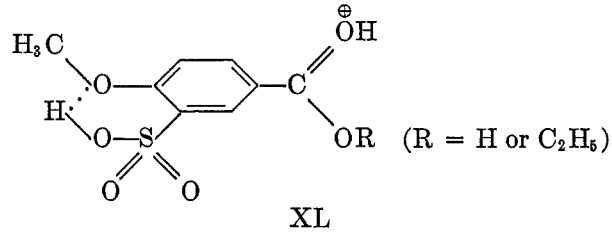


XXXIX

Koch (187) has postulated hydrogen bonding between the carbonyl and methoxyl groups to account for the unchanged infrared carbonyl frequency in

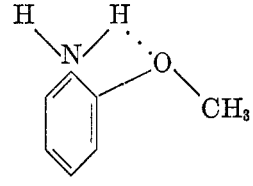
the tropolone methyl ether, colchicine, and in the corresponding hydroxy compound.

Since hydrogen bonding between ortho-situated methoxyl and carboxylic acid groups is well substantiated, it seems likely that a sulfonic acid group may behave in a similar manner. Bradley (56) accounts in this way for the unlikely diprotonation in 100 per cent sulfuric acid of *p*-methoxybenzoic acid and its methyl ether when sulfonated ortho to the methoxyl group (XL).

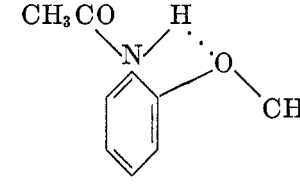


XL

N—H···O(CH_3): The density of *o*-anisidine at 55°C. and at 90°C. is less than that of *p*-anisidine (235, 273), and its viscosity at 55°C. is also lower (273). This is evidence that the amino group in *o*-anisidine forms a hydrogen bridge with the neighboring methoxyl group (XLI). The bond is, however, readily broken, and in contrast with *o*-methoxyphenol, *o*-anisidine and its meta and para isomers are associated intermolecularly at 131°C. (208).



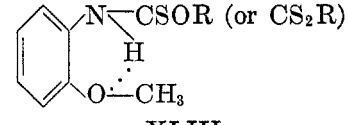
XLI



XLII

o-Methoxyacetanilide (XLII) is only feebly associated (13) and has a weak internal hydrogen bond. Supporting evidence is provided by its ultraviolet spectrum. The wavelengths of corresponding bands in the ortho and meta isomers are identical (276). The absence of an ortho-effect is explained by the assumption that the acetyl group is turned away from the methoxyl group, the configuration being stabilized by a weak hydrogen bond, and by the electrostatic repulsion between the two oxygen atoms. When hydrogen bonding is not possible, as in *o*-methoxydimethylaniline, a steric effect is observed. The primary band at 245 mμ has approximately half the intensity of the corresponding band in the meta isomer at 255 mμ (146).

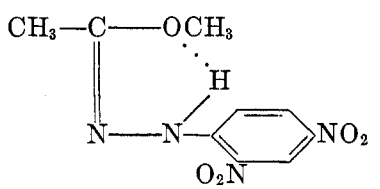
Burrows and Hunter (73) have found the N—H···O(CH_3) bond in *o*-methoxythion- and dithiocarbamic esters (XLIII).



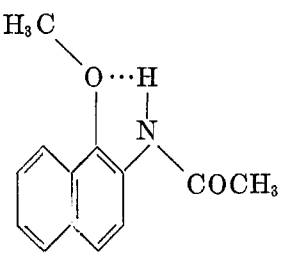
XLIII

With no ortho substituents the compounds have a high molecular association due to N—H···S bonds. This association is completely suppressed in the *o*-methoxy compounds, and it was proved that the effect was not a steric influence of the methoxyl group. With the *p*-methoxy compound there is association through intermolecular bonding.

The postulate of N—H···O(CH_3) bonding has been used to assign a configuration to 2,4-dinitrophenylhydrazones of methoxyketones of which geometrical isomers have been isolated (240). The N—H stretching vibration in one of each pair is shifted to a slightly lower frequency and is broadened and strengthened. This isomer is assumed to be the *syn* form (e.g., XLIV).



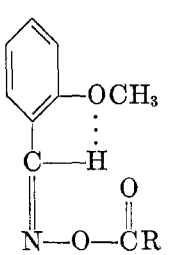
XLIV



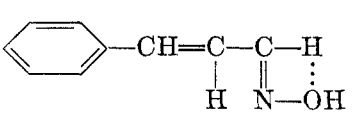
XLV

An interesting difference has been noted in the acetylation of the 1- and 4-methoxy derivatives of 2-naphthylamine (112). The 1-methoxy compound gives only a monoacetyl compound, a restriction possibly imposed by hydrogen bonding (XLV). The 4-methoxy compound can be diacetylated.

C—H···O(CH_3): Certain observations in the chemistry of the aldoximes are considered to be due to this bonding. In the formation of nitriles by the pyrolysis of acyl derivatives of aldoximes ortho substituents capable of hydrogen bonding favor the decomposition, possibly by assisting the rupture of the carbon–hydrogen bond (9) (XLVI).



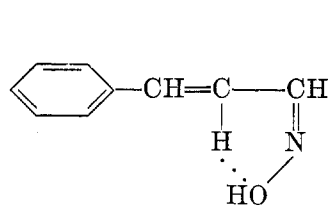
XLVI



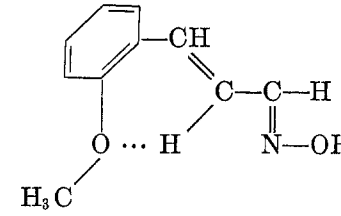
XLVII

Cinnamaldehyde on oximation in alkaline solution gives a mixture of α- and β-isomers (XLVII, XLVIII), with the β-isomer predominating. Under the same conditions *o*-methoxycinnamaldehyde gives mainly the α-aldoxime (XLIX). The decrease in the proportion of the β-form may be due to the weak-

ening of the hydrogen bond between the oximino oxygen and the methine hydrogen by the competitive attraction of the methoxyl oxygen (44).



XLVIII



XLIX

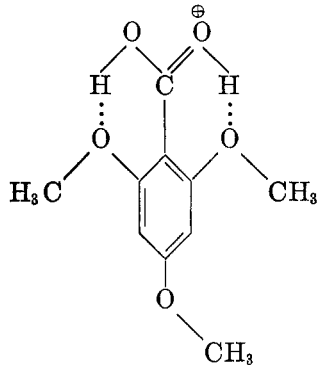
IV. The Physical and Chemical Influence of the Methoxyl Group

A. ACIDIC STRENGTHS

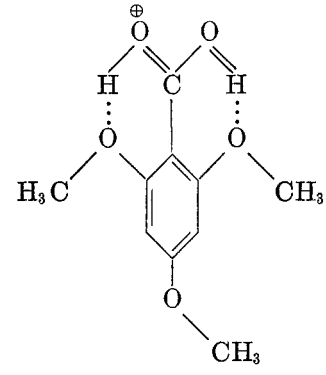
The effect of alkoxyl groups on the dissociation constants of acids has been reviewed (105). By its $-I$ effect the methoxyl group strengthens saturated acids, *m*-methoxybenzoic acids, and *m*-methoxy-*trans*-cinnamic acid in comparison with their parent acids. The $-I$ effect is so attenuated in *m*-methoxy-β-phenylpropionic acid that it does not alter the acid strength. *o*-Methoxybenzoic acid is stronger than benzoic acid; this is understandable if the joint $-I$ effects of C_{aryl}—O and O—CH_3 acting at short range more than counterbalance the opposing $+M$ effect. In *p*-methoxy-substituted acids $-I < +M$ and the acids are weakened.

The dissociation constants, in aqueous or alcoholic solution, of *m*- and *p*-methoxybenzoic and *m*-methoxycinnamic acids are unexpectedly higher than those of the corresponding hydroxy derivatives. The reversal of the normal effect of hydroxyl and methoxyl groups is accounted for by the formation of hydrogen bonds between the hydroxyl groups and the solvent. The hydroxyl group then becomes more electron-repelling than the methoxyl group. This explanation is supported by ultraviolet absorption measurements. In the absence of internal hydrogen bonding in phenols and of intramolecular steric effects in the methyl ethers, phenols absorb in hexane at shorter wavelengths but in ethyl alcohol at longer wavelengths than the corresponding methyl ethers (71).

A very marked difference exists in the strength of the corresponding *o*-hydroxy and *o*-methoxy acids. Salicylic acid ($pK_a = 1.0$), in which the anion is stabilized by hydrogen bonding, is a much stronger acid than *o*-methoxybenzoic acid ($pK_a = 4.1$). Similarly 2,4,6-trimethoxybenzoic acid ($pK_a = 3.6$) is weaker than 2,4,6-trihydroxybenzoic acid ($pK_a = 1.6$) (259). 2,4,6-Trimethoxybenzoic acid is a strong base in perchloric acid. The conjugate acid is stabilized by increased resonance interaction (over that in the free base) of the protonated carboxyl group with the methoxyl substituents, assuming no large steric inhibition of resonance, and there may be added the hydrogen-bond stabilization of the conjugate acid (L–LIII).



L



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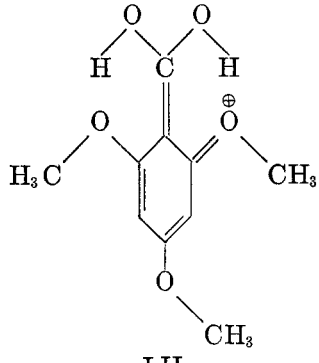
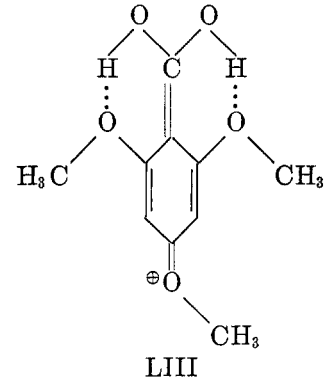


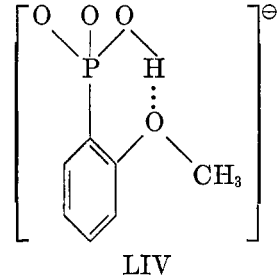
LII



LIII

The values of the free energy of ionization of many substituted benzoic acids have been calculated from their acid dissociation constants. The results agree well with the observed values and show the additive effects of substituents (264).

An appreciable reduction in the acid strength of *o*-methoxybenzenephosphonic acid is attributed to a hydrogen bond between the phosphono group ($—PO_3H_2$) and the ortho substituent (LIV) (176).



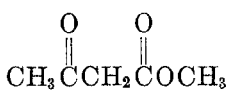
LIV

The acid strengths of *m*- and *p*-$CH_3XC_6H_4COOH$ (X = O, S, or Se) have been determined (28). In the para series the acid strengths are in the order Se > S > O in accordance with the increasing $+M$ effects Se > S > O. With

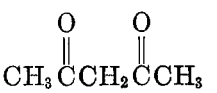
the meta-substituted acids the $-I$ effect strengthens all the acids, and the undisturbed operation of induction only should give the order $—CH_3O >$ $—CH_3S >$ $—CH_3Se >$ —H. Experimentally a possible inversion of the positions of S and Se may indicate the superposition of a second-order relay of the $+M$ effect (page 333).

The enolization and hence the acidity of β-diketones is diminished by a methoxyl group adjacent to a carbonyl group. The release of electrons reduces the attraction of the carbonyl group for the electrons of the methylene group, and it is therefore more difficult for a proton to separate. Methyl acetoacetate (LV) is less enolic than acetylacetone (LVI) (288), since the electron-release of methoxyl is greater than from methyl.

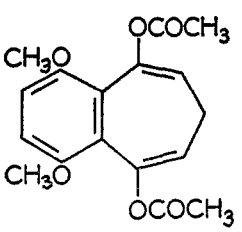
In a similar way a methoxyl group peri to a carbonyl group lowers the acidity of benzotropones by stabilizing the enol-ketones in the keto form (267, 268). Thus bromination of the dienol acetate (LVII), and subsequent treatment with alkali, gives the dione (LVIII) and not the enol-ketone (LIX).



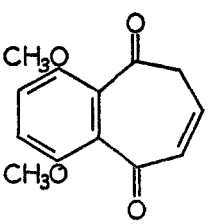
LV



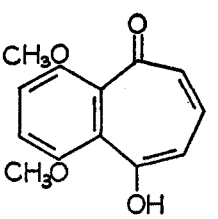
LVI



LVII

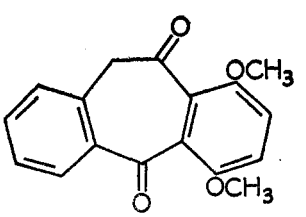


LVIII

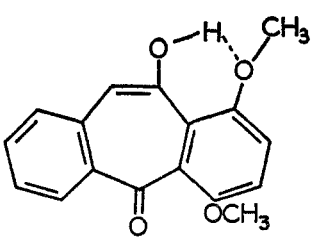


LIX

The least acidic of the dibenzotropones is the dimethyl ether (LX). This may be due to suppression of enolization by the peri-methoxy group, but in methanol solution the compound exists in the enol form, and this may be slightly stabilized by hydrogen bonding (LXI).



LX



LXI

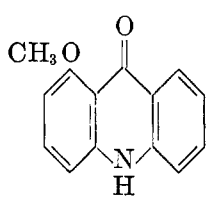
B. BASIC STRENGTHS

1. Nitrogen bases

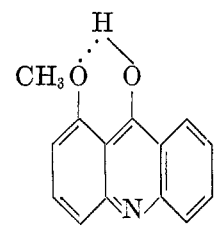
Very similar considerations apply to methoxy-substituted anilines as to benzoic acids. The pK_a values of aniline and of *o*-, *m*-, and *p*-anisidine are, re-

spectively, 4.6, 4.5, 4.2, and 5.3, so that an *o*-methoxy group has little effect on the basicity and a *m*-methoxy group is base-weakening by its $-I$ effect, while a *p*-methoxy group strengthens the basicity, since $-I < +M$.

For pyridine and 2-, 3-, and 4-methoxypyridine the pK_a values are 5.18, 3.06, 4.91, and 6.47 (221). In this series ortho substitution reduces considerably the basic strength. An interesting situation arises in the methoxyacridones. 4-Methoxyacridone (LXII) is a stronger base than acridone, other methoxyacridones, or the aminoacridones. There was the possibility that hydrogen bonding stabilized the compound in the 5-hydroxy form (3). Further development of this idea led to the conclusion that the high basic strength is due to hydrogen bonding in the cation between the two oxygen atoms (LXIII). The two canonical forms, depending on whether the carbonyl oxygen or the nitrogen has the positive charge, are sufficiently equivalent for a base-strengthening resonance to occur (4).



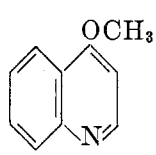
LXII



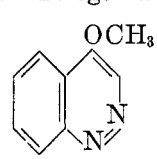
LXIII

The same pronounced basic strength caused by a substituted 4-methoxy group has been repeatedly noticed in *N*-methylacridones (92, 239). It is likely that these compounds are oxygen bases.

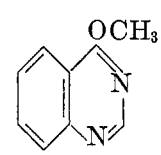
In some heterocyclic systems the effect of methoxyl on the basic strength is not understandable. A 4-methoxy group increases the base strength in the quinoline (LXIV) and cinnoline (LXV) series and this is to be expected. However, the same substituent in quinazolines (LXVI) lowers the basic strength (5, 184). The possibility that the basic center is the nitrogen atom ortho to the methoxyl group was not revealed by quaternization, since fusion with methyl toluene-*p*-sulfonate alkylated both nitrogen atoms (219).



LXIV



LXV



LXVI

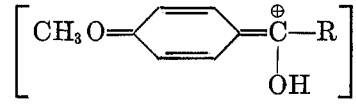
2. Oxygen bases

The increased basic strength of the carbonyl group in α,β-unsaturated ketones in the presence of *o*- and *p*-methoxy groups has long been recognized.

Baeyer and Villiger (24) studied methoxy derivatives of chalcones, comparing their basic strengths by titrating the halochromic salts formed in acetic–sulfuric acid solution with 75 per cent ethanol. The work was extended to many other

polymethoxychalcones (183). The basic carbonyl function has an increased negative charge conferred on its oxygen atom when conjugation with methoxyl is possible (LXVII). The color is due to the formation of a carbonium ion which is stabilized by an electron-releasing substituent (LXVIII) (page 373).

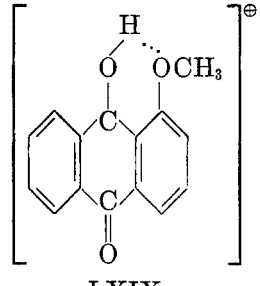
LXVII



LXVIII

The relative basic strength of the carbonyl group in ketones and esters has been estimated by their ability to decrease the rate of the acid-catalyzed self-etherification of benzhydrol (238). The basic strengths of para-substituted acetophenones and ethyl benzoates increase as the electron-releasing ability of the substituent is increased, and of the compounds measured was a maximum with methoxyl. This increase in basic strength, due to the ability of the substituent to alter the electron availability at the carbonyl and carbethoxyl groups, corresponds to a decrease in the infrared frequency of the carbonyl group as its double-bond character becomes less (266).

The pronounced basic character of a carbonyl group when there is a peri-methoxy group has been observed in many different classes of compounds. Thioxanthones, xanthones, and anthraquinones, in particular, have been carefully studied (202, 245, 246, 247, 293, 294). It was formerly considered that salts of these compounds owed their stability to the existence of a hydrogen bond which conferred resonance stabilization on the molecule. Thus one canonical form of the cation of 1-methoxyanthraquinone was represented as shown in formula LXIX.

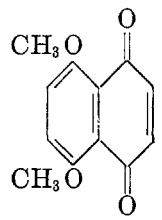


LXIX

It is now known that the hydrogen bond is largely electrostatic in nature. Moreover, the conjugation of the methoxyl group with the nucleus or with the carbonyl group will confer a positive charge on the oxygen atom. The hydrogen-bond structure therefore became doubtful, and it has recently been disproved for salts of α-methoxyanthraquinones (295). The infrared carbonyl frequency in the salt is shifted to a value only slightly lower (ca. 6 cm.$^{-1}$) than that in the parent ketone.

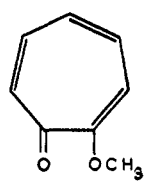
Naphthazarin dimethyl ether (LXX) is soluble in concentrated hydrochloric

acid, and the failure to bromomethylate and chloromethylate 2-bromo(and chloro)naphthazarin dimethyl ether with formaldehyde–halogen acid–acetic acid is probably due to salt formation with the acid (66).

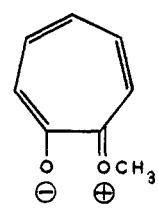


LXX

The methoxyl group increases the basic strength of tropolones. The pK_a values for tropolone, 4-methoxytropolone, and 5-methoxytropolone are 6.92, 7.24, and 7.75, respectively. Tropolone methyl ether and the two methyl ethers of β-methyltropolone form picrates whose yellow color suggests that they are salts rather than molecular compounds. This is understandable from the ionic resonance structures (LXXI, LXXII).

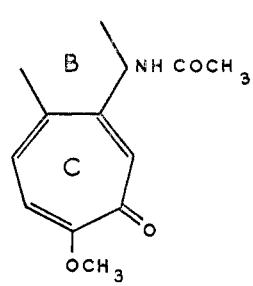


LXXI



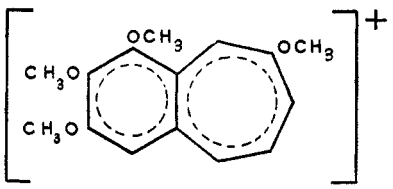
LXXII

The benzotropolone colchicine forms compounds with acids. Windaus (297) isolated two hydrochlorides from trimethylcolchicinic acid. The monohydrochloride is a colorless, crystalline solid. Saturation of an alcoholic solution of this hydrochloride with hydrogen chloride at 0–4°C. precipitates a dark yellow dihydrochloride. Presumably the monohydrochloride is concerned with protonation of the nitrogen in ring B, while the halochromic salt is formed by adding a second proton to the oxygen of the α,β-unsaturated ketone present in ring C (probable structure as shown in formula LXXIII).



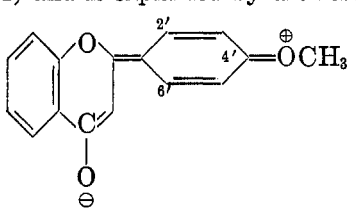
LXXIII

The first isolation of a salt of the cycloheptatrienylium cation may be attributed to the increased basic strength conferred by the methoxyl groups. The reduction of tetramethylpurpurogallin with lithium aluminum hydride and decomposition of the product with sulfuric acid gave a salt, the cation of which is written as in LXXIV (116, 156).



LXXIV

The importance of a 4′-methoxy group to the basic strength of the carbonyl group in flavones has been demonstrated from the ultraviolet absorption spectrum in sulfuric acid (101) and is explained by the resonance structure LXXV.



LXXV

The presence of methyl groups at the 2′- and 6′-positions destroys the coplanarity of the molecule, and the basic strength of the compound is then less than that of flavone.

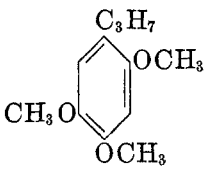
Many workers have studied the enhancement of the basic strength of triphenylcarbinol by *o*- and *p*-methoxy groups. The earliest comparisons were by Baeyer and Villiger (24), who found that a *p*-methoxy group had the greatest effect. Brand (61) compared the stabilities of methoxytriphenylcarbinol salts and found an increase according as one, two, or all three para positions were substituted. The substituent provides an alternative seat for the positive charge, which would otherwise tend to be localized on the central carbon atom. The stability of many *o*- and *p*-polymethoxytriphenylcarbonium ions was also measured by Lund (207) and by Kolthoff (191). *p*-Methoxytriphenylmethyl perchlorates are strong electrolytes (302) and are ionic in the solid state (104).

C. OXIDATION

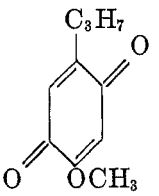
1. Oxidative demethylation

This aspect of the cleavage of ethers was not covered in a recent review (76). The term implies the formation of a quinone from the corresponding dimethoxy compound by an oxidizing agent. Nitric acid has commonly been used, but chromic acid may be employed, and a comparable type of demethylation has been brought about by peroxidase in hydrogen peroxide.

The oxidative demethylation of phenolic ethers was studied many years ago (275), and was extended to methoxyketones and methoxychalcones by Indian workers (241) in their research on flavones. Dimethoxybenzenes yield nitro products. An accumulation of methoxyl groups impedes the entrance of nitro groups, so that tri- and tetramethoxybenzenes form quinones and a nitro group enters only when the para positions are free. When 1-*n*-propyl-2,4,5-trimethoxybenzene (LXXVI) reacts with fuming nitric acid at −18°C. the principal product is the quinone LXXVII.

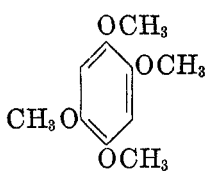


LXXVI

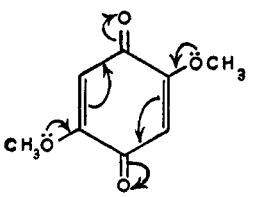


LXXVII

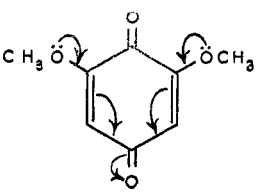
1,2,4,5-Tetramethoxybenzene (LXXVIII) gives 2,5-dimethoxy-1,4-benzoquinone (LXXIX), while the 1,2,3,5-tetramethoxy compound gives 2-hydroxy-6-methoxy-1,4-benzoquinone (LXXXI) by quinone formation from two *p*-methoxy groups and demethylation of one of the methoxyl groups ortho to carbonyl.



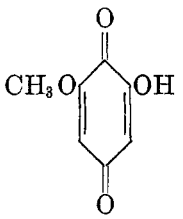
LXXVIII



LXXIX



LXXX

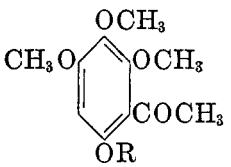


LXXXI

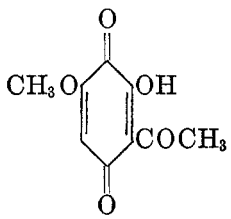
The difference in behavior is accounted for by Seshadri (261) in the following way: 2,5-dimethoxybenzoquinone has two independent systems of the type $CH_3C{=}C{-}C{=}O$, which are ester groups extended by a $-C{=}C-$ chain. The compound is readily hydrolyzed by alkali. In 2,6-dimethoxybenzoquinone (LXXX) both methoxyl groups are conjugated with the same carbonyl group and the compound does not fully behave as an ester. When one methoxyl group is hydrolyzed in acid media the compound (LXXXI) contains a strongly neu-

tralized system and the carbonyl group involved is not capable of activating the remaining methoxyl group.

Methoxyacetophenones also undergo similar changes. 2,3,4,6-Tetramethoxyacetophenone (LXXXII: R = CH_3) and 2-hydroxy-4,5,6-trimethoxyacetophenone (LXXXII: R = H) both give the same hydroxyquinoketone (LXXXIII).

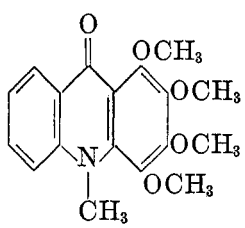


LXXXII



LXXXIII

It is also possible to produce *o*-quinones by oxidative demethylation. Oxidation of brucine (*o*-dimethoxystrychnine) by nitric acid gives a red bruciquinone which can be isolated as its perchlorate (201). From the alkaloid melicopicine (LXXXIV) the *p*-quinone is the main product, but the *o*-quinone is also produced (91).

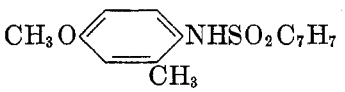


LXXXIV

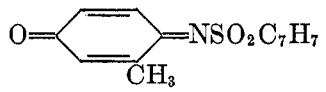
Related to the foregoing examples are cases in which a compound containing a methoxyl group and a different group in the para position is oxidized to form a quinone. 2,6-Dibromo-4-fluoroanisole is converted by fuming nitric acid to 2,6-dibromo-1,4-benzoquinone (161). The corresponding 4-chloro and 4-bromo compounds are nitrated in the 3-position, and the iodine of the 4-iodo compound is replaced by nitro.

Saunders and Watson (255) reported that 4-methoxy-2,6-dimethylaniline was readily oxidized by hydrogen peroxide in the presence of the peroxidase class of enzymes to 2,6-dimethyl-*p*-benzoquinone. The eliminated methoxyl group appears as methyl alcohol in the product. Oxidation of *p*-anisidine under similar conditions gives complex quinone anils with elimination of one methoxyl group (97).

The ready removal of methoxyl para to a substituted amino group is shown by the conversion of 5-methoxy-2-toluene-*p*-sulfonamidotoluene (LXXXV) by dilute nitric acid to the quinone imide, 2-methyl-*p*-benzoquinone-1-toluene-*p*-sulfonimide (LXXXVI) (43).

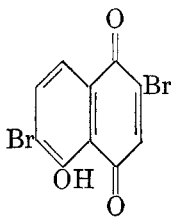


LXXXV



LXXXVI

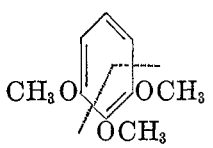
An unusual oxidative demethylation is that of 1,5-dimethoxynaphthalene by bromine in glacial acetic acid to 2,6-dibromo-5-hydroxy-1,4-naphthoquinone (LXXXVII) (45).



LXXXVII

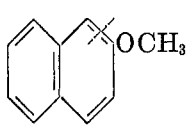
2. Oxidations with per acids and with hydrogen peroxide

The substitution of an aromatic nucleus by electron-supplying groups results in ring cleavage by per acids. Pyrogallol trimethyl ether (LXXXVIII), with a large excess of perbenzoic acid in boiling benzene, gives dimethyl oxalate (121).

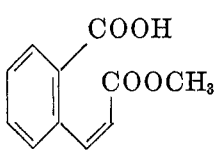


LXXXVIII

Similarly, 2-methoxynaphthalene (LXXXIX) gives *o*-carboxycinnamic acid methyl ester (XC) (122).



LXXXIX

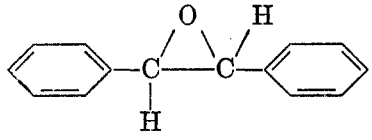


XC

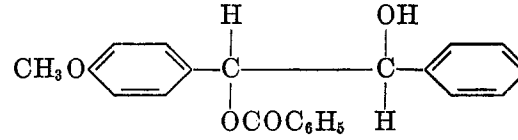
Less severe conditions will also disrupt the nucleus (131, 132), and there are differences in reactivity when different solvents are employed. Particularly easily oxidized are 1,3-dimethoxy- and 1,3,5-trimethoxybenzene, compounds which have positions of high electron density between the methoxyl groups. In addition to cleavage products *p*-quinones have been isolated from many of the reactions. Thus 1,3-dimethoxybenzene gives 3-hydroxy-6-methoxy-1,4-benzoquinone.

The conventional preparation of stilbene oxide (XCI) by the reaction of stilbene and perbenzoic acid cannot be used to prepare *p*-methoxystilbene

oxide, since the ring is opened, and the product at 0°C. is the glycol benzoate (XCII).

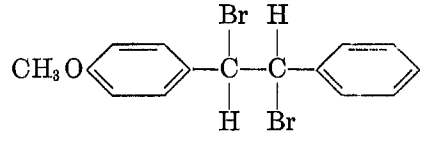


XCI



XCII

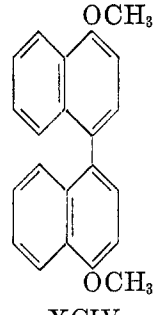
It may be noted that this benzoate is also formed by refluxing the methoxy compound with benzoic acid in chloroform solution, whereas stilbene oxide similarly treated is recovered unchanged. *p*-Methoxystilbene dibromide (XCIII) with sodium carbonate in aqueous acetone gives the oxide in 60 per cent yield, yet the corresponding *p*-tolylstilbene dibromide shows no reaction (57).



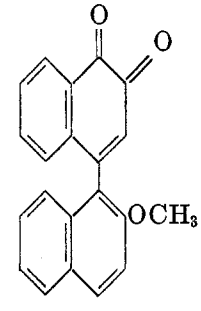
XCIII

The action of perbenzoic acid on 4-methoxystyrene also gives the benzoate and not the oxide (16).

Performic acid unexpectedly converts 1- and 2-methoxynaphthalene to the dimeric products 4,4′-dimethoxy-1,1′-binaphthyl (XCIV) and 2′-methoxy-1,1′-binaphthyl-3,4-dione (XCV), respectively (123).

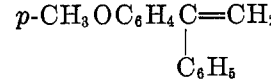


XCIV



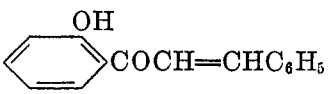
XCV

The oxidation of 1-*p*-anisyl-1-phenylethylene (XCVI) with per acids is anomalous (94). The product with hydrogen peroxide in formic acid is not the hydroxyformate, but a mixture of acetophenone and *p*-hydroxyanisole. In contrast, *p*-chloro-1,1-diphenylethylene reacts in a normal manner.

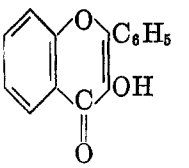


XCVI

The oxidation of 2′-hydroxychalcones with alkaline hydrogen peroxide yields flavonols when the chalcones are unsubstituted in the 6′-position: e.g., XCVII gives XCVIII.

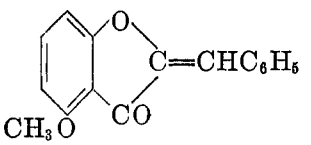


XCVIII



XCVII

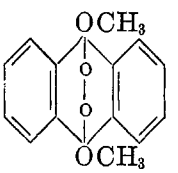
When a methoxyl group is in the 6′-position the predominant product is a benzalcoumaranone, e.g., XCIX (139).



XCIX

3. *Photoöxidation*

Methoxyl groups in the peri positions facilitate the photoöxidation of anthracene. 9,10-Dimethoxyanthracene is oxidized in sunlight in a few seconds and the high rate may indicate a chain mechanism (107). This photo oxide (C) is so stable that it can be sublimed without decomposition (108).



C

Methoxyl substituents in the anthracene rings cause wide variation in the stability of the photo oxide. 1,4-Dimethoxy-9,10-diphenylanthracene gives a crystalline oxide which loses this oxygen even in the dark (109), but the 1,8-dimethoxy isomer is more stable (108).

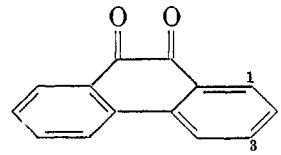
D. REDUCTION

1. *Electrochemical reduction*

There is a considerable literature on the effect of methoxyl on the electrochemical reduction of carbonyl compounds.

When the methoxyl group is in the 2-position of 1,4-naphthoquinone and in the 4-position of 1,2-naphthoquinone, the oxidation–reduction potential is lowered (126). When the substituent is not in the quinonoid ring but is con-

jugated with one of the carbonyl groups, e.g., as in 1- or 3-methoxyphenanthraquinone (CI), the potential is again lowered but to a lesser extent (124).

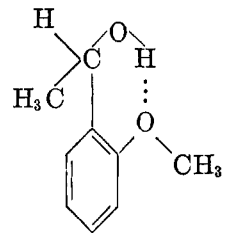


CI

The acquisition of electrons on reduction converts the quinone into the hydroquinone ion, and the electron-repelling methoxyl group decreases the attractive power of the quinone oxygen atoms for external electrons.

Several workers have investigated the polarographic reduction of methoxybenzaldehydes in different solvents and at widely varying pH values (29, 141, 162, 253, 254, 256). Their results for the order of reduction are not wholly in accord. Gergely and Iredale (141) found that the half-wave potentials were *o*-methoxybenzaldehyde < benzaldehyde < *m*-methoxybenzaldehyde for strongly acid and aqueous tetraethylammonium bromide solutions, and there is general agreement that *p*-methoxybenzaldehyde is the most difficult to reduce. The restraining effect of a *p*-methoxyl group on the reduction of a carbonyl group has also been shown in acetophenone (33, 254) and in benzophenone (62, 254). The release of electrons to the carbonyl group renders the carbon atom less electron-deficient and therefore less ready to accept an electron in the reduction process.

In contrast, the effect of a methoxyl group ortho to a carbonyl group shows considerable variation in different compounds. It causes easier reduction in benzaldehyde, but more difficult reduction in acetophenone. The large negative half-wave potential in the latter case is attributed to hydrogen bonding in the carbinol (CII).

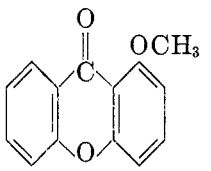


CII

In the flavone series the 5-methoxy group which is ortho to carbonyl again renders reduction more difficult (115). In methoxytropolones an ortho group makes reduction easier. Thus, β-methyltropolone methyl ether is more readily reduced than the hydroxy compound (222), and it is suggested that methylation has interfered with the ionic resonance (LXXI and LXXII). Similarly, the methoxy compound colchicine is more readily reduced than colchiceine.

In the anthraquinones an unusual situation arises. Compounds with meth-

oxyl groups ortho to both carbonyl groups are not reducible in strongly acid solutions; all other methoxyanthraquinones are reducible (293). Investigation of other markedly basic *o*-methoxyketones shows that irreducibility in solutions of low pH is not common. Thus 1-methoxyxanthone (CIII) has a half-wave reduction potential of −0.77 v. in a solution of apparent pH = 1.24 (290). The reductions of xanthone and its monomethyl ethers are one-electron reversible processes, while those anthraquinones which undergo reduction do so irreversibly.



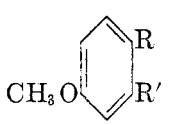
CIII

It is noteworthy that the *o*-, *m*-, and *p*-dimethoxydiphenyl disulfides are reversibly reduced in a neutral 50 per cent ethanol solution, whereas the unsubstituted and methyl-substituted isomers are irreversibly reduced under the same conditions (88).

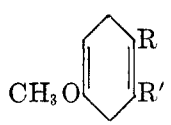
2. Chemical reduction

(a) Reduction of ethers and carboxylic acids

The methoxyl group has played an important part in the study of the reduction products obtained when sodium dissolves in alcohols or in liquid ammonia, or in mixtures of ethanol and liquid ammonia. Birch (48) found that substituted anisoles (CIV) gave dihydroanisoles (CV) by the action of sodium in liquid ammonia in the presence of a proton donor such as alcohol.

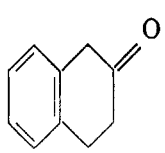


CIV



CV

Reduction by sodium and alcohol has enabled tetralones to be obtained from methoxynaphthalenes. For example, 2-methoxynaphthalene on reduction and hydrolysis gives β-tetralone (CVI) (89).



CVI

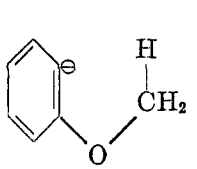
The fission of an ether, ROR′, can follow the course RH + R′OH or R′H + ROH, and the group which contains less electron-repelling or more electron-

attracting groups appears as RH (50). The one exception is the methoxyl group, whose influence depends on its position relative to the charged carbon atom formed in the reduction:

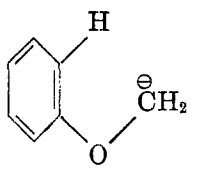
$$p\text{-}CH_3OC_6H_4OC_6H_5 \rightarrow p\text{-}CH_3OC_6H_4OH$$

$$o\text{-}CH_3OC_6H_4OC_6H_4OCH_3\text{-}p \rightarrow HOC_6H_4OCH_3\text{-}p$$

In the para position the methoxyl group is charge-destabilizing, as expected from its electron-repelling character, but in the ortho position it is charge-stabilizing. This might mean that in the ortho position the inductive effect predominates. Birch prefers to explain the effect in the ortho position by a hyperconjugation which stabilizes the negative charge by partially transferring it to the carbon of the methoxyl group (CVII, CVIII).

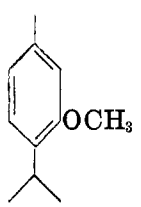


CVII

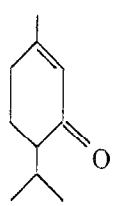


CVIII

The reduction of phenolic ethers to ketones by lithium dissolving in liquid ammonia gives good yields when reduction by sodium in ammonia is difficult (292). By this means thymol methyl ether (CIX) has been converted to piperitone (CX) in excellent yield (111). Using sodium, only traces of piperitone were obtained (47).

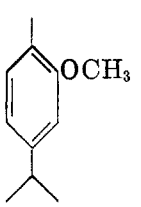


CIX

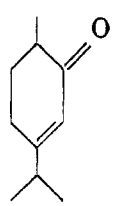


CX

In a similar manner carvacrol methyl ether (CXI) gives carvenone (CXII) but the yields are not so good.



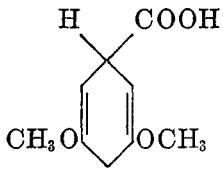
CXI



CXII

Many compounds are demethoxylated during these reductions. 2(and4)-Alkoxybenzoic acids lose the alkoxyl group. The reduction of 3-methoxybenzoic

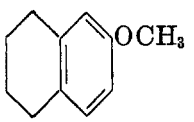
acid surprisingly results in a 3-methoxytetrahydrobenzoic acid. The same product is obtained from 3,4-dimethoxybenzoic acid by removal of the 4-methoxy group (51). Semmler (260) found that 3,4,5-trimethoxybenzoic acid with sodium in ethanol gave 3-methoxybenzoic acid, and the intermediate 1,4-dihydro-3,5-dimethoxybenzoic acid (CXIII) has been isolated (51).



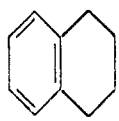
CXIII

Removal of the 4-methoxy group is doubtless facilitated by the carboxyl group, but 1,2,3-trimethoxybenzene also loses the central group (48), since reduction and hydrolysis form 1,3-diketocyclohexane. 1,3,5-Trimethoxybenzene gives the same product.

2-Methoxynaphthalene can be catalytically hydrogenated almost exclusively in the substituted or in the unsubstituted ring (270). In acetic acid–ethanol solution over Raney nickel the product is largely 6-methoxytetralin (CXIV), while in alkaline solution it is mainly tetralin (CXV).

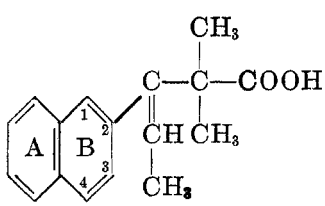


CXIV



CXV

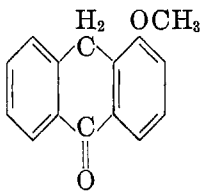
The preferential reduction of an aromatic ring or of a side-chain containing an ethylenic double bond has been carefully investigated for compounds of the type of CXVI (175). The aliphatic double bond is difficult to attack, but the Adams platinum catalyst at ordinary temperature and pressure is generally satisfactory. With methoxyl at any position in ring A the double bond is reduced ten times more quickly than ring B. If methoxyl (or methyl) occupies positions 1, 3, or 4, nucleus A is much more sensitive to hydrogenation and the aliphatic double bond loses much of its ability to add a molecule of hydrogen. With methoxyl (or methyl) in the 1-position the double bond is totally inert. The effect is ascribed to steric hindrance.



CXVI

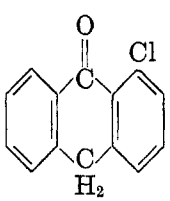
(b) Reduction of carbonyl, nitrile, and sulfone groups

The presence of methoxyl groups can produce unusual results in the reduction of carbonyl compounds. This is particularly the case with α-methoxyanthraquinones. 1-Methoxyanthraquinone with sodium hydrosulfite, $Na_2S_2O_4$, in strongly alkaline solution gives 4-methoxy-10-anthrone (CXVII) as the only product, i.e., only the keto group peri to methoxyl is reduced.

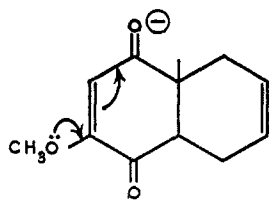


CXVII

However, if the α-substituent is electron-attracting, the reaction pursues an entirely different course. Thus 1-chloroanthraquinone gives 4-chloro-9-anthrone (CXVIII) as the sole product (87). If the reductions are carried out in chlorobenzene solution, using nickel as a catalyst under pressure and a temperature of 200°C., 1-methoxy-, 1,8-dimethoxy-, 1,2-dimethoxy-, and 1,4-dimethoxyanthraquinone all form the 10-anthrone compounds (300). Very unusual indeed is the reduction of 1,4-dimethoxyanthraquinone with sodium hydrosulfite in alkaline solution to give 1,4-dimethoxy-2,3-dihydroanthraquinone; i.e., the nucleus is reduced but not the carbonyl groups (301).



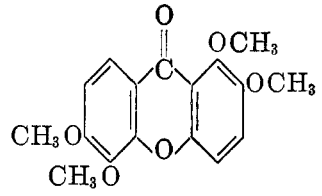
CXVIII



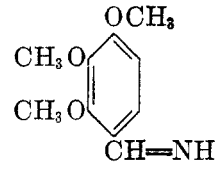
CXIX

An interesting difference in the reactivity of the carbonyl groups in a methoxy-substituted *p*-quinone is shown in the compound CXIX. The carbonyl group meta to the methoxyl group is much less susceptible to reduction than the other (298).

There are a number of reductions of methoxy compounds by lithium aluminum hydride in which the products are different from those usually expected. With this reagent the carbonyl group generally gives carbinols, but with some methoxyxanthones and methoxyflavones the reduction goes a step further to the methylene derivatives. Thus 1,2,5,6-tetramethoxyxanthone (CXX) gives the corresponding xanthene (262).



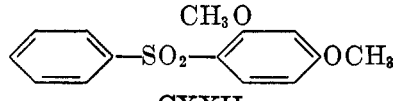
CXX



CXXI

Lithium aluminum hydride reduces aromatic nitriles such as benzonitrile and tolunitrile to the corresponding primary amine in good yield. 2,3,4-Trimethoxybenzonitrile, on the other hand, gives a 50 per cent yield of the aldimine (CXXI) (150). This is attributed in part to the neutralization of the electron-deficient carbon atom of the nitrile group, which is the point of attack by the nucleophilic aluminohydride anion, by the electron-releasing methoxyl groups.

Diaryl and alkyl aryl sulfones undergo reductive fission by sodium amalgam and boiling ethanol to a sulfinic acid and a hydrocarbon. The latter is derived from the radical of the greater electron-releasing character. Thus 2,4-dimethoxydiphenyl sulfone (CXXII) gives 1,3-dimethoxybenzene as one product (95).



CXXII

E. AROMATIC SUBSTITUTION

The nucleophilic replacement of methoxyl and also its effect on the nucleophilic substitution of other groups have been covered in reviews (68; 76, page 660; 217). This article is therefore restricted mainly to aspects of electrophilic and free-radical reactions of methoxy compounds.

1. Protophilic substitution

In a few types of aromatic substitution inductive effects play a more important part than electromeric effects in determining the rate of reaction. Nuclear metalation reactions show that the activation of the nucleus by substituent groups is in the order —F > —OCH_3 > —CF_3 > —H (244). The inductive effects of the groups increase the acidity of the ring hydrogen atoms, and the abstraction of a proton is the rate-determining stage. Such reactions have been termed protophilic substitutions (67). In the exchange of deuterium for protium in the presence of a strong base (NH_2^-) and a proton-donating solvent (NH_3), electronegative substituents (—F, —CF_3, and —OCH_3) increase the rate. The inductive effect decreases the electron density at the carbon where deuterium is attached, thereby increasing the ease with which a deuteron can be removed by a base, and the π-electron system of the ring is not involved in an important way (152).

2. Electrophilic substitution

The influence of the methoxyl group in aromatic bromination has been studied quantitatively (213). The meta position is activated slightly so that the second-order relay of the $+T$ effect exceeds the $-I$ effect of the group. The corresponding para and ortho positions are activated, in comparison, by a factor of 10^8, and the $\frac{1}{2}o:p$ ratio for the bromination of anisole is ca. 1:40. Steric hindrance and the $-I$ effect of the methoxyl group reduce the yield of the ortho compound. The bromination of 2,6-dimethylanisole shows steric inhibition of conjugation of the methoxyl group (page 337).

The nitration of anisole gives no measurable amount (<0.1 per cent) of the meta compound (70), while the $\frac{1}{2}o:p$ ratio is 1:8 (103). The kinetics and mechanism of the nitration of phenol and phenol ethers (chiefly of anisole and its derivatives) have been carefully studied (69). These nitrations are accelerated by nitrous acid, and there is a tendency for dealkylation and for side reactions to occur. The acceleration by nitrous acid is due to a special mechanism of nitration given by the equation

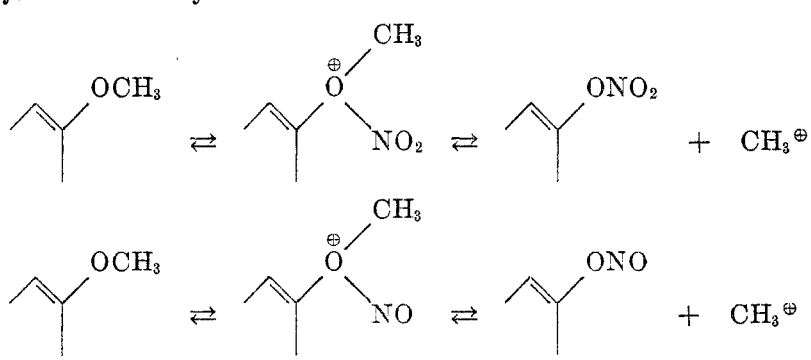
$$\text{Rate} \propto [\text{ArH}]^1[\text{HNO}_2]^1$$

with nitric acid in excess. This special process is superimposed on the general nitration process given by the relation

$$\text{Rate} \propto [\text{ArH}]^0/(a + b)[\text{HNO}_2]^{\frac{1}{2}}$$

The change from the special to the general mechanism is effected by increasing $[HNO_3]$, i.e., the concentration of the nitronium ion, NO_2^+, and by decreasing $[HNO_2]$.

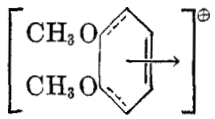
These two mechanisms were isolated in the nitration of *p*-chloroanisole, but it was not possible to do so completely with anisole. In the special mechanism the nitrosonium ion, NO^+, plays the part that the nitronium ion does in the general mechanism. In the special mechanism nitrosation is followed rapidly by nitration. Dealkylation may occur by either of the two mechanisms by attachment of the nitrosonium or nitronium ion to the ether oxygen followed by the ejection of an alkyl radical.



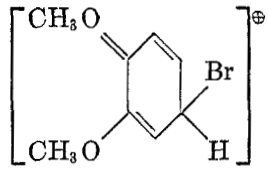
The aryl nitrate, or nitrite, will undergo acidolysis and may be isolated as a phenol. The methyl group will combine with an anion, e.g., an acetate ion if

the solvent for nitration is acetic acid, and may be isolated as methyl acetate. Alternative mechanisms for the dealkylation have been suggested (69, page 2653).

Dewar (102) calculated that *o*- and *p*-dimethoxybenzene should form π (i.e., unsaturation) complexes (e.g., CXXIII) and should therefore react more readily than anisole with electrophilic reagents. The argument is that CXXIV should be adversely affected by the *m*-methoxy group, whereas both methoxyl groups facilitate the reaction of CXXIII.

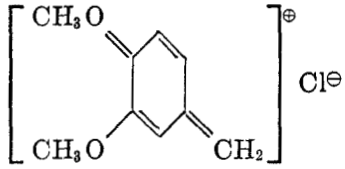


CXXIII



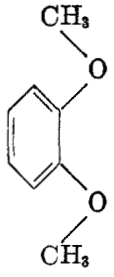
CXXIV

In fact, *p*-dimethoxybenzene is brominated at about $\frac{1}{10}$ the rate of anisole, while the ortho compound (veratrole) is brominated more rapidly in a ratio of 3.4:1 (213). Baddeley and Smith (20) found that the rate of the unimolecular alcoholysis of veratryl chloride was much faster than that of anisyl chloride. The rate of formation of the cation (CXXV) gives a measure of the ease of formation of the complex (CXXIV), and it is concluded that both methoxyl groups facilitate the formation of this complex.

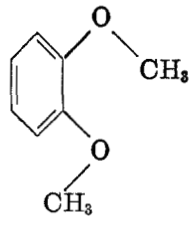


CXXV

Comparison of the rate of bromination of anisole, veratrole, and various cyclic ethers has led to an interesting relationship between electrostatic interaction and intramolecular configuration (19, 21). Veratrole may have the *trans-trans* (CXXVI) and the *cis-trans* (CXXVII) structures.



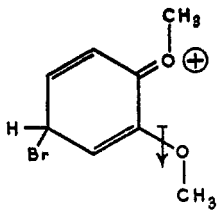
CXXVI



CXXVII

The calculated dipole moments for these configurations are 0.5 D and 2.1 D, respectively. Curran (93) observed the moment as 1.23 D, from which it is

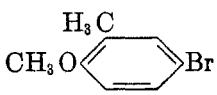
concluded that veratrole exists in both forms. In these configurations the dipoles (e.g., CXXVIII) are oriented so that they assist the conjugation of the neighboring methoxyl group with the nucleus and therefore contribute towards the stability of the intermediate quinonoid structure.



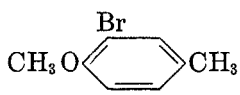
CXXVIII

This explains why the reactivity of anisole is less than that of veratrole. The rapid and smooth nitration of veratrole by cold dilute nitric acid, conditions under which anisole is completely unreactive (7, 82), is similarly understood.

The interaction between the methoxyl group and other groups is clearly shown by the chlorination of CXXIX at a rate 0.612 that of the isomeric CXXX (54).



CXXIX



CXXX

Naphthyl ethers are highly reactive and only preliminary results on the kinetics of their halogenation are available (181). Data based on the rate of chlorination of the 2- and 4-nitro- and the 2- and 4-chloro-1-naphthyl methyl ethers show that whereas in the benzene series the ortho-substituted ether is more reactive than the corresponding para compound, in the naphthalene series the reverse is the case.

1,5-Dihydroxynaphthalene and its mono- and dimethyl ethers are substituted differently by halogen, and the direction of substitution is influenced by the nature of the solvent (45, 83). 1,5-Dihydroxynaphthalene in both acetic acid and carbon tetrachloride solution is brominated in the 2- and 6-positions. 1,5-Dimethoxynaphthalene in carbon tetrachloride gives the 4,8-dibromo compound and in benzene the 2,6-dibromo derivative. 1-Hydroxy-5-methoxynaphthalene in carbon tetrachloride gives the 2,8-dibromo compound, and in benzene a molecular compound of that with the 2,6-dibromo compound. The bromine is therefore directed by hydroxyl into the ortho position and by methoxyl (when in carbon tetrachloride solution) into the para position.

Anisole is acetylated by concentrated aqueous perchloric acid in an excess of acetic anhydride to form *p*-methoxyacetophenone (74). The reaction involves the production of the acetylium (CH_3CO^+) ion.

$$(CH_3CO)_2O + H^{\oplus} \rightleftarrows (CH_3CO)_2OH^{\oplus} \rightleftarrows CH_3CO^{\oplus} + CH_3COOH$$

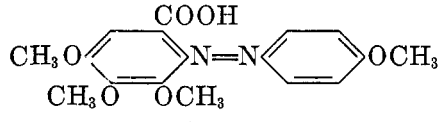
The acetylation reaction regenerates a proton which is then available for further reaction with acetic anhydride, and the yields are greater than would be stoichi-

ometrically possible on the amount of perchloric acid used. Solutions of perchloric acid in acetic acid, involving the acetic acidium ion ($CH_3COOH_2^{\oplus}$), are not acetylating agents. Further evidence for the reactivity of the acetylium ion is that a solution of acetylium perchlorate ($CH_3CO^{\oplus}ClO_4^{\ominus}$), prepared *in situ* from equimolecular amounts of acetyl chloride and silver perchlorate in an inert solvent of relatively high dielectric constant (e.g., nitromethane), converts anisole into *p*-methoxyacetophenone rapidly and in high yield (75).

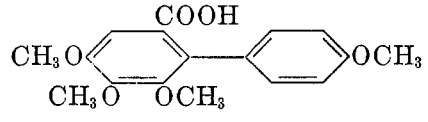
3. Free-radical reactions

Reactions between methoxy compounds and free radicals are steadily being investigated. Methoxy-substituted biaryls have been successfully prepared from free aryl radicals by the decomposition of diazo compounds and of *N*-nitrosoacetylamines (14). Thus, diazotized *p*-anisidine can be coupled with benzene to give 4-methoxybiphenyl in 25 per cent yield (113), and *p*-methoxyacetanilide and benzene by the nitroso reaction form the same product in 55 per cent yield (155). Anisole reacts with diazotized aniline, *m*-nitroaniline, and *p*-anisidine, unexpectedly giving the *o*-methoxybiphenyl in each case (110).

When a reaction can occur by an ionic or by a free-radical mechanism the former type may be preferred. A diazonium compound can react as the ion ArN_2^+ to give an azo compound, or as the radical Ar• to form a biaryl. The radical reaction is retarded by electron-donating groups (148). The Gomberg reaction of diazotized *p*-anisidine and sodium 3,4,5-trimethoxybenzoate produces the azo compound CXXXI and not the biphenyl derivative CXXXII (129).

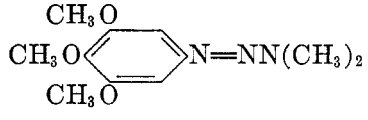


CXXXI

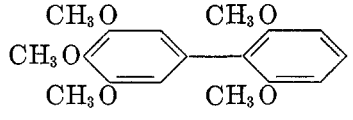


CXXXII

Alkoxyl groups ortho or para to a strongly electron-withdrawing group can be displaced during Grignard reactions (135), and it may be assumed that the attacking agent is the anion R^- from the Grignard reagent RMgX. The reaction of the triazene CXXXIII with 1,2,3-trimethoxybenzene results, however, in the replacement of the central of the three methoxyl groups by the 3,4,5-trimethoxyphenyl radical to give a pentamethoxybiphenyl (CXXXIV) (234).

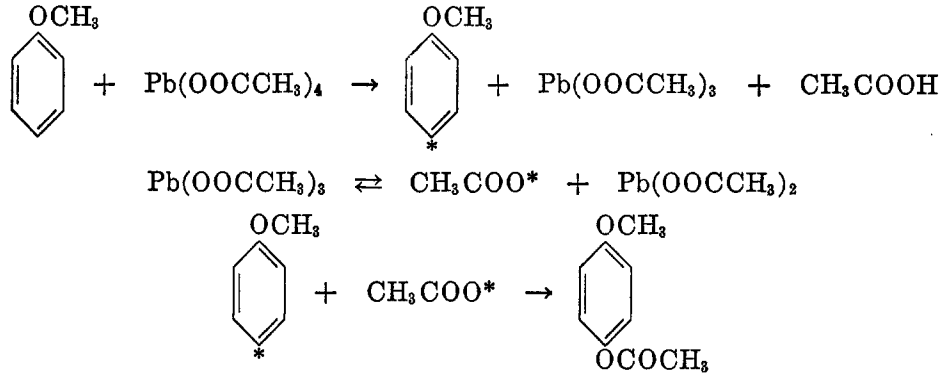


CXXXIII



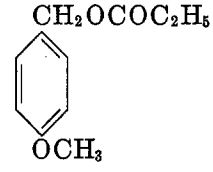
CXXXIV

Benzenoid compounds having a powerful electron-donating substituent undergo nuclear acetoxylation by lead tetraacetate (84), but methylation by this reagent is favored in compounds with electron-attracting substituents (125). Anisole in acetic acid at 80°C. gives *p*-acetoxyanisole by the following proposed mechanism.



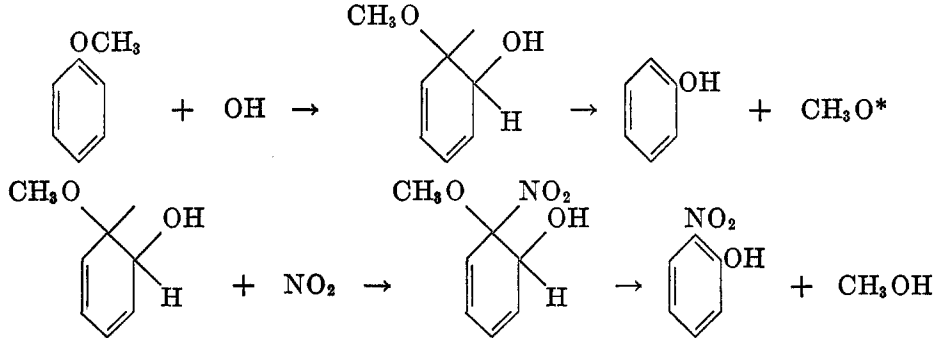
Similarly 1- and 2-methoxynaphthalene give the 4-acetoxy and 1-acetoxy compounds, respectively (283).

Anisole, the dimethoxybenzenes, and 2-methoxynaphthalene on heating with ethyl diazoacetate at 150°C. are attacked by a radical mechanism to form aryloxy derivatives of ethyl acetate. Anisole gives ethyl *p*-methoxyphenylacetate (CXXXV) (145).



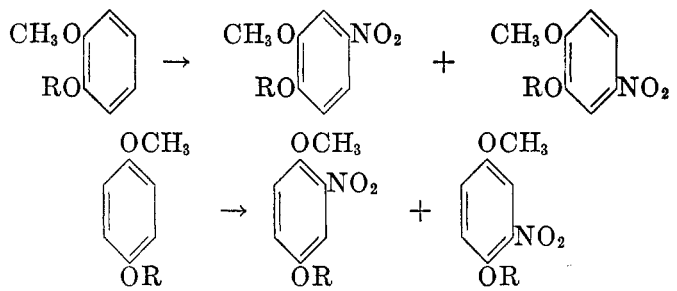
CXXXV

Anisole with pernitrous acid gives phenol and nitrophenols (151). It is considered that the acid undergoes homolytic fission $HO_2NO \rightarrow HO + NO_2$ and that the following sequence occurs:

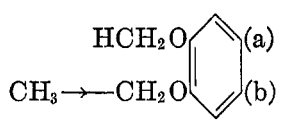


4. Competitive effects in electrophilic substitution

The first comprehensive study of the influence of alkoxyl groups on aromatic substitution was the mononitration of a series of alkyl methyl ethers of 1,2- and 1,4-dihydroxybenzene (6, 7, 230, 250).



The compounds were independently synthesized, and by a melting-point curve for mixtures of the two isomers any mixture produced on nitration was analyzed. The inductive effect of the alkyl group assists the mesomeric release from the oxygen atom so that considering the ethyl ether (CXXXVI), the directing effect of ethoxyl to position (a) should exceed that of methoxyl to position (b).



CXXXVI

The directing power rose and then fell in the order $-OCH_3 > -OC_2H_5 >$ isopropoxy $<$ *n*-propoxy $<$ *n*-butoxy. The decreasing values are attributed to the inductive effect of the group —OR being exerted partially against the oxygen of the methoxyl group. In the para series the inductive effect of R— assists the mesomeric release from —OR and operates against the oxygen of $-OCH_3$. The directive power is now higher than in the ortho series and rises progressively throughout the alkoxyl series.

A more direct method of evaluating the relative directing power of alkoxyl groups is the nuclear halogenation of phenolic ethers of the types *p*-ROC_6H_4X and 2,4-$X_2C_6H_3OR$. In these only the ortho position to the alkoxyl group is substituted and the velocities were measured (53, 55). The results differed somewhat from those found by the nitration method. On chlorination there was a gradual rise from methyl to butyl, and further lengthening of the chain was accompanied by a slight but progressive decrease in directive power (180). The sequence is the same in the bromination of aromatic ethers by hypobromous acid (60). Although bromination and chlorination are comparable processes, it could not be foreseen that the relative directive effects of a wide range of alkoxyl groups would be so similar, especially since in bromination in 75 per cent acetic acid the attacking reagent is either the brominium ion or the solvated cation H_2OBr^+, while in chlorination in 99 per cent acetic acid it is the chlorine molecule. A similar rise from methyl to butyl, followed by a constant value, was obtained from the alkaline hydrolysis of saturated aliphatic esters (117).

Table 2 summarizes the relative directing effects of methoxyl and other groups in electrophilic substitution.

TABLE 2

The relative directing effects of methoxyl and other groups in electrophilic substitution

Compound	Reaction	Products	Directing Effect	References
Guaiacol	Nitration	4-Nitroguaiacol and 6-nitroguaiacol	—OH > —OCH_3	(186)
	Bromination	4-Bromoguaiacol	—OH > —OCH_3	(248, 281)
	Sulfonation	4-Guaiacolsulfonic acid and 5-guaiacolsulfonic acid	—OH = —OCH_3	(243)
	tert-Butylation	4-*tert*-Butylguaiacol and 5-*tert*-butylguaiacol	—OH = —OCH_3	(251)
2-Methoxyacetanilide	Nitration	Mainly 2-methoxy-4-nitroacetanilide and 2-methoxy-6-nitroacetanilide	—$NHCOCH_3$ > —OCH_3	(173)
4-Methoxyacetanilide	Nitration	4-Methoxy-2-nitroacetanilide	—$NHCOCH_3$ > —OCH_3	(120)
2-Cresyl methyl ether	Nitration	2-Methoxy-3,5-dinitrotoluene	—OCH_3 > —CH_3	(190, 249)
4-Cresyl methyl ether	Sulfonation	4-Methoxytoluene-3-sulfonic acid	—OCH_3 > —CH_3	(8)
2-Fluoroanisole	Nitration	Mainly 2-fluoro-4-nitroanisole and 2-fluoro-6-nitroanisole	—OCH_3 > —F	(164)
2-Acetoxyanisole	Nitration	2-Acetoxy-5-nitroanisole	—OCH_3 > —$OCOCH_3$	(82, 173, 186, 242)
	Bromination	2-Acetoxy-5-bromoanisole	—OCH_3 > —$OCOCH_3$	(281)

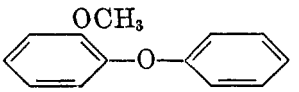
Directing effects become very complex when compounds containing more than two substituents are further substituted.

The literature contains many examples of conflicting orientation when different electrophilic reagents are used on the same compound, so that the relationships given in table 2 may be reversed.

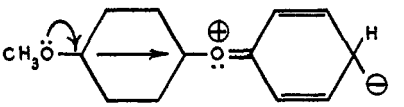
The bromination of 2,4-dimethoxyphenol produces 5-bromo-2,4-dimethoxyphenol. The activating effect of the two methoxyl groups on the 5-position surpasses that of the hydroxyl group on the 6-position (35).

The interaction of a strong ortho–para-directing group such as methoxyl with a powerful meta-directing group like the nitro group produces unusual further orientation. *m*-Nitroanisole on nitration gives 2,3-dinitroanisole as one product (163). The para position to the nitro group is deactivated to a greater extent than the ortho position. Similarly 4-methoxy-2-nitroanisole is further nitrated in the 3-position (223).

The phenoxyanisoles show reversal of the directing powers of the methoxyl and phenoxyl groups (277). *o*-Phenoxyanisole (CXXXVII) is brominated and nitrated in the 5-position. *p*-Phenoxyanisole is nitrated ortho to the methoxyl group, but it is brominated first in the para position of the unsubstituted ring by transmission of the mesomeric effect of the methoxyl group across the ether link (CXXXVIII). In *o*- and *p*-phenoxyanisole therefore the orientation is determined by the methoxyl group. On the other hand, *m*-phenoxyanisole is brominated and nitrated in the 6-position, so that the orientation is here apparently determined by the phenoxyl group.

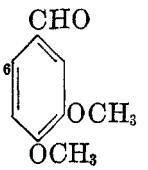


CXXXVII

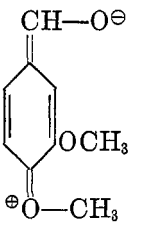


CXXXVIII

The electrophilic substitution of veratraldehyde (CXXXIX) has interesting features. Nitration and bromination take place in the 6-position. A partial explanation (216) of this orientation is that the quinonoid resonance structure (CXL) leaves only the 3-methoxy group free to exert its normal orienting effect.

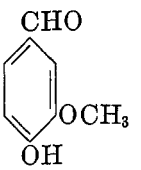


CXXXIX

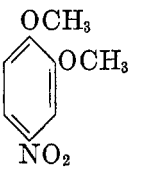


CXL

This explanation, while plausible, cannot be wholly correct since compounds similar in structure to veratraldehyde are differently orientated. Thus vanillin (CXLI) is nitrated and brominated at the 5-position (96, 280), and 4-nitroveratrole (CXLII) is brominated at the 6-position but nitrated at position 5.

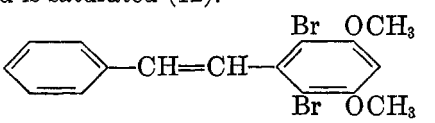


CXLI



CXLII

When competition exists between bromination of a methoxy-substituted nucleus and an olefin double bond in a side-chain, the result depends on the degree of activation of the nucleus. In general the speed of addition of bromine to the central double bond of a stilbene is greater than that of nuclear substitution (46), but 3,5-dimethoxystilbene is brominated in the ring (CXLIII) before the double bond is saturated (12).



CXLIII

5. Side-chain reactivity and the methoxyl group

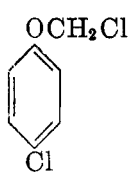
The Hammett substituent constant, σ, relates the effect of a meta or a para substituent and the reactivity of a side-chain. The σ values of *m*- and *p*-methoxy are $+0.115$ and -0.268, respectively (153), the difference of sign being accountable for by conjugation of a *p*-methoxy group and the lack of conjugation of a *m*-methoxy group. It was formerly considered that the σ value depended

only on the nature and position of the substituent, but it is becoming increasingly clear that the value may vary with the type of reaction. For a number of reactions a plot of the rate constants with different substituents against the σ constants for the substituents shows marked divergencies for the methoxyl group. One of these has already been mentioned (229). In the reaction of substituted acetophenones with perbenzoic acid the positive σ value for *m*-methoxy suggests that the ketone should have a smaller rate of reaction than that of the unsubstituted ketone, whereas the reverse is the case (132). In the epoxidations of substituted *trans*-stilbenes with perbenzoic acid and of substituted perbenzoic acids with *trans*-stilbene, the plots of Hammett σ functions and rate constants for the reactions show divergencies for the methoxyl group in both cases (210). A study of the rates of solvolysis of meta- and para-substituted benzyl tosylates in acetone–water mixtures gives only a limited correlation with the Hammett equation (189). Thus, *p*-methoxy has an apparent σ value of -2.5, whereas the value for *m*-methoxy agrees well with that derived from the ionization constant of *m*-methoxybenzoic acid. The deviation of the para group is attributed to the resonance stabilization of the benzylcarbonium ion (page 373).

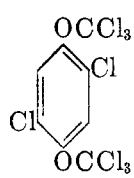
The Hammett relation has generally been useful in correlating equilibrium and rate data, but where the seat of the reaction is in the benzene ring it applies less accurately. From the relative rates of bromination of anisole, the dimethoxybenzenes, and methyl *p*-tolyl ether the sequence of activating power is *m*-methyl > *m*-methoxy > *m*-H (213). This sequence cannot be explained in terms of the σ values, which require a strongly deactivated position meta to the methoxyl group (methyl > hydrogen > methoxyl). Moreover, the results cannot be correlated with the rates of para substitution or with the σ values for this position, which are in the order methoxyl > methyl > hydrogen (212).

6. Substitution of chlorine in a methoxyl group

Aryl methyl ethers are chlorinated at room temperature almost wholly in the nucleus. Anisole at 145–160°C. gives largely *p*-chloroanisole and a small amount of 4-chlorophenoxymethyl chloride (CXLIV).



CXLIV



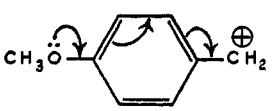
CXLV

Chlorination of chloroanisoles in the presence of phosphorus pentachloride at 200°C. produces side-chain substitution. Thus 4-chloroanisole gives 4-chlorophenoxymethyl chloride in 93 per cent yield (36). Under these conditions 1,4-dimethoxybenzene is first substituted in the 2- and 5-positions of the nucleus and the methoxyl groups are then substituted alternately, finally yielding the fully chlorinated compound (CXLV) (2).

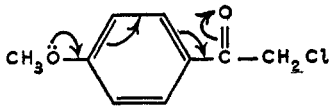
F. THE STABILIZATION OF CARBONIUM IONS

One aspect of this subject—*viz.*, the base-strengthening character of the methoxyl group in many oxygen bases—has already been described (page 350). The effect of the group on the dissociation of hexaarylethanes has been reëxamined (215). Earlier reports based the degree of dissociation upon molecular weight determinations by cryoscopy. Measured by the more delicate method of magnetic susceptibility the values are much smaller, and the effect of *o*-, *m*-, or *p*-methoxy is less than that of the corresponding methyl compound.

The stabilization of benzyl and substituted benzyl radicals by methoxyl is of considerable importance. In benzyl halides the mesomeric structure leads to incipient ionization into a benzyl cation, which is stabilized by resonance, and a halide ion. An electron-releasing group enhances this polarization, lowers the energy level of the transition complex, and weakens the carbon–halogen bond (CXLVI).



CXLVI



CXLVII

The tendency for ionization, and reaction rates depending on the rate of fission of the carbon–halogen bond in an S_N2 mechanism are increased. The first investigations of the reactivity of benzyl halides were measurements of hydrolysis rates of methoxy-, methyl-, and halogeno-substituted benzyl bromides (200, 263). The reactivity decreased in this order. The reaction rates for substituted benzyl bromides with pyridine are *p*-methoxybenzyl > benzyl > *p*-nitrobenzyl (32). The rate of reaction of benzyl chloride with pyridine is increased 160-fold when substituted with a *p*-methoxy group (26). On the other hand, the *p*-methoxy group has a small retarding effect in the corresponding reaction of ω-halogenoacetophenones (25). The methoxyl group will tend to satisfy the $-T$ effect of the carbonyl group (CXLVII) and thus diminish the polar effect of the group in inducing a positive charge on the ω-carbon atom.

The hydrolysis of benzyl chloride and of its *o*-, *m*-, and *p*-methoxy derivatives in aqueous acetone is first order and the reactivity is *p*-methoxy > *o*-methoxy > H > *m*-methoxy. This is the same as the order of electron concentrations calculated for the carbon atom at which the side-chain is linked (265). Benzyl chloride and *m*-methoxybenzyl chloride in aqueous alcohol containing caustic potash follow a simultaneous S_N1, S_N2 mechanism. Hydrolysis of phenylethyl chloride and its *o*-, *m*-, and *p*-methoxy compounds with 0.1 *N* caustic potash in aqueous alcohol involves substitution (S_N2) and also elimination (E2) to form styrenes. The hydrolysis of phenylethyl chloride and its *p*-methoxy compound is first order in aqueous ethyl alcohol. These last results conflict partly with those of Baddeley and Bennett (18) on the bimolecular reaction with potassium iodide in acetone.

There have been a number of determinations of the effect of substituents on

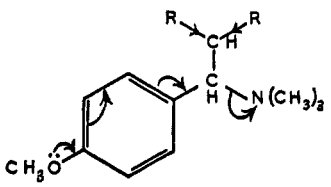
the rate of hydrolysis of benzoyl chlorides. The rate is decreased by *p*-methoxy but increased by *o*-methoxy (226, 227). The rate of alcoholysis of 2,6-dimethoxybenzoyl chloride at 0°C. was immeasurably fast. The rate of hydrolysis of para-substituted benzoyl chlorides in acetone and dioxane solutions containing 5 per cent water by volume has been followed (64). The reactions are of the S_N2 type. With increasing water content there is a tendency with electron-releasing groups such as methoxyl to react by the S_N1 mechanism.

The lability of the halogen atom in benzhydryl (biphenylmethyl) halides is strongly affected by electron-releasing substituents. *p*-Methoxybenzhydryl chloride is estimated to react 1000 times faster than the parent halide (225).

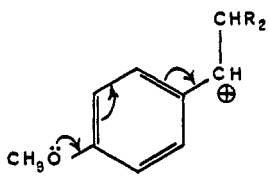
The reaction of nuclear-substituted benzyl alcohols with synthesis gas ($2H_2$:1CO) in the presence of dicobalt octacarbonyl, $[Co(CO_4)]_2$, to produce a mixture of *p*-methoxytoluene (by reduction) and 2-(*p*-methoxyphenyl)ethanol (by homologation), probably involves the formation of a carbonium ion as an intermediate (282). Thus *p*-methoxybenzyl alcohol reacts about 10^4 times as fast as benzyl alcohol, while the meta compound only reacts at ⅓ of the rate. The *m*-methoxybenzyl carbonium ion is not stabilized by resonance, and if this ion is formed in the transition stage the energy of activation will be greater than for the para compound. The relative order of reactivity of various substituted benzyl alcohols corresponds to the order of their Hammett substitution constants.

The marked reactivity of *p*-methoxybenzyl compounds is further shown by the polymerization of *p*-methoxybenzyl tosylate at −60°C. It cannot be isolated pure at room temperature. The meta compound is much more stable (188). The instability of *p*-methoxybenzyl nitrate has also been noted (30).

Quaternary ammonium iodides are readily decomposed in solution at 100°C. but only when there is a *p*-methoxy group, and particularly if it is assisted by the inductive effect from the alkylation of the β-carbon atom (224) (CXLVIII).



CXLVIII



CXLIX

The carbonium ion CXLIX can either lose a proton from the β-carbon atom to give an unsaturated product, or combine with an anion such as a hydroxyl ion.

Several instances of this type of decomposition have been investigated (39, 40, 63, 232).

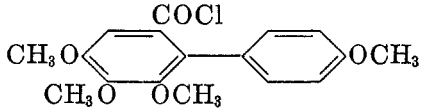
The ability of the methoxyl group to stabilize a carbonium ion has led to important studies on the alkyl–oxygen fission of carboxylic esters, aryl alcohols, organic peroxides, and ethers. The work has recently been reviewed (98).

G. CYCLIZATION REACTIONS

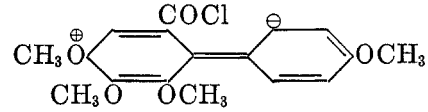
1. Monocarboxylic acids

The formation of cyclic ketones by intramolecular acylation, frequently of methoxyl compounds, was the subject of an article published in 1944 (177). Accordingly this review outlines the main features and covers the newer aspects in greater detail.

The activating influence of the methoxyl group when suitably placed to the point of ring closure is very marked. Cyclization may then occur under the mildest conditions in high yield (15), and activation can produce a seven-membered ring in preference to one with six members (192, 193). Ring closure in the meta position may be difficult (81, 179), but there are considerable variations. The cyclization of CL to give 2,3,4,7-tetramethoxyfluorenone occurs spontaneously, and this is ascribed to the high electron density in the 2′-position due to resonance forms such as CLI (129).

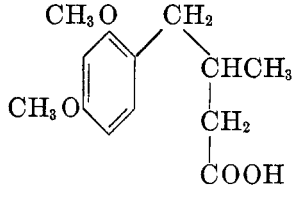


CL

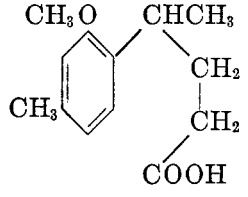


CLI

Using polyphosphoric acid as the cyclizing agent the closure of CLII has been successful (257). This is particularly interesting, since there are two *m*-methoxy groups. Using the method of Lockett and Short (204) the compound CLIII has been cyclized in 78 per cent yield despite the presence of a methoxyl group and a methyl group in the meta positions (203).

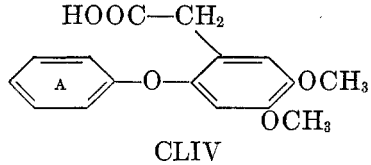


CLII



CLIII

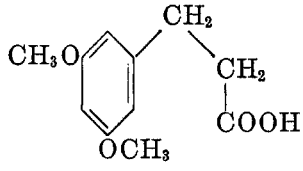
Some difficulties in ring closures in the meta position may be connected with steric hindrance (127, 204). In the cyclodehydration of *o*-phenoxyphenylacetic acids (CLIV) by means of anhydrous hydrofluoric acid the unsubstituted ring (A) gave 50–60 per cent yields, whereas the presence of a 2-methoxy group lowered the yield greatly, probably for steric reasons. Methoxyl in positions 3 and 4 had little effect (197).



CLIV

Other instances of cyclization meta to a methoxyl group may be found in the literature (38, 158, 220, 252, 274).

Difficulty was experienced in cyclizing CLV; this result is surprising, since the methoxyl groups are favorably placed for ring activation. The yield was 4–6 per cent (99).

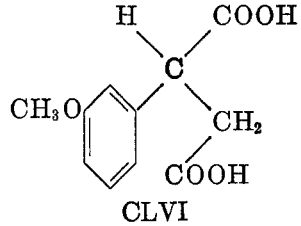


CLV

If there is a meta substituent, ring closure is possible at the ortho and para positions. Generally it occurs at the para position, but the isomeric ketone arising from ortho cyclization may be present in small proportion (174, 178).

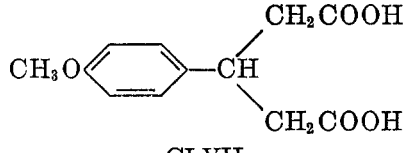
2. Dicarboxylic acids

The Friedel–Crafts and the hydrofluoric acid methods have been applied to arylsuccinic and arylglutaric acids. *m*-Methoxyphenylsuccinic acid (CLVI) gives 6-methoxy-3-oxoindane-1-carboxylic acid, and probably a small amount of the isomer by cyclization ortho to the methoxyl group.



CLVI

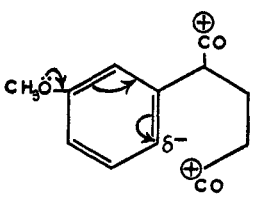
In contrast, *p*-methoxyphenylsuccinic acid could not be cyclized (11). However, by the Friedel–Crafts method β-(*p*-methoxyphenyl)glutaric acid (CLVII) has been cyclized under drastic conditions with simultaneous demethylation (157).



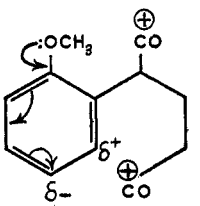
CLVII

This result is confirmation of the deactivating effect of a carboxyl group alpha to a phenyl nucleus (10, 22). The effect is most pronounced in cyclizations by hydrofluoric acid, a reagent which is very sensitive to activating and deactivating processes. β-(*m*-Methoxyphenyl)glutaric acid is cyclized by aluminum chloride in nitrobenzene at 150°C. in 83 per cent yield and, in contrast with the para isomer, the methoxyl group remains unattacked (157).

Cyclization experiments with α-methoxyphenylglutaric acids (158) and with γ-carboxy-γ-methoxyphenylpimelic acids (159) again show that there is a retarding effect on cyclization attributed to the nearer carboxyl group which in the reaction medium would be converted into —CO^+. In the case of α-(*m*-methoxyphenyl)glutaric acid the deactivating inductive effect due to the nearer —CO^+ is overcome by the tautomeric effect of the methoxyl group (CLVIII) and cyclization is easy. In the *o*-methoxy compound (CLIX) and in the para isomer this is not the case, and reaction is more difficult.

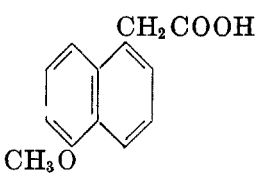


CLVIII

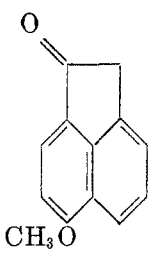


CLIX

Intramolecular acylation experiments have been extended to methoxy-substituted 1-naphthyl aliphatic acids (147). A methoxyl group at the 5- or 7-position assists cyclization at the 8-position, e.g., CLX gives the peri-naphthone (CLXI), but when the methoxyl group is in the 6-position ring closure occurs at the 2-position (CLXII).

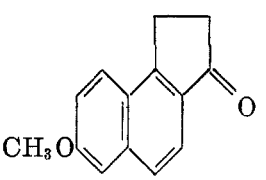


CLX

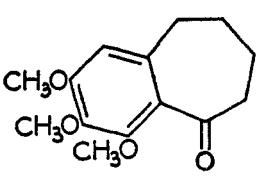


CLXI

Much use has been made of polyphosphoric acid in the synthesis of benzosuberones and related compounds having the carbon ring system of the type shown in formula CLXIII; this type is present in colchicine (136, 138, 194, 195, 196).

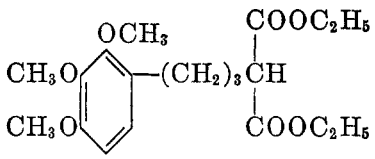


CLXII

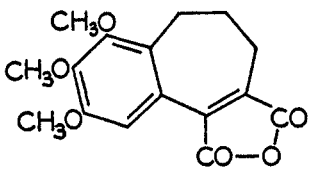


CLXIII

The Bougault glyoxylate cyclization reaction gives benzosuberonedicarboxylic acid anhydrides with a methoxyl group activating the position of ring closure: e.g., CLXIV gives CLXV (165).

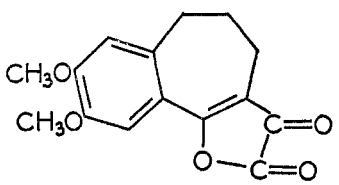


CLXIV

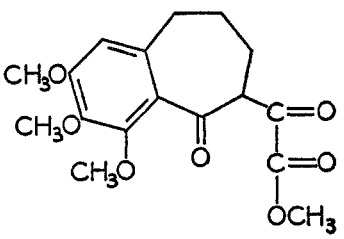


CLXV

Glyoxylation of benzosuberone and of certain substituted benzosuberones unexpectedly gives the enol lactone instead of the glyoxylate (167). Thus 2,3-dimethoxybenzosuberone gives the lactone CLXVI, but the 2,3,4-trimethoxy compound forms the expected glyoxylate (CLXVII).

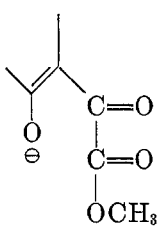


CLXVI



CLXVII

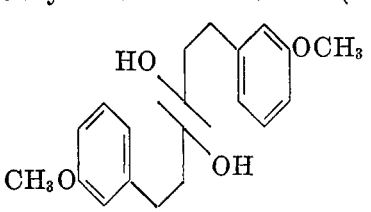
The proximity of the electron-releasing 4-methoxy group may suppress the formation of the resonance hybrid (CLXVIII) on which the mechanism of ring closure is based.



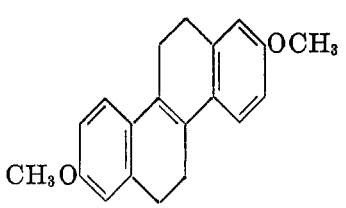
CLXVIII

3. Other cyclizations

An interesting double ring cyclization of a methoxy compound is the conversion of the acyloin CLXIX to CLXX (52).



CLXIX



CLXX

The important role of the methoxyl group in cyclizations leading to isoquinolines by the Bischler–Napieralski, Pictet–Spengler, and Pomeranz–Fritsch reactions has been emphasized in lengthy articles (140, 284, 285).

The reviewer expresses his thanks to those who assisted the compilation of this article by expert advice on their work, and particularly for permission to include research not yet published.

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