

METALATIONS WITH ORGANOSODIUM COMPOUNDS

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I. INTRODUCTION

The term metalation has been proposed for reactions which involve replacement of a hydrogen atom by a metal to give a true organometallic compound (26). Since the replacement of the hydrogen of active methylene groups results in salts which are not generally thought of as true organometallics, this type of replacement will not be considered in this discussion.

Metalations with organosodium compounds have not been studied as extensively as the corresponding reactions with organolithium compounds. From the available data, however, it is clearly seen that organosodium compounds are more potent metalating agents than the lithium compounds and frequently lead to dimetalated products along with some monometalated material. The orientation is the same in many cases as with the organolithium compounds. Thus, in aromatic compounds containing elements such as oxygen, nitrogen, and sulfur, metalation tends to occur ortho to the hetero atom. Furan (14, 26, 68) and thiophene (81, 89) are metalated to give 2-furylsodium and 2-thienylsodium, respectively. Likewise, dibenzofuran (20, 27, 28), diphenyl sulfide (12), diphenyl ether (33, 34), dibenzothiophene (12), and dimethylaniline (12, 56) give ortho metalation.

A review of metalations with organolithium compounds has appeared (21) recently. This similar review with organosodium compounds makes possible a

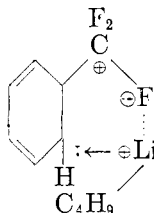
ready comparison of the two systems. Metalations which have been observed with a variety of organosodium compounds for the period from 1907 through October 1956 are reported.

It will be noted that organosodium compounds, because of their salt-like nature, general insolubility in organic solvents, and conductivity in certain solvents like diethylzinc, are considered ionic in nature. They are therefore best represented as ion-pairs: R^-Na^+ . For simplicity in reproduction, however, this ionic notation has not been adhered to in this review, and a simple covalent bond has been used in many places.

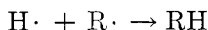
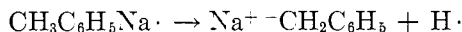
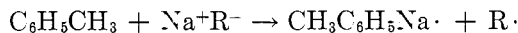
II. MECHANISM

The mechanism of the metalation reaction has been the subject of discussion for many years. Generally speaking, three different interpretations of the reaction path have been set forth (21, 30, 39, 40, 49, 79, 92).

One of these views (39, 40) stresses the electrophilic character of the organometallic compound. It pictures an initial coordination by the metal atom, followed by an electrophilic attack of the metal cation on the carbon holding the hydrogen to be removed. The role of the carbanion in removing the proton is considered of secondary importance. Thus, the preponderantly ortho metalation of benzotrifluoride by *n*-butyllithium is thought to occur as follows:

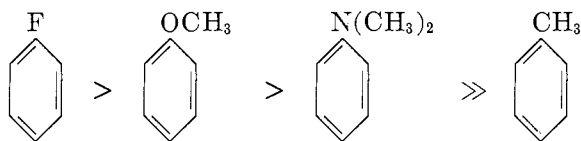


More recently it has been suggested that the reaction can be interpreted on the basis of the organoalkali salts acting as free-radical pairs (47, 49). Toluene has been pictured as undergoing metalation as follows under this scheme:



A third view (6, 30) stresses the nucleophilic character of the organometallic reagent and considers the anion attack on *hydrogen* as the rate-determining step. It has been shown that fluorobenzene, benzotrifluoride, and anisole substituted with deuterium in the ortho, meta, and para positions undergo deuterium-protium exchange with potassium amide in liquid ammonia. The exchange rates were found to be greatest for the ortho compounds and smallest for the para. On the other hand, deuterotoluene reacted too slowly for the rate to be measured. Hydrogen isotope effects were demonstrated earlier (7) in the metalation of benzene and toluene. Similar results were noted in the attempted metalation

of fluorobenzene, toluene, dimethylaniline, and anisole with phenyllithium (93). The relative rates were in the following order:



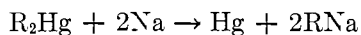
All of the above compounds were metalated in the ortho position except toluene, which did not react. These results form a consistent picture which suggests that it is the combined inductive and field effects of the substituent group which govern the orientation of metalations. On this basis one is forced to conclude that resonance effects are only of minor importance in such anionic reactions. This is perhaps understandable, since the primary attack is on *hydrogen* rather than the aromatic ring. Also, the demands of an anionic reagent would not call into play the electron-releasing ability of groups substituted on the ring. On the contrary such electron release would undoubtedly be suppressed by the approach of such reagents.

Earlier (79) it had been postulated that a coordination complex was formed between the metalating agent and the hetero atom (e.g., the oxygen in anisole). The anion was thus placed in a favorable position to remove an ortho hydrogen via a five-membered-ring transition state. In view of the recent findings above it would seem that it is no longer necessary to assume such a coordination complex in order to explain the great tendency for ortho orientation in metalations.

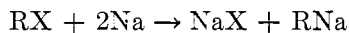
III. PREPARATION AND NATURE OF THE ORGANOSODIUM COMPOUND

A variety of sodium compounds have been used successfully for metalations. These include ethyl-, *n*-propyl-, *n*-butyl-, *n*-amyl-, *n*-octyl-, *n*-decyl-, phenyl-, benzyl-, allyl-, and *p*-tolylsodium. Of these, *n*-amylsodium has been used most widely.

In early work reported on metalations with organosodium compounds, the latter were prepared from the dialkyl- or diarylmercury compound and metallic sodium in an inert hydrocarbon solvent (8, 11, 13, 14, 18, 19, 24, 26, 27, 28, 55, 81, 88, 89).



Most organosodium compounds are now more conveniently prepared by the reaction of the appropriate halide (usually the chloride) with metallic sodium in an inert solvent. The use of finely divided or dispersed sodium greatly facilitates control of this reaction (72).



Thus *n*-amylsodium (12, 32, 51, 54, 55, 56, 57, 62, 63, 65, 67, 68) and phenylsodium (12, 24, 33, 34, 71, 72, 73) have been prepared in this manner.

All organosodium compounds are not of equal reactivity. It has been reported (69) that *n*-propylsodium and *n*-butylsodium are progressively less reactive to-

ward benzene and toluene than is *n*-amylsodium. This apparent decrease in reactivity is reportedly so great that benzene can be used as solvent in the preparation of these organometallics. That there should be such a marked difference between the reactivities of the C₅, C₄, and C₃ organosodium derivatives is rather puzzling. It is possible that the effective concentration of propylsodium and *n*-butylsodium in toluene and benzene is less than that of *n*-amylsodium as a result of decreased solubility, lesser thermal stability, or lower yield realized in their preparation. At any rate it will be necessary to assess the importance of such variables before a definite decision can be made concerning the relative reactivities of various aliphatic sodium derivatives.

Metalation reactions with organosodium compounds are customarily carried out directly in the inert hydrocarbon solvents in which the organometallics are prepared. Frequently the compound to be metalated is employed as the solvent, but when such is the case the temperature of the preparation must be kept low to prevent metalation during formation of the original organosodium compound.

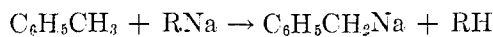
IV. COMPOUNDS METALATED BY ORGANOSODIUM COMPOUNDS

A. HYDROCARBONS

1. Aromatic hydrocarbons

The first successful metalation of benzene was reported by Schorigin (87) when he treated benzene with ethylsodium prepared *in situ* from diethylmercury and sodium. The presence of phenylsodium was established by the isolation of benzoic acid upon carbonation. Subsequently benzene has been metalated also by *n*-butylsodium (19), *n*-amylsodium (55), *n*-octylsodium (51), and vinylsodium (65). Yields as high as 90 per cent for phenylsodium have been reported (63), although it can be prepared directly from chlorobenzene and sodium in 99 per cent yield (72). Further study of the reaction of ethylsodium, prepared from diethylmercury and sodium, with benzene revealed that small amounts of terephthalic and phthalic acids could be isolated as a result of dimetalation, along with benzoic acid (18). The more recent work of Bryce-Smith and Turner (8) on the metalation of benzene with ethylsodium reports that the carbonation products contain benzoic acid and a mixture of terephthalic and isophthalic acids, the latter in an approximate ratio of 7:3. With *n*-amylsodium prepared from amyl chloride and sodium, however, after carbonation there was isolated along with benzoic acid a 24 per cent yield of a mixture of terephthalic and isophthalic acids in which isophthalic acid predominated by a ratio of 4:1 (52, 55). Further investigation (63) of the metalation of benzene with amylsodium showed that under improved conditions, involving a restricted amount of benzene and improved stirring, 85 per cent of the benzene consumed could be dimetalated to give *m*-phenylenedisodium, which upon carbonation gave the expected isophthalic acid. The orientation in the dimetalation of benzene appears to be extremely sensitive and to depend on the experimental conditions, such as the mode of preparation of the organosodium compound, the presence of alkoxides, and the rate of stirring.

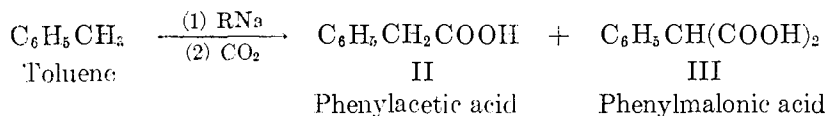
Toluene is metalated laterally by ethylsodium (88), phenylsodium (9, 72, 73), and vinylsodium (65) to give benzylsodium (I).



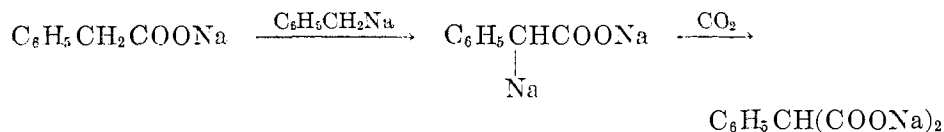
I

Benzylsodium

Metalation with *n*-amylsodium, isobutylsodium (56), and phenylsodium (72) followed by carbonation gives phenylacetic (II) and phenylmalonic (III) acids.

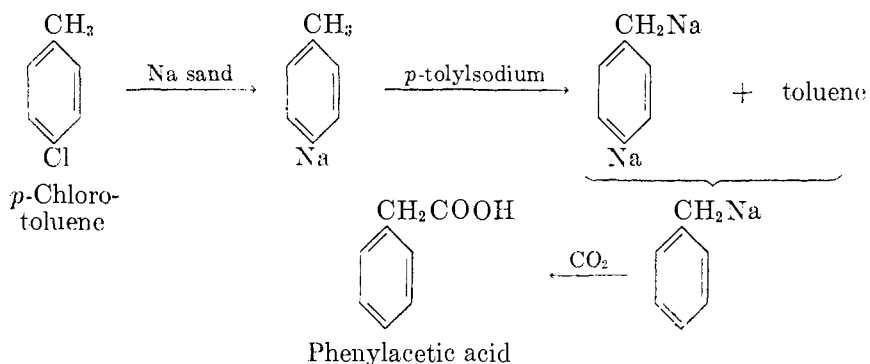


The latter was shown to result from metalation and subsequent carbonation of sodium phenylacetate (53).



By controlling the conditions of carbonation either phenylacetic acid or phenylmalonic acid can be produced in yields of 99 per cent and 70 per cent, respectively (72).

It is interesting that when the chlorotoluenes are refluxed with sodium sand in either benzene or petroleum ether (b.p. 85–100°C.) for prolonged periods, and then carbonated, phenylacetic acid can be isolated (22, 24). One possibility is that this acid is formed by a process similar to the following:

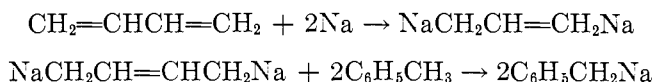


In the case of *p*-chlorotoluene an 80 per cent yield¹ of phenylacetic acid can be realized. Even a mixture of *o*- and *p*-chlorotoluenes will give phenylacetic acid in 60–70 per cent yield. At lower temperatures and short reaction time, the chlorotoluenes give good yields of the corresponding tolylsodium product, and subsequently the toluic acids on carbonation.

¹ Unpublished studies by John F. Nobis.

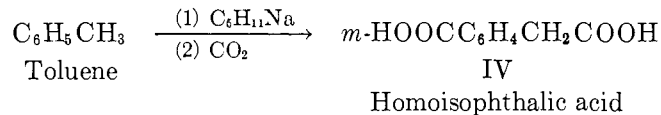
Toluene also undergoes metalation with *n*-octyl- and *n*-decylsodium. This is indicated by the formation of nonylbenzene (51 per cent yield) and undecylbenzene (74 per cent yield) when sodium and toluene are heated with *n*-octyl chloride and *n*-decyl chloride, respectively (50).

There is evidence (80) to indicate that in the sodium-catalyzed polymerization of butadiene and isoprene in the presence of toluene, the chain initiator is benzylsodium, which is derived as follows:

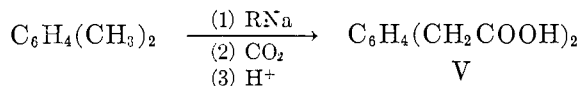


All the low-molecular-weight polymers obtained have the general formula $\text{C}_6\text{H}_5\text{CH}_2[\text{monomer}]_n\text{H}$, and acids like phenylacetic are obtained on carbonation of the polymerizing system. Chain termination might conceivably occur by reaction with the solvent toluene to regenerate benzylsodium.

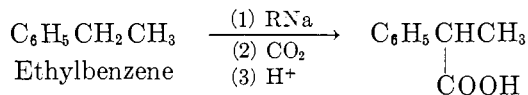
The conditions which cause the dimetalation of benzene also effect the dimetalation of toluene, with the second sodium atom entering the nucleus. The diacid formed on carbonation is exclusively homoisophthalic acid (IV), indicating only meta substitution (63).



As might be expected, the xylenes undergo monometalation with *n*-amylsodium preferentially on the methyl groups with the ease of metalation being para > meta > ortho as shown by alkylation of the organosodium derivatives with *n*-amyl chloride to yield 54, 32, and 22 per cent, respectively, of methylhexylbenzenes (63). Dimetalation by the method used for benzene and toluene occurs exclusively on the two methyl groups with *p*- and *m*-xylenes. With *o*-xylene, some nuclear metalation is also observed. The yields of the corresponding phenylenediacetic acids (V) are 36, 37, and 19 per cent, respectively, for the para, meta, and ortho isomers.

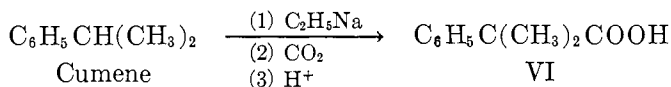


Ethylbenzene with ethylsodium (88) and *n*-amylsodium (62) undergoes exclusively α -metalation but only in low yields.



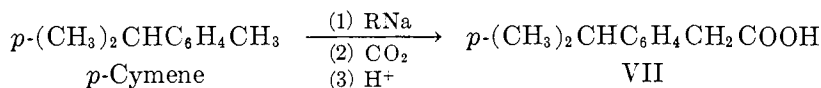
The reluctance of ethylbenzene to undergo metalation compared to toluene can be traced to the +*I* effect of the additional methyl group, together with the greater steric interference it offers to anion attack.

The metalation of cumene with amylsodium is beclouded by contradictory results. In three separate reports (46, 62, 66) it is claimed that predominantly *para* nuclear attack occurs in petroleum ether or in cumene itself, as judged by the isolation of the *para* acid on carbonation. More recently (6), in a seemingly careful study, a *meta/para* ratio of monocarboxylic acids of nearly 1:1 is claimed. Only traces of *ortho* isomer were detected, along with small amounts of material resulting from side-chain attack. Ethylsodium prepared from diethylmercury and sodium in cumene as solvent, however, is reported to give lateral metalation, for, upon carbonation, a 41 per cent yield of phenyldimethylacetic acid (VI) was isolated (24).



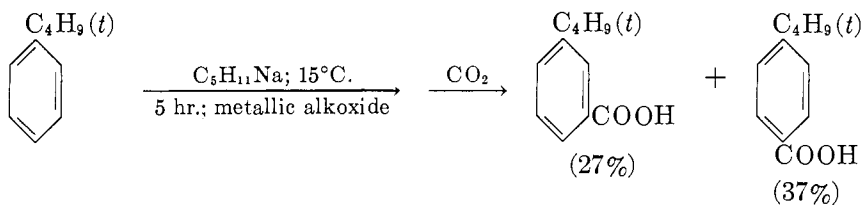
This appears to be another instance in which the orientation is dependent upon the experimental conditions. The reason for a difference in the positions of metalation by *n*-amylsodium and ethylsodium may in part be steric in nature, with the bulkier *n*-amyl group finding it difficult to attack the α -hydrogen.

p-Cymene with both ethylsodium (89) and *n*-amylsodium (62) is metalated on the methyl group. A 29 per cent yield of 4-isopropylphenylacetic acid (VII) can be isolated from the metalation reaction employing *n*-amylsodium (62).



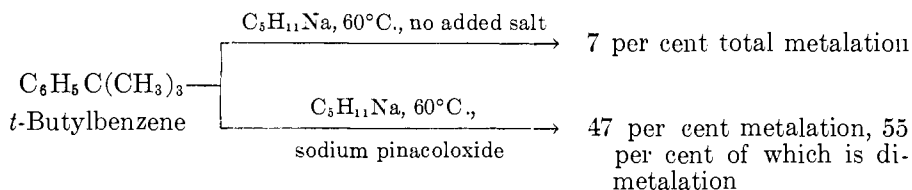
Since one of the methyl hydrogens is replaced by sodium, it can be concluded that these are more acidic than the hydrogen of the isopropyl group. On the basis of the electron-releasing electrical effects of the methyl groups (+*I* effect), this would be the predicted order. Accompanying this electrical effect may be a steric effect which would also favor metalation of the methyl group. It was reported in 1949 that *tert*-butylbenzene undergoes nuclear metalation with amylsodium in 48 per cent yield (62). The *para* position was said to be attacked principally, with only minor amounts of *meta* isomer and dimetalation occurring.

Different results have been noted in recent reports (47, 49), where it has been claimed that metalation of *tert*-butylbenzene by amylsodium occurs only in low yield (5–10 per cent) *unless* a metallic alkoxide is present. In the latter case the yield is said to be considerably improved.



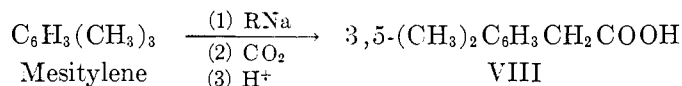
It is claimed that at 20°C. and below, metalation of *tert*-butylbenzene occurs chiefly in the *para* position, but in the presence of sodium and potassium alkoxides

the meta position is favored, as shown above. At 60°C. the presence of these alkoxides is said to increase the yield of the 3,5-dimetalated product (49). The effectiveness of alkoxides in influencing orientations has been questioned (6), and additional data of a more precise nature are desirable before this question can be settled.

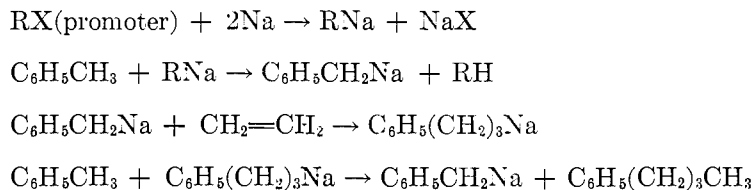


Recently Morton (48) has shown that anylsodium will metalate *m-tert*-butylphenylsodium in the presence of sodium *tert*-pentoxide to produce the 3,5-disodio product in 16 per cent yield as judged by carbonation to 5-*tert*-butylisophthalic acid. Under similar conditions *p-tert*-butylphenylsodium does not react.

3,5-Dimethylphenylacetic acid (VIII) is isolated after carbonating the product obtained from the metalation of mesitylene by ethylsodium (89) and phenylsodium (24), showing that mesitylene is laterally monometalated.



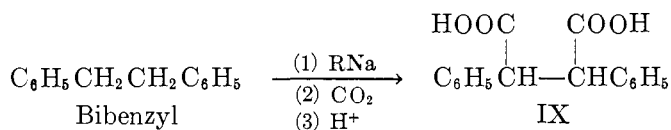
Pines and coworkers (78) have disclosed an interesting method of introducing an ethyl group into the side chain of alkyl aromatics. The method involves treating the latter with sodium, ethylene, and a "promoter" (anthracene, *o*-chlorotoluene, pyridine, etc). The reaction has been postulated to proceed through an organosodium intermediate via the following route:



The observation that only alkyl aromatics with at least one α -hydrogen on the side chain will undergo reaction lends credence to the above mechanistic proposal. A variety of alkylated and polyalkylated benzenes have been found to undergo both mono- and diethylation by this procedure.

Triphenylmethane and diphenylmethane are both metalated in high yield by anylsodium (56) and phenylsodium (3, 62) to yield triphenylmethylsodium and diphenylmethylsodium. Bibenzyl undergoes lateral dimetalation with *n*-butylsodium in tri-*n*-butylamine and in benzene to give 30 and 50 per cent yields, respectively, of α,β -diphenylsuccinic acid (IX) after carbonation (12). *n*-Amyl-

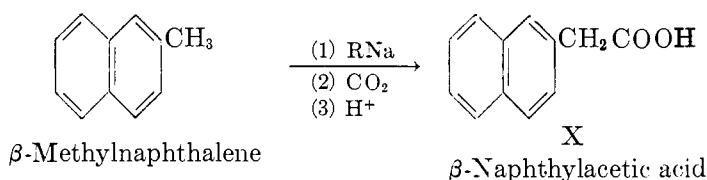
sodium also dimetalates dibenzyl laterally, giving a 70 per cent yield of *meso*- α,β -diphenylsuccinic acid after carbonation (62).



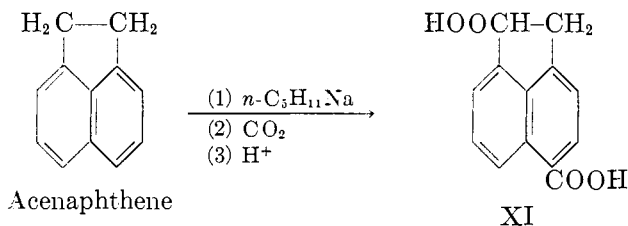
2. Polynuclear hydrocarbons

Naphthalene undergoes monometalation with *n*-butylsodium in tri-*n*-butylamine to give a 28 per cent yield of a mixture of α - and β -naphthylsodium as judged by carbonation to the acids; likewise with phenylsodium in benzene, but in this case the yield of monometalated product is only 5 per cent (12). With *n*-amylsodium (51) mono-, di-, and trisubstitution occur, with carbonation resulting in a 26 per cent yield of carboxylic acids. The mono acids were identified as α - and β -naphthoic acids; the dicarboxylic acids were the 1,3-, 1,8-, and 2,6-naphthalenedicarboxylic acids. No trisubstituted acids were identified. *n*-Octylsodium (51) also gives a mixture of mono-, di-, and trimetalated products.

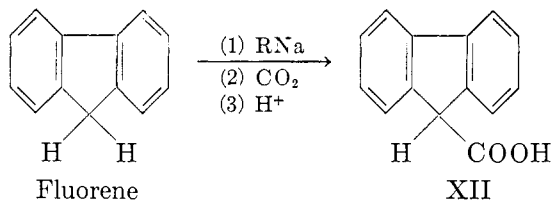
β -Methylnaphthalene, on the other hand, is metalated laterally by phenylsodium in benzene and *n*-butylsodium in petroleum ether to give the expected β -naphthylacetic acid (X) after carbonation (24). Although the yield of β -naphthylacetic acid, when phenylsodium is the metalating agent, is low (4 per cent), yields of 31 and 64 per cent are reported when *n*-butylsodium and *n*-amylsodium (62) are used.



Biphenyl is metalated in small yield by both *n*-butylsodium (5 per cent) (12) and *n*-amylsodium (67) to give *p*-xenylsodium. No reaction was observed when phenylsodium was the metalating agent. *o*-Phenylbiphenyl is likewise not attacked by phenylsodium; however, *n*-amylsodium gives a small yield of a mixture of mono- and dimetalated products (67). *n*-Amylsodium with acenaphthene followed by carbonation yields 1,5-acenaphthenedicarboxylic acid (XI), indicating both lateral and nuclear metalation (67).

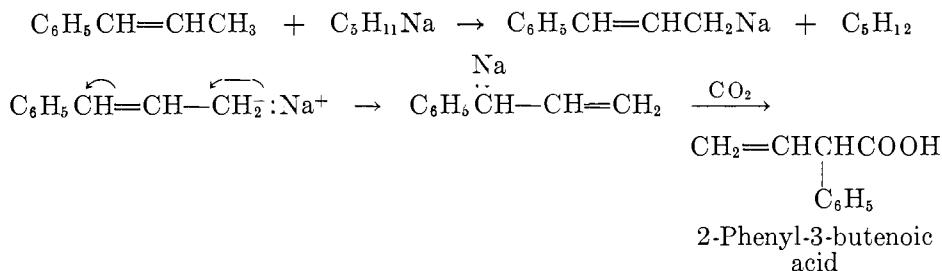


The metalation of fluorene takes place with extreme ease and in high yield with a number of sodium compounds. The yields of 9-fluorencarboxylic acid (XII) obtained after carbonation are 100 and 88 per cent after metalation with *n*-amylsodium (62) and vinylsodium (65), respectively.



The disodium adduct of stilbene (5) also has been reported to metalate both indene and fluorene (91).

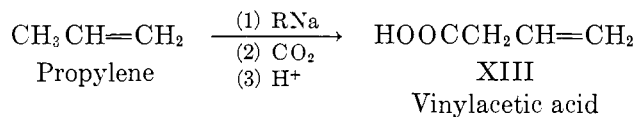
Metalation of α - and β -methylstyrenes was carried out with *n*-amylsodium in the presence of sodium isopropoxide,—a salt which is claimed to increase the metalating activity of the reagent (54). With both isomers the predominant reaction is one of metalation rather than addition to the unsaturated center. From α -methylstyrene the acid formed after carbonation was hydrogenated and isolated as its methyl ester and found to be methyl β -phenylbutyrate, $\text{CH}_3\text{CH}(\text{C}_6\text{H}_5)\text{CH}_2\text{COOCH}_3$. Some dimetalation which was thought to involve the aromatic ring was also observed. With β -methylstyrene 85 per cent of the reaction proceeded by replacement of hydrogen. Of the acids formed on carbonation, 32 per cent was 2-phenyl-3-butenic acid, $\text{CH}_2=\text{CHCH}(\text{C}_6\text{H}_5)\text{COOH}$, and 48 per cent β -benzalpropionic acid, $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{COOH}$. The 2-phenyl-3-butenic acid arises from carbonation of the sodium compound, $\text{CH}_2=\text{CHCH}(\text{C}_6\text{H}_5)\text{Na}$, which results from isomerization of the initial metalation product, $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{Na}$.



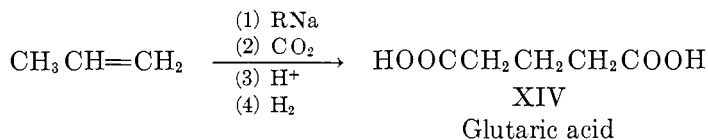
3. Olefins

Straight-chain and branched-chain alkenes normally undergo metalation on the methylene or methyl groups which are adjacent to a double bond, i.e., the allylic positions. It will be noted that this is the same orientation observed in the side-chain metalation of alkylbenzenes which also possess allylic hydrogens. If no allylic hydrogen is present, metalation is claimed to occur even on a vinyl carbon atom. Isomerization of the metalated straight-chain olefins to give a mixture of the possible allylic isomers readily occurs.

Propylene is readily metalated to give exclusively allylsodium, as evidenced by the 69 per cent yield of vinylacetic acid (XIII) obtained on carbonation (57).



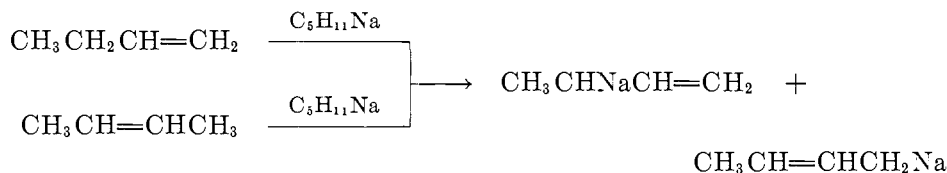
A small amount of dimetalation also occurs, for upon carbonation and hydrogenation a 15 per cent yield of glutaric acid (XIV) is obtained.



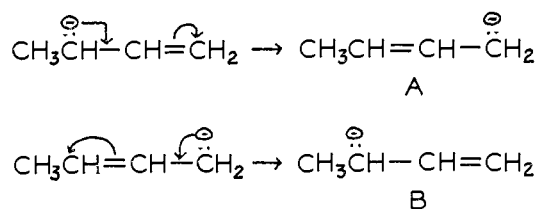
No α -methylsuccinic acid, $\text{HOOCCH}(\text{CH}_3)\text{CH}_2\text{COOH}$, could be detected, showing that the sodium atoms tend to assume positions as far apart as possible. This is a general tendency which has been observed in the dimetalation of olefins. These observations are consistent with the ionic character of organosodium compounds (39), since the proximity of a double negative charge would not be favored.

The formation of allylsodium from the reaction of propylene with *n*-amylsodium is an important step in the formation of the alfin catalyst (64).

The results of the metalation of 1-butene and 2-butene indicate that the total percentage of allylic isomers formed is roughly constant regardless of the isomer used (45, 57).



This clearly illustrates the ease with which isomerization of the allylic anions occurs.



Of the two allylic isomers, A and B, the latter at first sight would seem to be the predominating structure based upon the relative yield of acids isolated after carbonation (see table 2). It is to be noted, however, that a 23 per cent yield of adipic acid can be realized from these preparations if the carbonation product is

TABLE I

Metalation of aromatic hydrocarbons by various organosodium compounds followed by carbonation to yield carboxylic acids

Formula	Compound	RNa	Mode of Preparation of RNa	Solvent	Product(s)	Yield	References	
C ₆ H ₆	Benzene	Allyl	C ₃ H ₅ + C ₆ H ₅ Na	Benzene	Benzoic acid	31	(57)	
		Isoamyl	C ₅ H ₁₁ Br + Na	Benzene	Benzoic acid	10	(87)	
		<i>n</i> -Amyl	(C ₅ H ₁₁) ₂ Hg + Na	Benzene	Benzoic acid	75	(55)	
						Isophthalic acid	24	(55)
						Terephthalic acid		
		<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na	Benzene and pentane	Benzoic acid	78	(56)	
		<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na		Benzoic acid	4.5	(63)	
				<i>n</i> -Octane	Isophthalic acid	51	(63)	
		<i>n</i> -Butyl	C ₄ H ₉ Cl + Na	Benzene	Benzoic acid	27	(69)	
		<i>n</i> -Butyl	(C ₄ H ₉) ₂ Hg + Na	Benzene	Benzoic acid	77	(19)	
		Ethyl	(C ₂ H ₅) ₂ Hg + Na	Benzene	Benzoic acid	41	(18)	
					Phthalic acid	—	(18)	
					Terephthalic acid			
		Ethyl	(C ₂ H ₅) ₂ Hg + Na	Benzene	Benzoic acid	12	(88)	
		Ethyl	(C ₂ H ₅) ₂ Hg + Na	<i>n</i> -Pentane	Benzoic acid	23	(8)	
					Terephthalic acid	1.5	(8)	
					Isophthalic acid			
<i>n</i> -Octyl	C ₈ H ₁₇ Cl + Na	Ligroin	Benzoic acid	33	(51)			
<i>n</i> -Propyl	C ₃ H ₇ Cl + Na	Benzene	Benzoic acid	12	(69)			
			Phthalic acids	6	(69)			
			Benzoic acid	11	(65)			
C ₇ H ₈	Toluene	Vinyl	C ₂ H ₄ + C ₆ H ₅ Na + <i>i</i> -C ₃ H ₇ ONa	Pentane	Benzoic acid			
		<i>n</i> -Amyl	(C ₅ H ₁₁) ₂ Hg + Na	Toluene	Phenylacetic acid	13	(55)	
					Phenylmalonic acid	45	(55)	
		<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na	Toluene	Phenylacetic acid	40	(56)	
		<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na	<i>n</i> -Octane	Phenylacetic acid	51	(63)	
					Homaisophthalic acid	40	(63)	
		Isobutyl	<i>i</i> -C ₄ H ₉ Cl + Na	Ligroin and toluene	Phenylacetic acid	11	(56)	
					Phenylmalonic acid	20	(56)	
		Ethyl	(C ₂ H ₅) ₂ Hg + Na	Toluene	Phenylacetic acid	14	(88)	
		<i>n</i> -Octyl	C ₈ H ₁₇ Cl + Na	Toluene	Nonylbenzene	51	(50)	
		<i>n</i> -Decyl	C ₁₀ H ₂₁ Cl + Na	Toluene	Undecylbenzene	74	(50)	
Phenyl	C ₆ H ₅ + C ₆ H ₅ Na	Benzene	Phenylacetic acid	23	(53)			
			Phenylmalonic acid	29	(53)			
Phenyl	C ₆ H ₅ Cl + Na	Toluene	Phenylacetic acid	99	(72)			

C ₈ H ₁₀	<i>o</i> -Xylene	Phenyl	C ₆ H ₅ Cl + Na	Toluene	Phenylacetic acid	77	(73)	
		Phenyl	C ₆ H ₅ Cl + Na	Toluene	Phenylacetic acid	25	(72)	
		<i>n</i> -Propyl	C ₃ H ₇ Cl + Na	Toluene	Phenylmalonic acid	70	(72)	
		Vinyl	C ₂ H ₄ + C ₆ H ₅ Na + i-C ₂ H ₅ O ₂ Na	Pentane	(Butylbenzene)	43	(69)	
		<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na		Phenylacetic acid	53	(69)	
	<i>m</i> -Xylene	Ethyl	<i>n</i> -Amyl	(C ₂ H ₅) ₂ Hg + Na C ₅ H ₁₁ Cl + Na	<i>n</i> -Octane	<i>o</i> -Methylphenylacetic acid	—	(63)
						<i>o</i> -Phenylenediacetic acid	19	(63)
						Dimethylbenzoic acid	Trace	(63)
						<i>o</i> -Tolylacetic acid	17	(89)
						<i>m</i> -Tolylacetic acid	8	(63)
<i>p</i> -Xylene	Ethyl	<i>n</i> -Amyl	(C ₂ H ₅) ₂ Hg + Na C ₅ H ₁₁ Cl + Na	<i>n</i> -Octane	<i>m</i> -Phenylenediacetic acid	37	(63)	
					<i>m</i> -Tolylacetic acid	8	(88)	
					<i>p</i> -Tolylacetic acid	5	(63)	
					<i>p</i> -Phenylenediacetic acid	36	(63)	
					<i>p</i> -Tolylacetic acid	4	(89)	
Ethylbenzene	Ethyl	<i>n</i> -Amyl	(C ₂ H ₅) ₂ Hg + Na C ₅ H ₁₁ Cl + Na	<i>p</i> -Xylene	<i>α</i> -Phenylpropionic acid	28	(62)	
					<i>α</i> -Phenylpropionic acid	10	(88)	
					1-Indenecarboxylic acid	50	(10)	
					1-Indenecarboxylic acid	50	(10)	
					(2-Phenyl-2-propenylsodium)	20	(54)	
C ₉ H ₈	Indene	Triphenylmethyl	C ₂₅ H ₁₉ Cl + Na-Hg (C ₆ H ₅) ₃ CCl + Na-Hg	Petroleum ether	2-Phenyl-3-butenoic acid	27	(54)	
					<i>β</i> -Benzalpropionic acid	41	(54)	
					<i>p</i> -Isopropylbenzoic acid	47	(62)	
					<i>o</i> -Isopropylbenzoic acid	6	(62)	
					<i>p</i> -Isopropylbenzoic acid	—	(66)	
C ₉ H ₁₁	<i>α</i> -Methylstyrene <i>β</i> -Methylstyrene	<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na	Cumene	<i>o</i> -Isopropylbenzoic acid	—	(66)	
					Phenyldimethylacetic acid	41	(24)	
					3,5-Dimethylphenylacetic acid	18	(89)	
					3,5-Dimethylphenylacetic acid	20	(24, 71, 73)	
					<i>α</i> - and <i>β</i> -Naphthoic acids	14	(51)	
C ₉ H ₁₂	Cumene	<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na	Petroleum ether	1,3-, 1,8-, and 2,6-Naphthalenedicarboxylic acids	10	(51)	
					Naphthalenetetracarboxylic acid	2	(51)	
					<i>α</i> - and <i>β</i> -Naphthoic acids	28	(12)	
					<i>α</i> - and <i>β</i> -Naphthoic acids	17	(51)	
					1,3-, 1,8-, and 2,6-Naphthalenedicarboxylic acids	15	(51)	
C ₁₀ H ₈	Naphthalene	<i>n</i> -Amyl	C ₅ H ₁₁ Cl + Na	Cumene	Naphthalenetetracarboxylic acid	5	(51)	
					Mesitylene	3,5-Dimethylphenylacetic acid	18	(89)
					Mesitylene	3,5-Dimethylphenylacetic acid	20	(24, 71, 73)
					Ligroin	<i>α</i> - and <i>β</i> -Naphthoic acids	14	(51)
					Tri- <i>n</i> -butylamine	1,3-, 1,8-, and 2,6-Naphthalenedicarboxylic acids	2	(51)
C ₁₀ H ₁₄	<i>n</i> -Butylbenzene	<i>n</i> -Propyl	C ₅ H ₁₁ Cl + Na C ₃ H ₇ Cl + Na	Benzene	<i>α</i> - and <i>β</i> -Naphthoic acids	5	(12)	
					Ligroin	1,3-, 1,8-, and 2,6-Naphthalenedicarboxylic acids	15	(51)
					—	Naphthalenetetracarboxylic acid	5	(51)
					—	<i>α</i> - and <i>β</i> -Naphthoic acids	5	(12)
					—	(<i>p</i> - <i>n</i> -Butylphenylsodium)	—	(63)

TABLE 1—Concluded

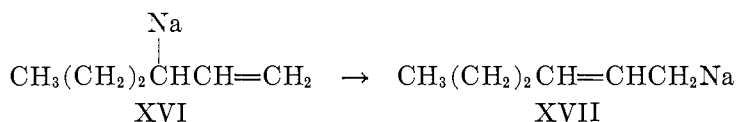
Formula	Compound	RNa	Mode of Preparation of RNa	Solvent	Product(s)	Yield	References
C ₁₀ H ₁₄ contd.	<i>t</i> -Butylbenzene	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	<i>m</i> - <i>t</i> -Butylbenzoic acid	8	(62)
		<i>n</i> -Amyl, potassium oxide	C ₈ H ₁₁ Cl + Na	Petroleum ether	<i>p</i> - <i>t</i> -Butylbenzoic acid Dicarboxylic acids	31 7	(62) (62)
	<i>p</i> -Cymene	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	4-Isopropylphenylacetic acid Dicarboxylic acids	29 23	(62) (62)
		Ethyl	(C ₂ H ₅) ₂ Hg + Na	<i>p</i> -Cymene	4-Isopropylphenylacetic acid		(80)
C ₁₁ H ₁₀	β -Methylmethylthalene	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	β -Naphthylacetic acid	64	(62)
		<i>n</i> -Butyl	(C ₄ H ₉) ₂ Hg + Na	Petroleum ether (85–100° C.)	β -Naphthylacetic acid	31	(24)
C ₁₂ H ₁₀	Acenaphthene	Phenyl	C ₆ H ₅ Cl + Na	Benzene	β -Naphthylacetic acid	4	(24, 73)
		<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	1,5-Acenaphthenedicarboxylic acid	50	(51, 62)
C ₁₂ H ₁₀	Fluorene	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	<i>p</i> -Phenylbenzoic acid	—	(67)
		<i>n</i> -Butyl	C ₄ H ₉ Cl + Na	Petroleum ether	<i>p</i> -Phenylbenzoic acid	5	(12)
C ₁₃ H ₁₀	Fluorene	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	9-Fluorencarboxylic acid	100	(56, 62)
		C ₂₅ H ₁₇ Na†	C ₂₂ H ₁₇ Cl + Na-Hg	Ether	9-Fluorencarboxylic acid	40-70	(10)
		C ₂₅ H ₁₉ Na*	C ₂₅ H ₁₉ Cl + Na-Hg	Ether	9-Fluorencarboxylic acid	40-70	(10)
		(C ₆ H ₅) ₃ CNa	(C ₆ H ₅) ₃ CCl + Na-Hg	Ether	9-Fluorencarboxylic acid	40-70	(10)
		Vinyl	C ₂ H ₄ + C ₂ H ₅ Na	Pentane	9-Fluorencarboxylic acid	88	(65)
C ₁₅ H ₁₂	Diphenylmethane	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	Diphenylacetic acid	92	(56, 62)
		Ethyl	(C ₂ H ₅) ₂ Hg + Na	Ether and diphenyl- methane	Diphenylacetic acid		(89)
C ₁₄ H ₁₄	Bibenzyl	Phenyl	C ₆ H ₅ Cl + Na	Benzene	Diphenylacetic acid	—	(2)
		<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	<i>meso</i> - α,β -Diphenylsuccinic acid	70	(62)
		<i>n</i> -Butyl	C ₄ H ₉ Cl + Na	Tri- <i>n</i> butylamine	α,β -Diphenylsuccinic acid	30	(12)
		<i>n</i> -Butyl	C ₄ H ₉ Cl + Na	Benzene	α,β -Diphenylsuccinic acid	50	(12)
C ₁₈ H ₁₄	<i>o</i> -Phenylbiphenyl	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	Mono- and dicarboxylic acids	—	(67)
C ₁₉ H ₁₄	9-Phenylfluorene	C ₂₅ H ₁₉ Na*	C ₂₅ H ₁₉ Cl + Na-Hg	Ether	9-Phenylfluorene-9-carboxylic acid	60	(10)
		(C ₆ H ₅) ₃ CNa	(C ₆ H ₅) ₃ CCl + Na-Hg	Ether	9-Phenylfluorene-9-carboxylic acid	60	(10)
C ₁₉ H ₁₆	Triphenylmethane	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Petroleum ether	Triphenylacetic acid	93	(62)

* Diphenyl-*p*-xenylmethylsodium.

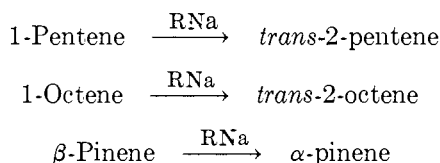
† Diphenyl-2-naphthylmethylsodium.

hydrogenated (table 2). This probably arises from a second metalation attack on the allylic position of anion A. Thus if the yield of the adipic acid is taken into account, it would appear that structures A and B are formed initially in about equal amounts.

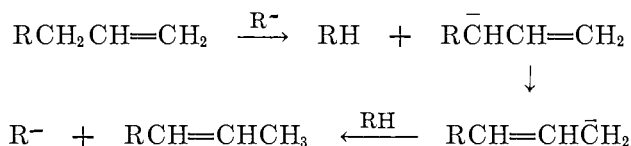
The metalation and carbonation of 1-hexene (65) with *n*-amylsodium results in 2-propyl-3-butenic acid (51 per cent), 3-heptenoic acid (32 per cent), and 2-heptenoic acid (6 per cent). The first two acids undoubtedly arise from carbonation of organosodium compounds XVI and XVII resulting from metalation on the allylic carbon atom followed by rearrangement.



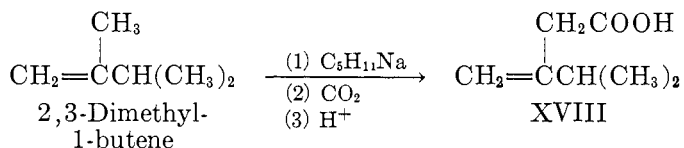
In this connection Morton (58) has recently reported that various organosodium compounds (e.g., amyl-, benzyl-, phenyl-, allylsodium, etc.) can isomerize terminal olefins to non-terminal *trans* types. For example:



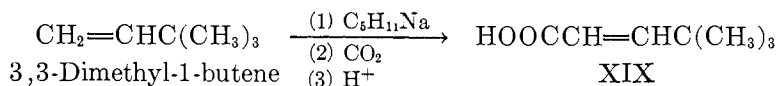
This is best viewed as an anion attack on an allylic hydrogen, followed by an electron shift:



With a branched-chain olefin such as 2,3-dimethyl-1-butene metalation occurs readily again with replacement of an allylic hydrogen. Carbonation results in a 59 per cent yield of 3-isopropyl-3-butenic acid (XVIII).

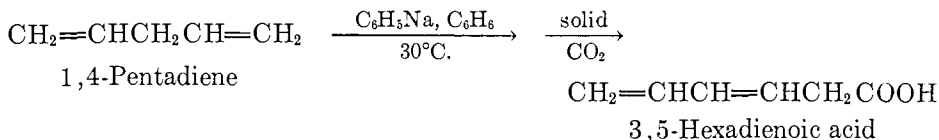


When, however, no allylic hydrogen is present, as in 3,3-dimethyl-1-butene, metalation will occur on the terminal vinyl carbon atom. A 61 per cent yield of 4,4-dimethyl-2-pentenoic acid (XIX) is obtained on carbonation.



1,4-Cyclohexadiene reacts with one mole of amylsodium to give a monosodium derivative. The latter reacts with carbon dioxide (74) to yield benzene and sodium formate. Likewise 1,4-dihydronaphthalene, upon treatment with amylsodium followed by carbonation, gives a 20 per cent yield of 1,4-dihydro-1-naphthoic acid along with a 55 per cent yield of naphthalene and sodium formate (74).

When phenylsodium reacts with 1,4-pentadiene in benzene at 30°C. and the product is carbonated, a 61 per cent yield of 3,5-hexadienoic acid is produced (75).



A number of other 1-alkenes, branched-chain olefins, and conjugated dienes which have been metalated, are reported in table 2, along with their carbonation products.

B. OXYGEN-CONTAINING COMPOUNDS

Furan and 2-methylfuran are metalated by a number of organosodium compounds to introduce a sodium atom ortho to the oxygen atom. Thus ethyl-, phenyl-, benzyl-, and triphenylmethylsodium give 2-furylsodium and 5-methyl-2-furylsodium (14, 26). Mono- and dimetalation of furan occur with *n*-amylsodium (68). Dimetalation of dibenzofuran occurs in relatively high yields with *p*-tolylsodium and benzylsodium. Yields of 86 per cent of 4,6-dibenzofurandicarboxylic acid (XX) are obtained after carbonation, when dibenzofuran is metalated by *p*-tolylsodium in toluene (20). *n*-Butylsodium likewise effects dimetalation in high yield, for upon methylation with dimethyl sulfate, a 90 per cent yield of 4,6-dimethyldibenzofuran (XXI) can be obtained (28).

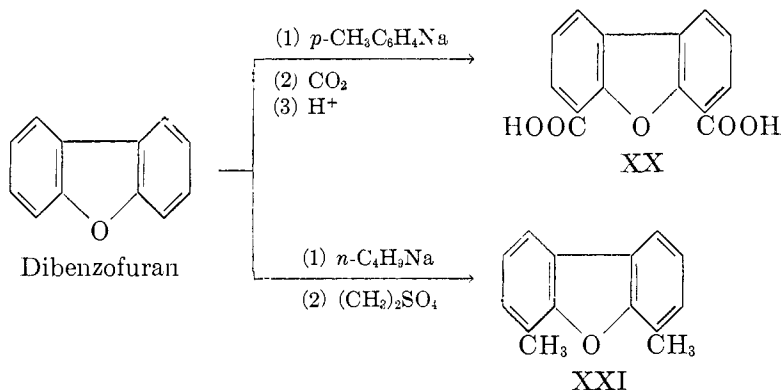


TABLE 2

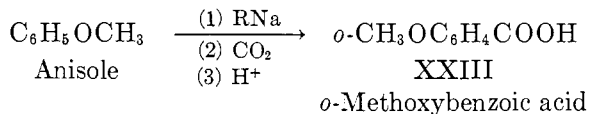
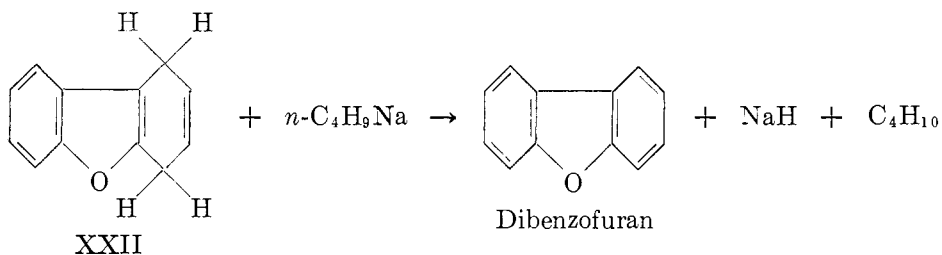
Metalation of olefins by various organosodium compounds and carbonation products

Formula	Compound	RNa	Acid(s)	Yield	References	
				<i>per cent</i>		
C ₂ H ₄	Ethylene	<i>n</i> -Amyl	Acrylic	—	(65)	
C ₃ H ₆	Propylene	<i>n</i> -Amyl	Vinylacetic	69	(45, 57)	
			Glutaric*	15		
		Benzyl	Vinylacetic	—	(45)	
C ₄ H ₁₀	1-Butene	<i>n</i> -Amyl	2-Methyl-3-butenoic	40	(45, 57)	
			3-Pentenoic	20		
			2-Pentenoic	5		
			Adipic*	23		
	2-Butene	<i>n</i> -Amyl	2-Methyl-3-butenoic	40	(45, 57)	
			3-Pentenoic	23		
			2-Pentenoic	5		
			Adipic*	21		
	Isobutene	<i>n</i> -Amyl	3-Methyl-3-butenoic	37	(41, 44, 45)	
			3-Methylene-1,5-pentanedioic	26		
		Benzyl	3-Methyl-3-butenoic	24	(44)	
			3-Methylene-1,5-pentanedioic	5		
C ₆ H ₈	Piperylene	<i>n</i> -Amyl	Hexa-3,5-dienoic	—	(65)	
	1,4-Pentadiene	Phenyl	Hexa-3,5-dienoic	61	(65, 75)	
	1-Pentene	<i>n</i> -Amyl	2-Ethyl-3-butenoic	48	(45, 57, 65)	
			2-Hexenoic	5		
			3-Hexenoic	32		
			Dicarboxylic acids	16		
	3-Methyl-1-butene	<i>n</i> -Amyl	3-Ethyl-3-butenoic	22		(65)
	Diallyl	<i>n</i> -Amyl or benzyl	2-Vinyl-4-pentenoic	30		(44, 65)
			Hepta-2,6-dienoic	62		
			Hepta-2,5-dienoic	—		
			Octa-2,5-dien-1,8-dioic	—		
C ₆ H ₁₂	1-Hexene	<i>n</i> -Amyl	2-Propyl-3-butenoic	51	(65)	
			3-Heptenoic	32		
			2-Heptenoic	6		
			Dicarboxylics	12		
		Vinylsodium, sodium isopropoxide	2-Propyl-3-butenoic	42	(65)	
	3,3-Dimethyl-1-butene	<i>n</i> -Amyl	4,4-Dimethyl-2-pentenoic	61	(65)	
	2,3-Dimethyl-1-butene	<i>n</i> -Amyl	3-Isopropyl-3-butenoic	59	(65)	
	2-Ethyl-1-butene	<i>n</i> -Amyl	2-Methyl-3-ethyl-3-butenoic	28	(65)	
C ₇ H ₁₄	2,3,3-Trimethyl-1-butene	<i>n</i> -Amyl	3- <i>t</i> -Butyl-3-butenoic	57	(65)	
C ₈ H ₁₆	1-Octene	<i>n</i> -Amyl	2-Amyl-3-butenoic	48	(65)	
			3-Nonenoic	30		
			2-Nonenoic	2		
C ₁₀ H ₁₆	1,4-Dihydronaphthalene	<i>n</i> -Amyl	1,4-Dihydro-1-naphthoic	20	(75)	

* Isolated after hydrogenation of the carbonation product.

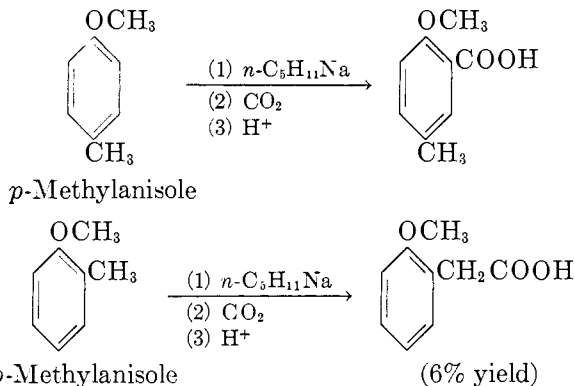
When 1,4-dihydrodibenzofuran (XXII) is metalated with *n*-butylsodium, a 66 per cent yield of dibenzofuran results. Elimination of sodium hydride accompanies metalation in this instance.

Anisole is metalated ortho to the methoxyl group by *n*-butyl-, phenyl-, and *n*-amylsodium (12, 42, 56). Carbonation yields the expected *o*-methoxybenzoic acid (XXIII).

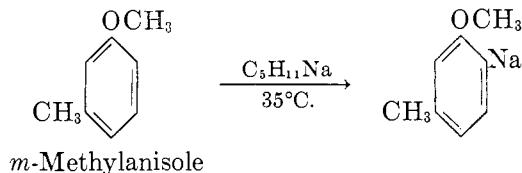


p-Chloroanisole reacts with sodium to give *p*-anisylsodium, which then metalates the unreacted halo ether. Carbonation gives 5-chloro-2-methoxybenzoic acid along with the expected *p*-anisic acid.¹

In the alkylanisoles there is the possibility of lateral and nuclear metalation. Although the series has not been studied extensively, several examples are available. *p*-Methylanisole undergoes nuclear metalation ortho to the methoxyl group with *n*-amylsodium, although no yield is reported (70). *o*-Methylanisole, on the other hand, undergoes lateral metalation (42, 43).



m-Methylanisole is metalated in the ring in about 50 per cent yield (42).

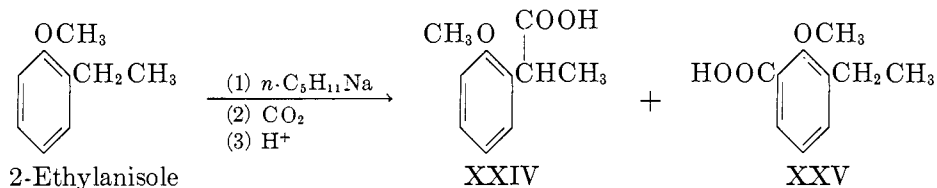


These results, while not compelling because of the seemingly low yields, would seem to indicate that at least in the case of a methyl group, a side chain ortho to a methoxyl group is metalated more readily than one which is substituted para to that group.

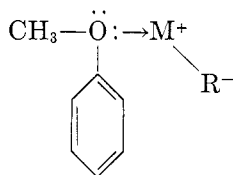
¹ Unpublished studies by John F. Nobis.

Amylsodium at 35°C. also metalates isobutyl phenyl ether (80 per cent yield), *n*-butyl phenyl ether (76 per cent yield), ethyl phenyl ether (72 per cent yield), and isopropyl phenyl ether (50 per cent yield). In every case the ring is attacked ortho to the ether linkage (42).

When an excess of amylsodium is added to anisole at 75°C., 2-methoxyisophthalic acid can be isolated in 27 per cent yield after carbonation (42). 2-Ethylanisole with *n*-amylna undergoes both nuclear and lateral metalation, as evidenced by the isolation of α -(*o*-methoxyphenyl)propionic acid (XXIV) and 3-ethyl-2-methoxybenzoic acid (XXV) on carbonation (no yield reported) (32).



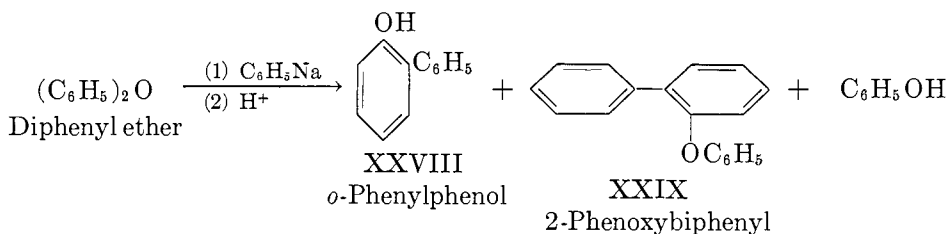
The orientation ortho to a hetero atom in metalations of the compounds such as anisole was, at one time, accounted for by assuming that the reaction proceeds through an intermediate coordination complex (40, 79, 92).



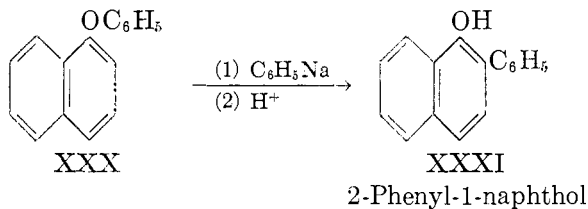
This explanation has also been used to account for nuclear metalation when the side chain is substituted para, but lateral metalation when the substituent is in the ortho position.

It should be kept in mind, however, that the latest interpretation accounts for metalation ortho to the oxygen in anisole and to any hetero atom for that matter by assuming that the inductive effect predominates in determining orientation. In the *o*-alkylanisoles, the possibility of resonance stabilization of the anions would also be important in leading to lateral metalation.

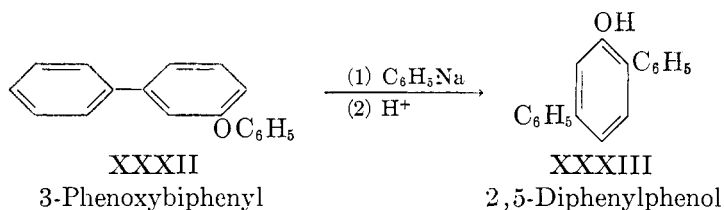
The reaction of phenyl- and alkylsodium compounds with diaryl ethers leads to an interesting rearrangement of the diaryl ethers to *o*-arylphenols (33, 34, 35, 36). Thus, diphenyl ether with phenylsodium gives a 45 per cent yield of *o*-phenylphenol (XXVIII), a 9 per cent yield of 2-phenoxybiphenyl (XXIX), and a 26 per cent yield of phenol.



Likewise, the action of α -naphthyl phenyl ether (XXX) with phenylsodium results in a 63 per cent yield of 2-phenyl-1-naphthol (XXXI).

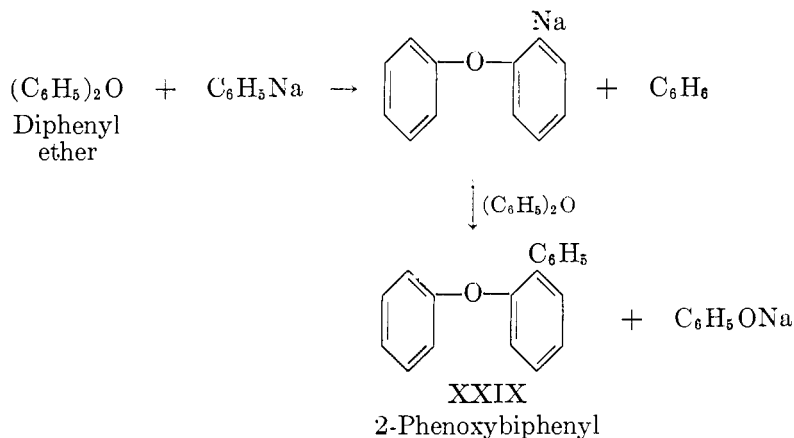


2,5-Diphenylphenol (XXXIII) is obtained in 54 per cent yield from 3-phenoxybiphenyl (XXXII).

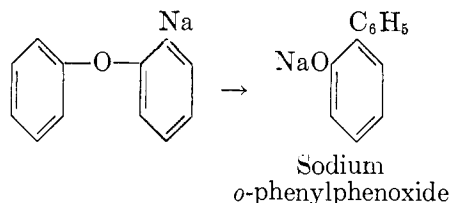


Direct ether fission by the phenylsodium seldom occurs with ethers of this type; instead, the first step is considered to be metalation in the position ortho to the oxygen atom. The presence of the ortho-metalated product has been established in the case of diphenyl ether by carbonation to *o*-phenoxybenzoic acid.

Once the sodium compound is formed, it is capable of reacting intermolecularly with the diaryl ether, forming ethers arylated in the ortho position as well as lower phenoxides. Thus, 2-phenoxybiphenyl (XXIX) and sodium phenoxide are formed in the case of diphenyl ether.



The predominant reaction, however, is intramolecular ether fission through which the ortho-arylated sodium phenoxides result.



No rearrangement was observed with phenyl *n*-butyl ether and phenylsodium. Instead the predominant reaction was cleavage of the ether linkage to give phenol. Likewise, diphenyl ether was cleaved by triphenylmethylsodium to give tetraphenylmethane (35).

R. Paul (76, 77) has studied the metalation of vinyl ethers with organosodium reagents. He concludes that at 0°C. the sodium reagent can attack either the α - or the β -position of the vinyl ether. The α -sodio derivatives are stable and can be carbonated, while the β -isomers rearrange to acetylene derivatives. The following examples are typical:

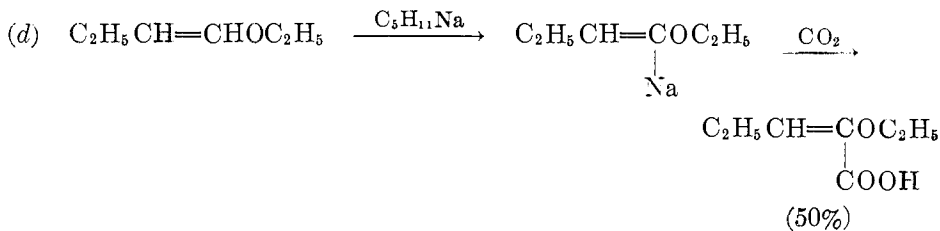
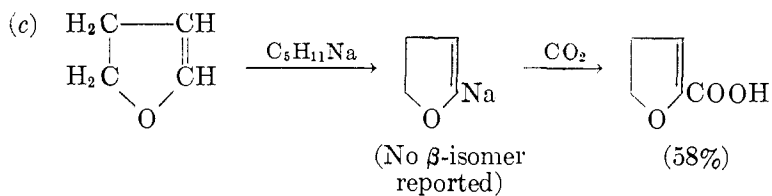
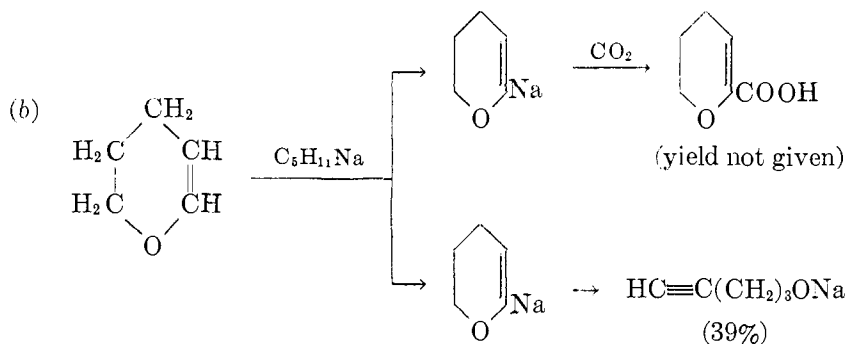
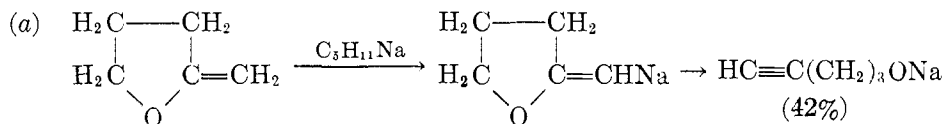


TABLE 3
Metalation and carbonation products of various oxygen-, sulfur-, and nitrogen-containing compounds

Formula	Compound	RNa	Preparation	Solvent	Acid(s)	Yield	References
C ₄ H ₄ O.....	Furan	<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	<i>n</i> -Octane	2-Furoic*	27	(68)
		Ethyl	(C ₂ H ₅) ₂ Hg + Na	<i>n</i> -Hexane	2,4-Furandicarboxylic	6.5	
		Phenyl	(C ₆ H ₅) ₂ Hg + Na	<i>n</i> -Hexane	2-Furoic	15-25	(14, 26)
		Benzyl	(C ₆ H ₅ CH ₂) ₂ Hg + Na	<i>n</i> -Hexane	2-Furoic	5-15	(14)
		2-Thienyl	2,2'-Dithienylmercury + Na	<i>n</i> -Hexane	2-Furoic	58	(14)
		(C ₆ H ₅) ₂ CNa	(C ₆ H ₅) ₂ CCl + Na	<i>n</i> -Hexane	2-Furoic	—	(14)
C ₄ H ₄ S.....	Thiophene	Ethyl	(C ₂ H ₅) ₂ Hg + Na	Thiophene	2-Thienoic	44	(81, 89)
		<i>n</i> -Amyl	<i>n</i> -C ₈ H ₁₁ Cl + Na	—	2,5-Thiophenedicarboxylic	50	(47)
		Ethyl	C ₂ H ₅ Cl + Na amalgam sand	Ether	2-Thienoic	60	(83)
		Phenyl	C ₆ H ₅ Br + Na amalgam sand	Ether	2-Thienoic	89	(83)
		<i>n</i> -Amyl	<i>n</i> -C ₈ H ₁₁ Cl + Na	—	4,5-Dihydrofuroic	58	(76)
		<i>n</i> -Amyl	<i>n</i> -C ₈ H ₁₁ Cl + Na	—	2-Carboxy-2-ethoxyethylene	—	(76)
C ₄ H ₆ O.....	2,3-Dihydrofuran	<i>n</i> -Amyl	<i>n</i> -C ₈ H ₁₁ Cl + Na	—	4,5-Dihydrofuroic	—	(14, 26)
C ₄ H ₈ O.....	Ethyl vinyl ether	<i>n</i> -Amyl	<i>n</i> -C ₈ H ₁₁ Cl + Na	—	2-Carboxy-2-ethoxyethylene	—	(14, 26)
C ₅ H ₆ O.....	2-Methylfuran	Ethyl	(C ₂ H ₅) ₂ Hg + Na	<i>n</i> -Hexane	5-Methyl-2-furoic	—	(14, 26)
		Phenyl	(C ₆ H ₅) ₂ Hg + Na	<i>n</i> -Hexane	5-Methyl-2-furoic	8	(14, 26)
		Benzyl	(C ₆ H ₅ CH ₂) ₂ Hg + Na	<i>n</i> -Hexane	5-Methyl-2-furoic	—	(14, 26)
C ₅ H ₈ O.....	Allyl vinyl ether	<i>n</i> -Amyl	<i>n</i> -C ₈ H ₁₁ Cl + Na	—	Acetylenedicarboxylic	88	(75)
		Benzyl	(C ₆ H ₅ CH ₂) ₂ Hg + Na	<i>n</i> -Hexane	5-Methyl-2-thienoic	21	(14)
C ₅ H ₈ S.....	2-Methylthiophene	Benzyl	(C ₆ H ₅ CH ₂) ₂ Hg + Na	<i>n</i> -Hexane	5-Methyl-2-thienoic	—	(82)
		Ethyl	C ₂ H ₅ Cl + Na-Hg	Ether	5-Methyl-2-thienoic	70	(84)
		Ethyl	C ₂ H ₅ Cl + Na sand	Ether	5-Methyl-2-thienoic	42	(84)
	3-Methylthiophene	Ethyl	C ₂ H ₅ Cl + Na sand	Ether	4-Methyl-2-thienoic	—	(82)
		Ethyl	C ₂ H ₅ Cl + Na-Hg	Ether	4-Methyl-2-thienoic	—	(82)
		<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Dodecane	Salicylic	5	(61, 31a)
C ₆ H ₅ O Na.....	Sodium phenoxide	<i>n</i> -Butyl	(C ₄ H ₉) ₂ Hg + Na	Petroleum ether	2-Hydroxyisophthalic	2	
		<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Dodecane	Hydroxyterephthalic	3	(31b)
		<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Dodecane	Salicylic	0.43	(11)
C ₆ H ₅ O K.....	Potassium phenoxide	<i>n</i> -Butyl	(C ₄ H ₉) ₂ Hg + Na	Petroleum ether	2-Hydroxyisophthalic	—	
		<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Dodecane	Hydroxyterephthalic	—	(61)
		<i>n</i> -Amyl	C ₈ H ₁₁ Cl + Na	Dodecane	Anthranilic	—	(39)
C ₆ H ₇ N.....	Aniline	<i>n</i> -Amyl	—	—	—	(39)	
C ₇ H ₈ O.....	Anisole	<i>n</i> -Amyl	C ₆ H ₁₁ Cl + Na	Ligroin-anisole	<i>o</i> -Methoxybenzoic	20	(56)
		<i>n</i> -Butyl	C ₄ H ₉ Cl + Na	Petroleum ether	<i>o</i> -Methoxybenzoic	42	(12)
		Phenyl	C ₆ H ₅ Cl + Na	Petroleum ether	<i>o</i> -Methoxybenzoic	44	(12)
		Phenyl	C ₆ H ₅ Cl + Na	Benzene	<i>o</i> -Methoxybenzoic	64	(12)
		<i>n</i> -Amyl (excess)	C ₆ H ₅ Cl + Na	—	2-Methoxyisophthalic	27	(42)
		Phenyl	C ₆ H ₁₁ Cl + Na	—	Phenylmercaptoacetic	9	(25)
C ₇ H ₈ S.....	Thioanisole	Phenyl	—	Benzene	—	†	

$C_8H_{10}O$	<i>p</i> -Methylanisole	<i>n</i> -Amyl	$C_8H_{11}Cl + Na$	Ligroin and <i>p</i> -methylanisole	5-Methyl-2-methoxybenzoic	—	(70)
	<i>o</i> -Methylanisole	<i>n</i> -Amyl	$C_8H_{11}Cl + Na$	Petroleum ether	<i>o</i> -Methoxyphenylacetic	—	(32)
	<i>m</i> -Methylanisole	<i>n</i> -Amyl	$C_8H_{11}Cl + Na$	Petroleum ether	2-Methoxy-4-methylbenzoic	52	(42)
	Plenctale	<i>n</i> -Amyl	$C_8H_{11}Cl + Na$	Petroleum ether	<i>o</i> -Ethoxybenzoic	72	(42)
$C_8H_{10}O$	Dimethylaniline	<i>n</i> -Amyl	$C_8H_{11}Cl + Na$	Ligroin and di-methylaniline	<i>N, N</i> -Dimethylanthranilic	18	(12, 56)
$C_8H_{12}S$	2- <i>t</i> -Butylthiophene	Ethyl	$C_8H_{13}Cl + Na$ sand	Ether	5- <i>t</i> -Butyl-2-thienoic	85	(81, 84)
$C_9H_{12}O$	2-Ethylanisole	<i>n</i> -Amyl	$C_9H_{13}Cl + Na$	Petroleum ether	α -(<i>o</i> -Methoxyphenyl)propionic	—	(32)
	Isopropyl phenyl ether	<i>n</i> -Amyl	$C_9H_{13}Cl + Na$	Petroleum ether	2-Methoxy-3-ethylbenzoic	—	(32)
					<i>o</i> -Isopropoxybenzoic	50	(42)
$C_9H_{14}S$	2- <i>t</i> -Amylthiophene	Ethyl	$C_9H_{15}Cl + Na$ sand	Ether	5- <i>t</i> -Amyl-2-thienoic	46	(81, 84)
$C_{10}H_{14}O$	<i>n</i> -Butyl phenyl ether	<i>n</i> -Amyl	$C_{10}H_{15}Cl + Na$	Petroleum ether	<i>o</i> -Butoxybenzoic	76	(42)
$C_{10}H_{16}O$	Dibenzofuran	Benzyl	—	Toluene	4, 6-Dibenzofurancarboxylic	80	(20)
		<i>n</i> -Butyl	$(C_4H_9)_2Hg + Na$	Petroleum ether	4-Dibenzofurancarboxylic	36	(27)
		<i>n</i> -Butyl	$(C_4H_9)_2Hg + Na$	Ether	4, 6-Dibenzofurancarboxylic	77	(28)
		Ethyl	—	—	4-Dibenzofurancarboxylic	—	(94)
		<i>p</i> -Tolyl	—	Benzene	4, 6-Dibenzofurancarboxylic	61	(20)
		<i>p</i> -Tolyl	—	Toluene	4, 6-Dibenzofurancarboxylic	88	(20)
$C_{10}H_{16}S$	Dibenzothiophene	<i>n</i> -Amyl	$C_{10}H_{17}Cl + Na$	Petroleum ether	4-Dibenzothiophenecarboxylic	37	(12)
		Phenyl	$C_8H_9Cl + Na$	Benzene	4-Dibenzothiophenecarboxylic	23	(12)
$C_{12}H_{16}O$	1, 4-Dihydrobenzofuran	<i>n</i> -Butyl	$(C_4H_9)_2Hg + Na$	Petroleum ether	(Dibenzofuran)	66	(13)
					4-Dibenzofurancarboxylic	22	(13)
$C_{12}H_{16}S$	Diphenyl ether	Phenyl	$C_8H_9Cl + Na$	Benzene	<i>o</i> -Phenoxybenzoic	10	(33, 34)
$C_{12}H_{16}S$	Diphenyl sulfide	Phenyl	$C_8H_9Cl + Na$	Benzene	<i>o</i> -Phenylmercaptobenzoic	56	(12)
$C_{12}H_{16}N$	Diphenylamine	<i>n</i> -Butyl	—	—	<i>N</i> -Phenylanthranilic	—	(39)
$C_{12}H_{15}S$	2-(1-Phenylethyl)-thiophene	Ethyl	$C_{12}H_{15}Cl + Na$ sand	Ether	5-(1-Phenylethyl)-2-thienoic	60	(81, 84)
$C_{12}H_{18}S$	2-(1, 1, 3, 3-Tetramethylbutyl)thiophene	Ethyl	$C_{12}H_{17}Cl + Na$ sand	Ether	5-(1, 1, 3, 3-Tetramethylbutyl)-2-thienoic	66	(81, 84)
$C_{12}H_{16}O$	4-Methyl-dibenzofuran	<i>n</i> -Butyl	$(C_4H_9)_2Hg + Na$	Ether	6-Methyl-4-dibenzofurancarboxylic	46	(28)
	Xanthene	$C_{12}H_{17}Nu\ddagger$	$C_{12}H_{17}Cl + Na-Hg$	Ether	Xanthenecarboxylic	—	(10)
		$C_{12}H_{19}Nu\ddagger$	$C_{12}H_{19}Cl + Nu-Hg$	Ether	Xanthenecarboxylic	—	(10)
$C_{13}H_{16}O_2$	4-Methoxydibenzofuran	<i>n</i> -Butyl	$(C_4H_9)_2Hg + Na$	Ether	(4-Methoxy-6-dibenzofuryl-sodium)	—	(28)
$C_{14}H_{13}N$	5-Ethylcarbazole	<i>n</i> -Butyl	—	—	5-Ethylcarbazole-4-carboxylic (?)	—	(19)
					5-Ethylcarbazole-4, 6-dicarboxylic (?)	—	(19)

TABLE 3--*Concluded*

Formula	Compound	RNa	Preparation	Solvent	Acid(s)	Yield	References
$C_{14}H_{13}N$ <i>contd.</i>		Ethyl	5-Ethylcarbazole-4-carboxylic(?)	<i>per cent</i> —	(19)
$C_{16}H_{15}N$	Triphenylamine	Phenyl	$C_6H_5Cl + Na$	Benzene	5-Ethylcarbazole-4,6-dicarboxylic Benzoic	— 29	(15)

* Isolated as methyl ester.

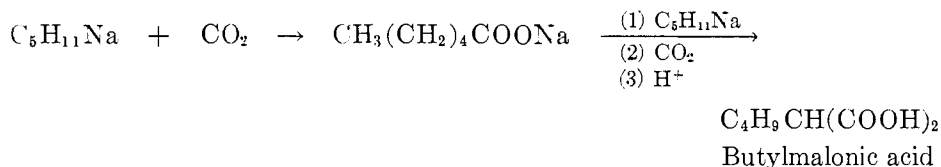
† Unpublished work by John F. Nobis.

‡ Diphenyl- α -naphthylmethylsodium.

§ Diphenyl-*p*-xenylmethylsodium.

In (*d*) metalation is claimed to occur only in the α -position, leading to the acid shown. This exclusive alpha attack can be rationalized in terms of the $-I$ effect of the oxygen in the ether grouping, which makes the hydrogen on the adjacent carbon more acidic.

Generally speaking there has been no investigation of the metalation of carboxylic acids or their salts with organosodium reagents. However, Gilman (23) has interpreted the formation of *n*-butylmalonic acid (60) and phenylmalonic acid (56) during the slow carbonation (gaseous carbon dioxide) of amylsodium and benzylnsodium as arising from a metalation of sodium caproate and sodium phenylacetate, respectively. If no α -hydrogen is present addition to the carbonyl occurs. Thus, a slow high-temperature carbonation of phenylsodium gives benzophenone and triphenylcarbinol.¹



Similar results were reported in the slow carbonation of dodecylsodium (38), from which a mixture of tridecyl and undecylmalonic acids resulted.

In a patent (3) it is claimed that camphor can be metalated with phenylsodium. The metalated product is said to undergo carbonation or coupling with allyl chloride or diethylaminoethyl chloride.

C. SULFUR-CONTAINING COMPOUNDS

Thiophene and alkylthiophenes are metalated by alkyl-, aryl-, and aralkylsodium compounds yielding the corresponding 2-thienyl- or alkyl-2-thienylsodium derivatives (1, 81, 82, 83, 84, 85) in excellent yields.

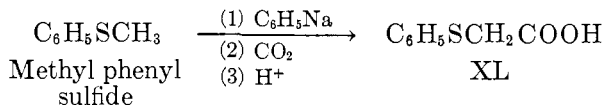
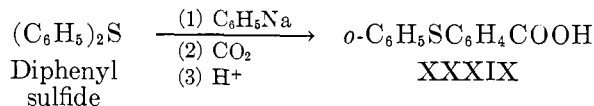
It is of interest that 3-alkylthiophenes are found to metalate almost exclusively in the 5- rather than in the 2-position (1, 84). Apparently steric factors are such as to disfavor reaction at the latter position.

It has also been reported that thiophene can be dimetalated with amylsodium to form the 2,5-disodio derivative in 50 per cent yield (47). In a competitive experiment thiophene was found to undergo dimetalation much more rapidly than *tert*-butylbenzene (47).

Dibenzothiophene is likewise metalated by *n*-amylsodium and phenylsodium ortho to the sulfur atom to give the 4-dibenzothienylsodium (12) in yields of 37 and 23 per cent, respectively. No metalation was observed with triphenylsodium.

Diphenyl sulfide, like diphenyl ether, with phenylsodium undergoes ortho nuclear metalation. Carbonation results in a 56 per cent yield of *o*-phenylmercaptobenzoic acid (XXXIX) (12). Methyl phenyl sulfide, on the other hand, is laterally metalated. Carbonation yields α -phenylmercaptoacetic acid (XL) (25) in 45 per cent yield.²

² In unpublished studies JOHN F. NOBIS reported a 45 per cent yield.



D. NITROGEN-CONTAINING COMPOUNDS

Aromatic amines are metalated in the nucleus by active metalating agents. Like previously mentioned hetero atoms such as sulfur and oxygen, the nitrogen directs the sodium atom to the ortho position. Thus aniline undergoes ortho nuclear metalation to give anthranilic acid on carbonation (39). Dimethylaniline also undergoes ortho nuclear metalation to yield *o*-dimethylaminophenylsodium (12, 56) in 18 per cent yield. Diphenylamine, likewise, with *n*-butylsodium is monometalated ortho to the nitrogen atom (39).

Acetonitrile has been reportedly metalated by the sodium-naphthalene complex (90). Likewise, diethylacetonitrile has been reported (4) to undergo metalation with ethylsodium. When the resulting product is treated with allyl chloride, diethylallylacetonitrile is said to form.

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STEREOCHEMISTRY AND HETEROGENEOUS CATALYSIS

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I. INTRODUCTION

The aim of this paper is the presentation of those aspects of stereochemistry and heterogeneous catalysis which are of potential interest in the development of our understanding of the mechanisms of heterogeneous catalytic reactions.

In 1937 Farkas and Farkas (85) surveyed the stereochemistry of the hydrogenation of carbon-carbon double and triple bonds to the same end. Other reviews which deal with aspects of the problem are those of Campbell and Campbell (52), Crombie (65), and Weidlich (200). Aside from the stereochemistry of the hydrogenation of multiple bonds, applications of stereochemistry to the study of the mechanism of heterogeneous catalytic reactions have aroused little interest until recently.

By determination of mechanism is meant the discovery of those geometric paths by which one grouping of atoms rearranges into another. The theory of organic mechanisms permits one to analyze a large number of organic reactions into a series of elementary steps small enough in number to be practical (S_N1 , S_N2 , etc., to use Ingold's terminology). It is not surprising that such development of elementary steps for heterogeneous catalytic reactions is much less advanced. All the difficulties of homogeneous reactions are present plus the problem of the surface.

A successful mechanism is the residuum left after the elimination of other conceivable mechanisms by any kind of information. The data of optical activity have proved particularly powerful in the unequivocal elimination of pos-

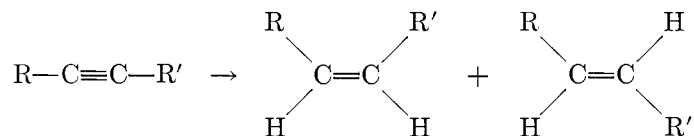
sible mechanisms. Optical activity was an essential tool in the development of the mechanistic theory of homogeneous organic reactions. One might suspect that it would prove equally important in heterogeneous catalysis, although studies of optical activity and heterogeneous catalysis are as yet too few to prove or disprove such a possibility.

Little of the work reported in this review was obtained for purposes of the determination of mechanism; rather, most of it is a by-product of preparative organic chemistry. Thus, whether isomerization occurred during reaction rather than before or after reaction often cannot be established. If a man in search of a certain *cis* isomer had obtained it and enough of it, there was usually no compelling reason why he should determine the exact *cis/trans* ratio in the original reaction mixture. One then knows, at best, that there was a mixture and that the *cis* isomer was at least a certain fraction of it. Such data are used where no others are available, but no attempt has been made to survey such preparative data completely.

II. HYDROGENATION OF THE ACETYLENIC LINKAGE

It is possible to hydrogenate the triple bond to a double bond on various palladium and nickel catalysts although, in general, if one stops such a hydrogenation after the reaction of one mole of hydrogen, one will find some unreacted acetylene and some saturated material. Platinum catalysts are not usually suitable for this reaction since they result in relatively large amounts of the latter two materials (66, 146). Lindlar's catalyst (palladium on calcium carbonate poisoned by lead and quinoline (17, 66, 96)) often brings about hydrogenation exclusively to the olefinic stage. Raney nickel modified by the addition of zinc acetate and piperidine is also relatively selective (154).

The hydrogenation of a disubstituted acetylene might conceivably lead to a mixture of *cis* and *trans* olefins in any ratio.



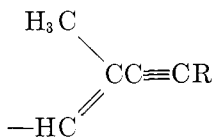
The enthalpies of the *cis* forms are higher than those of the *trans* forms by, for example, 4.0 kcal. for methyl cinnamate, 5.7 kcal. for stilbene, 4.2 kcal. for diethyl maleate (*vs.* fumarate) (204), and 1.3 kcal. for 2-butene (172). Nevertheless, as first reported for the hydrogenation of the sodium salt of phenylpropionic acid ($\text{C}_6\text{H}_5\text{C}\equiv\text{CCOONa}$) in aqueous solution with colloidal palladium by Paal and Hartmann (160) in 1909, the *cis* olefin predominates in the product.

Other instances in which the hydrogenation of acetylenes leads predominantly to *cis* olefins are: tolane ($\text{C}_6\text{H}_5\text{C}\equiv\text{CC}_6\text{H}_5$) (39); various $\text{RC}\equiv\text{CCOOH}$ derivatives (39); $\text{CH}_2\text{OHC}\equiv\text{CCH}_2\text{OH}$ (171); and cyclodecyne (to *cis*-cyclodecene) on Lindlar's catalyst (168) and on unmodified palladium on barium carbonate (29).

Also, *cis* olefins are predominantly formed in somewhat different heterogene-

ous processes. Tolane yields *cis*-stilbene when cyclohexene is used as the hydrogen donor (41) and *cis* olefins result from the electrolytic reduction of acetylenes at spongy nickel cathodes (65).

In general, then, the less stable olefin (the *cis* isomer) is formed. Two examples are available which involve the formation of relatively much less stable *cis* olefins than any reported above. In the preparation of carotene-like compounds, the grouping



is hydrogenated to *cis* diolefins which are sterically very crowded and the existence of which might appear to violate Pauling's rules (163). These *cis* compounds are formed both with Lindlar's catalyst (96) and with Raney nickel modified with zinc acetate and piperidine (154). Perhaps the most extreme case of formation of an unstable *cis* configuration occurs during the hydrogenation on Lindlar's catalyst of the compound $\text{CH}_3\text{CH}=\text{CHC}\equiv\text{CC}\equiv\text{CCH}=\text{CHCH}_3$, in which both double bonds have the *cis* configuration. The all-*cis*-decatetraene was isolated from the reaction mixture (106). The preferred planar configuration of conjugated polyenes is impossible, and the molecule may perhaps exist in the form of a helix of a turn and a half. Other examples of the formation of hindered *cis* polyenes are given in reference 155. However, certain hindered *cis* olefins cannot be made by this method. Thus, 4- Δ^1 -cyclohexenylbut-3-yne-2-one upon hydrogenation on palladium on calcium carbonate gives the *trans* but no *cis* ketone (186). The *cis* ketone may be so labile as to be unisolable.

Although the predominant olefinic product of the hydrogenation of a disubstituted acetylene is the *cis* form, the question remains as to whether any *trans* olefin is a direct product of the hydrogenation step. Paal and Hartmann (160) thought not, but in the succeeding years the detection of *trans* olefin was reported in several hydrogenations. In 1929, from the data of an extensive investigation, Bourguel (39) concluded that the *cis* form was the exclusive product. The view then prevailed that *trans* admixture resulted from isomerization subsequent to hydrogenation (52), although such an origin of *trans* product could rarely be rigorously established.

Actually, many compounds which were reported to have been pure *cis* must, in fact, have been mixtures (8, 104). Until recently, analysis into *cis* and *trans* depended upon isolation techniques. The difficulty of so demonstrating the absence of *trans* olefinic product is aggravated by contamination by unreacted acetylene and saturated material. Analyses employing more modern methods (infrared, chromatography, etc.) have often shown the presence of 5-20 per cent of the *trans* olefin.

Thus, the reduction of methyl stearolate ($\text{C}_8\text{H}_{17}\text{C}\equiv\text{CC}_7\text{H}_{14}\text{COOCH}_3$) on Raney nickel (127) yields 3.7 per cent of methyl stearate, 2.1 per cent of methyl

stearolate, and 94.2 per cent of methyl octadecenoate. The latter is 94 per cent *cis* and 6 per cent *trans*. On Lindlar's catalyst the product of similar hydrogenation is free of reactant and saturated acid but the oleic acid is 5 per cent *trans* (17). Ozonization detected no migration of the double bond. However, with more quinoline only 1-2 per cent of the *trans* acid was formed.

3-Hexen-1-ol ($\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{OH}$), prepared by hydrogenating the acetylene with palladium on calcium carbonate, contained substantial amounts of the *trans* carbinol (183), but a high yield of nearly pure *cis* carbinol upon hydrogenating 3-pentyn-1-ol on a similar catalyst has been reported (67).

In the hydrogenation of 2-octyne on nickel-kieselguhr at 30-80°C. and 1-3 atm. pressure, Henne and Greenlee (104) obtained 2-octene (20 per cent *trans*; 80 per cent *cis*). They found the product of a similar hydrogenation on Raney nickel by Campbell and Eby (53) to contain 17 per cent of the *trans* isomer.

Romanet (171) has investigated the hydrogenation of 2-butyn-1,4-diol ($\text{HOCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$) on Raney nickel at 1 atm. and 20°C. In addition to reactant (10 per cent), saturated diol (11 per cent), and olefinic diol (66 per cent), 8.5 per cent of dihydro-2,5-furan (formed from the *cis* enediol) and 1.5 per cent of butenol were found. The olefinic diol was 21 per cent *trans*. Romanet showed that the *cis* diol was converted into the *trans* diol neither by distillation nor by contact with aged Raney nickel for protracted periods. The absence of isomerization under actual hydrogenation conditions was not, however, demonstrated.

Other workers using more active Raney nickel catalysts have apparently obtained higher proportions of *cis* products in the hydrogenation of 2-butyn-1,4-diol and related acetylenic glycols (99, 143, 196). It has been suggested several times that a high yield of *cis* product is associated with an active catalyst (21, 52).

Douglas and Rabinovitch (77) have studied the hydrogenation of acetylene with deuterium on nickel catalysts. The reaction is complicated by isotopic exchange. At -80°C. on nickel-kieselguhr, the product is 50 per cent *cis*- $\text{C}_2\text{H}_2\text{D}_2$, 20 per cent *trans*- $\text{C}_2\text{H}_2\text{D}_2$, 15 per cent $\text{C}_2\text{H}_3\text{D}$, and 10 per cent C_2HD_3 . At room temperatures on nickel and palladium catalysts, a much closer approach to statistical equilibrium is observed. Whether all-*trans*-dideuteroethylene originated from the subsequent isomerization of *cis*-dideuteroethylene could not be determined.

Thus, the formation of small amounts of *trans* olefins often accompanies that of the predominant *cis* olefins. In some cases the *trans* isomer is definitely formed by isomerization after reaction; for example, 1,1,4,4-tetraphenyl-2-butyn-1,4-diol gives a mixture of the *cis* and *trans* olefinic glycols on hydrogenation with Raney nickel (51). Although hydrogenation stops sharply at the olefinic state, the catalyst catalyzes the rearrangement of the *cis* to the *trans* glycol. Old Raney nickel largely loses the capacity for this isomerization while maintaining its capacity for hydrogenation.

In particular, with acetylenes devoid of adjacent substituents which might

interact during hydrogenation, there is no conclusive evidence as to whether the observed trans olefin is an initial product of reaction or whether it is formed by the isomerization of an initial cis olefin. A study of cis-trans isomerization under hydrogenation conditions on Lindlar's catalyst would be of interest. A study of the hydrogenation of acetylenes in the vapor phase would also be helpful, since all of the examples instanced above involved liquid-phase hydrogenation.

III. CIS-TRANS ISOMERIZATION

As detailed in the last section, the cis forms of secondary olefins are less stable than the trans (smaller-ring cyclic olefins are, of course, exceptions). At least under certain circumstances, cis-trans equilibration can occur under hydrogenation conditions at rates comparable to that of hydrogenation. This reaction has been studied extensively only for unsaturated fatty acids for which it is technically important. (References 86 and 199 are leading references to earlier work in this field.)

In the hydrogenation of methyl oleate (*cis*-C₈H₁₇CH=CHC₇H₁₄COOCH₃) at 200°C. on nickel, at 10 per cent hydrogenation to methyl stearate there is present 38 per cent of the trans esters. Beyond about 50 per cent hydrogenation, the cis and trans forms are in equilibrium (2 trans: 1 cis) (86). The rate of cis-trans isomerization relative to hydrogenation declines as the temperature is lowered, and at 150°C. at 10 per cent hydrogenation the amount of trans ester is 14 per cent. If hydrogen is replaced by nitrogen, the amount of cis-trans isomerization is very much reduced but it will occur at a measurable rate at 290°C. (199).

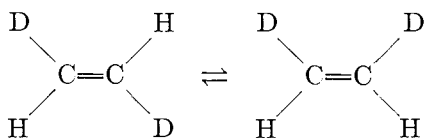
Formation of the trans ester also occurs on platinum black at 170°C., but again, in the absence of hydrogen, the rate is very much reduced (22). At about one-third hydrogenation, one finds $\frac{1}{3}$ of the trans esters. In hydrogenation with deuterium, the trans esters formed initially are nearly devoid of deuterium.

In all of these cases, double-bond migration accompanies cis-trans isomerization. Some of the reported trans esters probably are positional isomers, but accurate measurement of the positional isomerization has only recently become possible (26, 31). Actually, it appears probable that in molecules in which positional isomerization is possible (e.g., excluding stilbene), olefin which is desorbed from the surface without being hydrogenated is in cis-trans equilibrium and in positional equilibrium with respect to moving the double bond one step. For example, in the hydrogenation of oleic acid at low hydrogen pressures on nickel at 150°C., at 50 per cent saturation, 64 per cent of the residual unsaturated acid is Δ^9 (oleic), Δ^8 and Δ^{10} amount to 10 per cent each, and Δ^7 and Δ^{11} amount to 8 per cent each. The Δ^9 acid is 46 per cent trans. The other acids are in cis-trans equilibrium, as they are even at low saturations. At high saturations, Δ^6 and Δ^{12} acids appear. From the nature of the build-up of the positional isomers, it appears that the Δ^8 and Δ^{10} isomers are initial products and that the other acids are largely or entirely secondary products (7). By "positional equilibrium" above, one means that an adsorbed oleic acid molecule has an

equal chance of being desorbed either as Δ^9 or Δ^8 , or as Δ^9 or Δ^{10} . Thus the initial products of reaction would be: *cis*- Δ^9 , 2; *trans*- Δ^9 , 4; *cis*- Δ^8 and *cis*- Δ^{10} , 1 each; *trans*- Δ^8 and *trans*- Δ^{10} , 2 each.

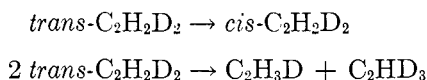
In the hydrogenation of 1-butene on palladium on barium sulfate in ethanol at -8°C ., at 20 per cent hydrogenation the residual olefin is 92 per cent 2-butene. Apparently *cis*-*trans* isomerization is also relatively rapid under these conditions (209).

From a careful study of the interaction of butenes and hydrogen or deuterium on metallic nickel, Taylor and Dibeler (187) reported that the *cis*-*trans* isomerization of 2-butene is nine to ten times faster than exchange with deuterium and four to five times faster than hydrogenation. Isomerization is inhibited in the absence of hydrogen or deuterium.



The *cis*-*trans* isomerization of dideuteroethylene could occur merely by intermolecular exchange of hydrogen isotopes. This is, of course, impossible with the 2-butenes. However, the isomerization of dideuteroethylenes occurs faster than interethylenic isotopic exchange both on nickel-kieselguhr at 25°C . and on nickel wire at 100°C . (77).

On evaporated nickel film at 23°C ., *trans*- $\text{C}_2\text{H}_2\text{D}_2$ is completely equilibrated in less than an hour. Two reactions occur as initial steps (87):



C_2D_4 , C_2H_4 , and *asym*- $\text{C}_2\text{H}_2\text{D}_2$ are secondary products (88). The kinetics of the first two steps are the same. The first step is much faster at low temperatures but only 1.4 times faster at 429°C . If, however, a large amount of C_2D_4 is added, the second step is faster. These rate differences apparently result from isotope effects (87).

These reactions are very much faster in the presence of hydrogen but, presumably, similar considerations would apply.

References exist to unpublished material reporting the isomerization of dimethyl maleate on palladium (84, 133) and platinum (133), but no experimental details are available. The isomerization of *cis*-stilbene has been similarly reported (133), but the absence of such isomerization *in the absence of hydrogen* has also been reported (195).

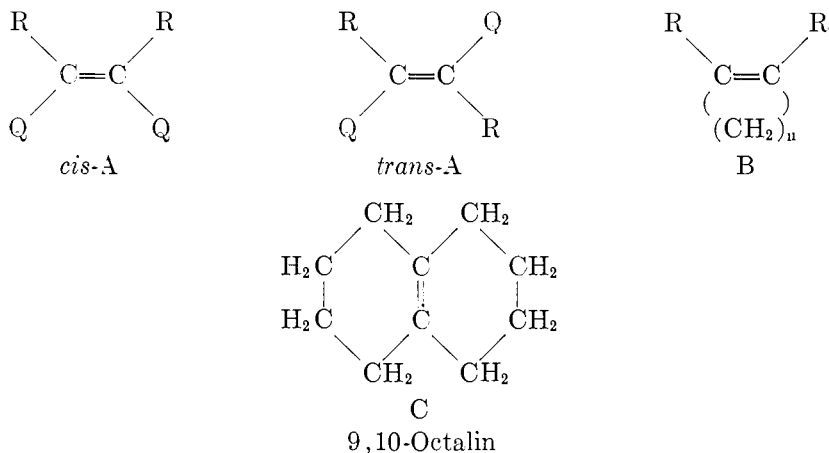
Further work on the interrelation of *cis*-*trans* isomerization, of hydrogenation, and of double-bond migration would be desirable.

IV. HYDROGENATION OF CARBON-CARBON DOUBLE BONDS

It has been generally considered that *cis* addition is involved in the catalytic hydrogenation of ethylenic bonds (52, 85). Unfortunately, of necessity, tests

of this have involved tetrasubstituted ethylenes,—a rather special class. As will be seen, the most interesting aspect of the stereochemistry is that the addition is not always exclusively *cis*.

The following types of tetrasubstituted ethylenes have been investigated.



If addition were exclusively *cis*, *trans-A* would be converted into *dl-AH₂*, that is, into a racemic mixture of the type of racemic tartaric acid. *cis-A* would give the *meso* form, the form which is optically inactive by internal compensation (it possesses a plane of symmetry). The situation is the same for B, but one now speaks of the product of *cis* addition as *cis-BH₂* (it is a *meso* form). The other form would be called *trans* (it is a *dl*-form). The stereochemistry here is of the type of *cis*- and *trans*-dimethylcyclohexane. *Cis* addition would convert C to *cis*-decalin; the other form is *trans*-decalin.

One might study the addition of deuterium to secondary olefins such as *cis*- and *trans*-2-butene and expect to deal with *meso*- and *dl*-2,3-dideuterobutane. However, isotopic exchange would confuse the picture as in the addition of deuterium to acetylene and probably much more seriously (198). Simple *cis* addition might, however, be possible with chromic oxide catalyst. Deuterium atoms can be added to a double bond with little accompanying isotopic exchange (142) on this catalyst.

The results of the hydrogenation of a variety of tetrasubstituted ethylenes are presented in table 1.

In those compounds in which a C=O group is conjugated to the carbon-carbon double bond, *trans* products might arise by initial hydrogenation to an enol (1,4-addition) followed by ketonization (201). The *trans* products resulting from the hydrogenation of the acyclic olefins might have originated from *cis*-*trans* isomerization of the olefin before hydrogenation. This possibility was not critically examined. Neither of these possibilities can account for *trans* products in the hydrogenation of dimethylcyclohexene or octalin. Furthermore, neither dimethylcyclohexane nor decalin is isomerized after formation (107, 181). The results of the hydrogenations of these two compounds are particu-

TABLE 1
 Stereochemistry of hydrogenation of tetrasubstituted olefins


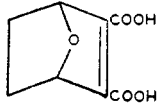
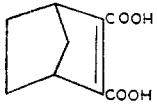
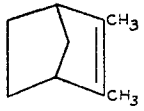
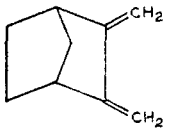

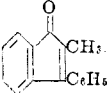
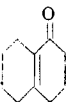
Substrate	Catalyst	Solvent and Conditions ^(a)	Products	References
$\text{cis-} \left(\begin{array}{c} \text{C}_6\text{H}_5\text{C}=\text{C} \\ \\ \text{CH}_3 \end{array} \right)_2$	Palladium black	Acetic acid	Meso, 2% <i>dl</i>	(202)
	Palladium-charcoal or nickel-charcoal	Ether + methanol	Meso	(156)
$\text{trans-} \left(\begin{array}{c} \text{C}_6\text{H}_5\text{C}=\text{C} \\ \\ \text{CH}_3 \end{array} \right)_2$	Palladium black	Acetic acid	<i>dl</i> , 2% meso	(202)
	Palladium-charcoal	Ether + methanol	<i>dl</i> , nearly pure	(156)
		Acetic acid	<i>dl</i> , nearly pure	(156)
		Acetic acid at reflux	60% meso, 40% <i>dl</i>	(156)
	Nickel-charcoal	180°C., 40 atm.	<i>dl</i> , pure	(156)
$\text{trans-} \left(\begin{array}{c} p\text{-CH}_3\text{OC}_6\text{H}_4\text{C}=\text{C} \\ \\ \text{C}_2\text{H}_5 \end{array} \right)_2$	Palladium black	Acetic acid	97% <i>dl</i>	(202)
$\text{trans-} \left(\begin{array}{c} p\text{-HOC}_6\text{H}_4\text{C}=\text{C} \\ \\ \text{C}_2\text{H}_5 \end{array} \right)_2$	Palladium black	Acetic acid	90% <i>dl</i> , 10% meso	(202)
$\text{cis-} \left(\begin{array}{c} \text{HOOC}=\text{C} \\ \\ \text{CH}_3 \end{array} \right)_2$	Palladium-charcoal or nickel-charcoal	Sodium salt, aqueous solution	86% meso, ^(e) 14% <i>dl</i>	(156)
$\text{trans-} \left(\begin{array}{c} \text{OOC}=\text{C} \\ \\ \text{CH}_3 \end{array} \right)_2$	Palladium-charcoal	Sodium salt, aqueous solution	70% <i>dl</i> , 30% meso	(156)
	Nickel-charcoal	Sodium salt, aqueous solution	<i>dl</i>	(156)
	Platinic oxide	Acetic acid 1 atm. 100 atm.	77% cis 86% cis	(181)
	Platinic oxide	Acetic acid	Endo-cis; at most a few per cent trans	(3, 208)
	Platinic oxide	Acetic acid Dimethyl ester ^(b)	Endo-cis ^(c) + 2-4% trans Almost pure ^(c) endo-cis	(5)
			Mainly ^(d) endo-cis	(4)
	Platinic oxide	Methanol	Mainly ^(e) endo-cis	(5)
	Platinum black	Acetic acid	2 cis, 1 trans ^(e)	(114)
		Ether	1 cis, 1 trans	(111)
		Ethanol (absolute)	trans > cis	(139)
		Acetic acid	1 cis, 1 trans	(131)

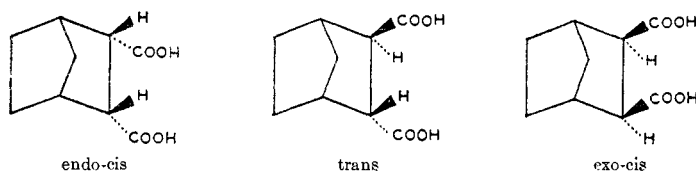
TABLE 1—(continued)

Substrate	Catalyst	Solvent and Conditions ^(a)	Products	References
	Platinic oxide	Ethyl acetate	7% or less ^(f) of trans	(212)
	Palladium-charcoal	Methanol or diethyl ether	Mixture of cis ^(e) and trans	(115) (199)

(a) Room temperature unless otherwise stated.

(b) Similar results in methanol.

(c) The products of the cyclic dicarboxylic acids have the following configurations:



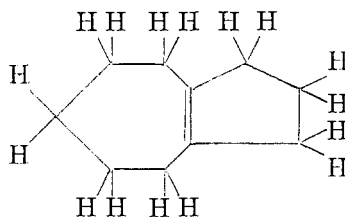
(d) Mainly endo-cis by density and refractive index. Whether isomers were exo-cis or trans or both was not determined. If the former, at least 80 per cent endo-cis; if the latter, at least 93 per cent endo-cis.

(e) $\Delta^1,9$ -Octalin is reported not to isomerize when shaken with hydrogen-saturated platinum (either platinum black or that prepared by reducing platonic oxide) in a nitrogen atmosphere in 10-15 hr. (115).

(f) The indenone forms an indanone with saturation of the double bond in the five-membered ring.

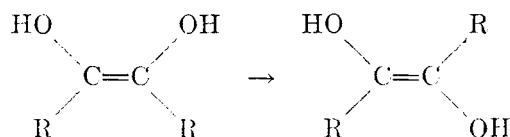
(g) The hydrogenation of dimethylmaleimide on platonic oxide in ethanol is reported to give nearly pure *meso*-dimethylsuccinimide (140).

larly important in any mechanistic considerations. Study of octalin should be coupled with that of the analogous octahydroazulene.

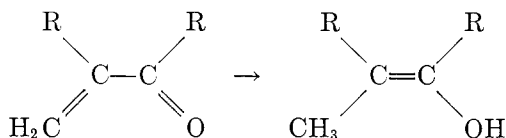


The hydrogenation of octahydroazulene with Adams' platinum oxide or with Raney nickel apparently gives a relatively pure perhydroazulene, presumably the cis form, instead of a mixture as obtained with octalin (131).

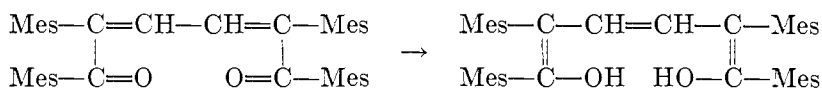
Interesting stereochemistry accompanies the hydrogenation of certain hindered diketones, RCOCOR , where R is mesityl or its triethylphenyl and triisopropylphenyl analog. What is probably the cis enediol is the initial product in hydrogenations with platinum oxide at room temperatures. On further treatment with platinum and hydrogen it isomerizes to the trans enediol (94, 95).



Steric hindrance from the alkyl groups in the 2- and 6-positions of R hinders the addition of a proton to give the ketone and likewise prevents further hydrogenation. Thus, this hydrogenation definitely involves 1,4-addition. The following compound is hydrogenated similarly (93).



The reaction must also involve 1,4-addition. Nothing seems to have been reported about its isomerism. Hydrogenation of the following compound (in which Mes is mesityl) involves 1,8-addition (92).



Hydrogenations can occur which are independent of any particular geometry of a solitary double bond and adsorbed species derived from it.

V. HYDROGENATION OF AROMATIC RINGS

A. Polyalkylbenzenes

In 1,2- and 1,4-disubstituted cyclohexanes the trans configurations are more stable, but in 1,3-disubstituted cyclohexanes the cis configuration is the more stable (173). For example, the cis/trans ratio in 1,3-dimethylcyclohexane is reported to be 10 (56). The configurations of 1,3 and 1,3,5 compounds reported in papers published before 1947 (173) are usually reversed.

The hydrogenation of polyalkylbenzenes gives stereoisomeric mixtures. Cis products predominate in hydrogenations at room temperature and at all temperatures with 1,3- and 1,3,5-substituted benzenes. At higher temperatures, however, the proportion of trans product rises in the hydrogenation of 1,2- and 1,4-dialkylbenzenes, and at temperatures of 150°C. and above the trans form may even predominate. As will be discussed in Section VI, metallic catalysts can epimerize polyalkylcyclohexanes at these temperatures. Thus, at higher temperatures the products of hydrogenation approach stereochemical equilibrium but the degree to which this occurs is rather unpredictable, depending as it does on the activity of the catalyst and the duration of the hydrogenation. Since the cis isomer is the more stable form of 1,3-disubstituted cyclohexanes, the hydrogenation of *m*-xylene, for example, gives about the same mixture of epimers at all temperatures.

Examples of these points are given in table 2. In the isolation of the hydrogenation product, unreacted benzene was often removed by treatment with sulfuric acid. This may lead to isomerization unless the acid is added rapidly and at low temperature (50).

Hydrogenations of other polyalkylbenzenes also lead to mixtures (182). Examples are: hexamethylbenzene (79), hexaethylbenzene (129), pentamethylbenzene (79), 1,2,4,5-tetraisopropylbenzene (129), and 1,4-di-*tert*-butyl-

TABLE 2
Hydrogenation of dialkylbenzenes and polyalkylbenzenes

Catalyst	Solvent ^(a)	Temperature ^(b)	Pressure	Products	References
<i>o</i> -Xylene					
		°C.			
Platinic oxide.....	Acetic acid		Low	5% trans	(181)
Platinum black.....	Acetic acid		Low	9% trans	(147)
Platinum-charcoal.....		170	Low	Mainly trans ^(c)	(210)
Osmium-asbestos.....		60	Low	Mainly cis ^(c)	(210)
Nickel.....		170	Low	Mainly trans ^(c)	(210)
Nickel-alumina.....		180	Low	~50% trans ^(d)	(148)
<i>m</i> -Xylene					
Platinic oxide.....	Acetic acid		Low	15% trans	(181)
			High	23% trans	(19)
Platinum black.....	Acetic acid		Low	~20% trans	(149)
Nickel.....		180	Low	~20% trans	(149)
<i>p</i> -Xylene					
Platinic oxide.....	Acetic acid		Low	28% trans	(181)
Platinum black.....	Acetic acid		Low	~20% trans	(149)
		200	Low	~80% trans	(149)
Platinum-charcoal.....		170	Low	Mainly trans ^(c)	(210)
Osmium-asbestos.....		60	Low	Mainly cis ^(c)	(210)
Nickel.....		180	Low	~80% trans ^(c)	(149, 210)
<i>o</i> -Ethyltoluene					
Platinic oxide.....	Acetic acid (?)			23% trans	(28)
Mesitylene					
Platinum or nickel.....		175	High (?)	10% trans ^(e)	(54, 57)
1,3,5-Triethylbenzene					
Platinum or nickel.....		175	High (?)	3% trans ^(e)	(54, 57)

(a) No solvent if no entry.

(b) Room temperature if no entry.

(c) Zelinsky and Margolis thought that osmium-asbestos gave pure cis isomer and that nickel or platinum-charcoal at 170°C. gave pure trans isomer. Modern values of the density and refractive indexes of these compounds show that this is incorrect. Actually these investigators had mixtures in all cases. From the API values, the product of the hydrogenation of *o*-xylene on osmium was about 29 per cent trans and that at 170°C. on nickel, about 75 percent trans.

(d) An increase in the temperature of hydrogenation resulted in more of the trans isomer.

(e) These were shown to be the equilibrium values.

benzene (129). *cis*-1,4-Di-*tert*-butylcyclohexane would be rather unstable, since at least one tertiary butyl group would have to be axial (if the molecule is in the rigid conformation).

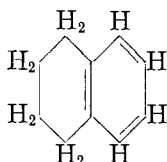
B. Dicycloaromatics

In general the stereochemistry of the products of the hydrogenation of dicycloaromatic compounds such as naphthalene and quinoline resembles that of ortho-disubstituted benzenes. Mixtures are obtained in which the cis form pre-

dominates in hydrogenations at lower temperatures and in which increasing amounts of the *trans* form appear at higher temperatures. As with *o*-dialkylbenzenes, the increased quantity of the *trans* isomer may result either from isomerization subsequent to reaction or from a relatively greater contribution of whatever reaction leads to the formation of the *trans* form at room temperatures. (At such temperatures isomerization after reaction does not occur.)

The more stable form of most perhydrobicyclics is the *trans* form. At 50°C. the equilibrium *trans/cis* ratio is 19 for decalin (58). *trans*-Hydrindane also seems more stable than the *cis* isomer (82).

Under some conditions, a tetrahydrobicyclic seems to be an intermediate (i.e., it is desorbed from the catalyst and must be reabsorbed to react); for example, tetralin in the hydrogenation of naphthalene.

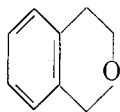


This seems to be particularly common in the hydrogenation of substituted naphthalenes such as naphthols (1, 114, 185). In such a case, the hydrogenation of the remaining ring sets the configuration.

The hydrogenation of naphthalene in glacial acetic acid on platinum black gives about a 5 per cent yield of *trans*-decalin (205) (this is more stereospecific than in the hydrogenation of 1,9-octalin). Similar hydrogenation with the Adams platinum oxide at 120 atm. gives a 23 per cent yield of *trans*-decalin (19); yet, surprisingly, the corresponding hydrogenation of tetralin gives nearly pure *cis*-decalin (19). Hydrogenation with nickel in the liquid phase at 190°C. gives about equal amounts of *cis*- and *trans*-decalin, while hydrogenation in the vapor phase at 160°C. gives predominantly *trans*-decalin (107).

Indane and indene also yield mixtures of *cis*- and *trans*-hydrindane upon hydrogenation with nickel catalysts at 160–200°C. (78, 83), but the hydrogenation of indene and of some of its derivatives on platinum catalysts at room temperatures leads predominantly to *cis*-hydrindane (116, 137).

Hydrogenation of isochroman at about 220°C. on Raney nickel at high pres-



Isochroman

sures gives *cis*- and *trans*-hexahydroisochroman in a ratio of about 3:1 (28).

The hydrogenation of quinoline in glacial acetic acid with colloidal platinum at 40°C. gives an 80 per cent yield of *trans*-decahydroquinoline; with added hydrochloric acid, a 35 per cent yield of the *trans* isomer is obtained (117). Hydrogenation on nickel at 210°C. gives predominantly the *trans* isomer (193).

At 25°C. the hydrogenation of isoquinoline in acetic acid plus sulfuric acid with platinum oxide gives 80 per cent *cis*-decahydroisoquinoline and 20 per cent *trans*-decahydroisoquinoline. The dehydrogenation of *cis*-decahydroisoquinoline on palladium at 210°C. proceeds more rapidly than that of the *trans* isomer (206). Similar behavior has been reported for the decahydroquinolines and the decalins on palladium (80).

C. Phenols and aromatic acids, etc.

By and large, the hydrogenation of substituted aromatic compounds at room temperatures with platinum catalysts leads to mixtures in which *cis* isomers predominate. Hydrogenation with nickel catalysts at higher temperatures (150–200°C.) is more apt to lead to mixtures in which the stable form predominates. A number of examples are presented in table 3.

In 1,4- and 1,2-substituted cyclohexanes the *trans* form is the stable one, but in 1,3-cyclohexanes the *cis* form is usually the more stable. For example, at equilibrium the ratio of *cis*- to *trans*-2-methylcyclohexanol is 1:99 and for 4-methylcyclohexanol, 12:88 (69). On the other hand, *cis*-3-methylcyclohexanol is the more stable isomer (153).




It seems clear that mixtures of isomers resulted in all of the examples in table 3. However, probably none of the isomeric compositions listed are of high accuracy. Those of the cresols, 2-*tert*-butylphenol, and sodium *m*-toluate depend upon the densities or refractive indexes of the isolated substituted cyclohexane mixtures. Minor amounts of by-products may lead to errors in such procedures. The other examples involved isolation procedures, and these usually merely put a lower limit to the fraction of the main isomer.

It is particularly noteworthy that hydrogenation at low temperatures with platinum catalysts of naphthols, tetralols, indanols, naphthoic acids, and indanoic acids yields mixtures in which the all-*cis* isomer predominates rather heavily; that is, the isomer in which the ring junction and the appended —OH or —COOH group are all-*cis*. This isomer is probably the least stable of the four possible isomers. Somewhat similar considerations apply to hydrogenations of phenanthrenes and diphenic acids; the *cis*-*syn*-*cis* configuration accounts, typically, for 75 per cent of the product, but other isomers are also generally present (138).

Interpretation of the results is somewhat confused by the possibility that cyclohexanones or decalones may be true intermediates, that is, that the reactant may be desorbed from the catalyst as a ketone and then be readsorbed (122, 151). This would be without much consequence for *o*- or *p*-cresol since, as will be shown later, the 2- and 4-methylcyclohexanones are preferentially hydrogenated to *cis*-cyclohexanols. However, 3-methylcyclohexanone preferentially leads to *trans*-3-methylcyclohexanol. Thus, if ketones were intermediates, *m*-cresol should give the *trans*-cyclohexanol preferentially. Unfortunately, no test of this seems to exist in the literature for low-temperature hydrogenation with platinum catalysts. Results with nickel at higher temperatures are confused by the possibility that nickel will isomerize the cyclohexanol after its

TABLE 3

Stereochemistry of hydrogenation of phenols, naphthols, aromatic carboxylic acids, etc.

Reactant	Catalyst	Solvent	Temperature ^(a)	Pressure	Products ^(b)	References
<i>Phenols:</i>						
<i>o</i> -Cresol	Raney nickel		180	High	68% trans	(118)
	Nickel		160	7 atm.	73% trans	(203)
<i>p</i> -Cresol	Raney nickel		180	High	82% trans	(118)
	Nickel		160	7 atm.	63% trans	(203)
<i>m</i> -Cresol	Raney nickel		180	High	85% cis	(144)
	Nickel		180	7 atm.	55% cis ^(c)	(203)
2- <i>tert</i> -Butylphenol	Nickel-kieselguhr		200	High	84% cis	(97)
2-Phenylphenol	Raney nickel		150	High	>80% cis ^(d)	(169)
	Colloidal platinum ^(e) Platinic oxide Platinum black	Water Acetic acid Acetic acid			Mixture; mainly all-cis	(112)
<i>Naphthols:</i>						
β -Naphthol; also both tetrahydro- β -naphthols	Colloidal platinum ^(e)	Acetic acid	50	Low	Mixture; mainly all-cis ^(f)	(114)
β -Naphthol	Platinic oxide	Acetic acid + ethyl ether		High	As above ^(g)	(72)
<i>ar</i> -Tetrahydro- α -naphthol	Colloidal platinum ^(e) Platinic oxide Platinum black	Water Ethanol Acetic acid	40 40 40	Low Low Low	ca. 85% all-cis ^(h) <85% all-cis ⁽ⁱ⁾ >85% all-cis ^(j)	(110) (110) (110)
α -Naphthol	Nickel Platinic oxide	Acetic acid	190	High Low	Mainly all-cis ^(k) Mixture; all-cis >63%	(110) (75)
<i>Acids, etc.:</i>						
α -Naphthoic acid	Platinic oxide	Acetic acid		Low	>85% all-cis	(75)
β -Naphthoic acid	Platinic oxide	Acetic acid		Low	Mixture; all-cis >65%	(71)
	Platinic oxide	Acetic acid		Low	Mixture; all-cis probably pre- dominant	(73)
<i>m</i> -Hydroxybenzoic acid	Raney nickel Platinic oxide	NaOH aq. Ethanol	150	High Low	Mainly trans Mainly cis	(153) (153)
Sodium <i>m</i> -toluate	Raney nickel Raney nickel	NaOH aq. Water	165 190	High High	61% cis 45% cis	(68, 105) (68, 105)
<i>p</i> -Hydroxybenzoic acid	Platinic oxide Platinic oxide	Acetic acid Ethanol + KOH		Low Low	78% cis cis > trans	(136)
Terephthalic acid	Platinic oxide	Acetic acid		Low	Mixture	(134)
α -Tetralone oxime	Platinum black	Acetic acid		Low	65% all-cis	(110)
	Colloidal platinum ^(e)	Acetic acid + HCl	40	Low	Mixture; mainly all-cis	(110)

(a) No entry if temperature is the ambient.

(b) Stereochemistry of the completely hydrogenated product with no hydrogenolysis of substituent groups. Where the percentage is given, the residuum is the other isomer or isomers.

(c) Apparently on the trans side of equilibrium, since further treatment with the catalyst under hydrogenation conditions increased the cis content to 83 per cent.

(d) No analysis, but 80 per cent cis isomer isolated.

(e) Colloidal platinum of Skita type.

(f) Also some decalin, and with β -naphthol some *ar*-tetrahydro- β -naphthol.(g) Probably the other cis isomer is the main by-product. Also decalin and *ar*-tetralols are formed.

(h) Also some decalin (80 per cent cis isomer) and a little decalone. Increase in temperature increases side reactions.

(i) No decalin.

(j) Little decalin.

(k) Only with very active nickel catalyst; otherwise trans isomers and decalins are the main products.

formation (45, 203). However, the report (table 3) that *m*-cresol with nickel at 160°C. gives a mixture on the trans side of equilibrium is suggestive of a ketone intermediate. The products of the hydrogenation (table 3) of *m*-hydroxybenzoic acid and of *m*-toluic acid on nickel also seem rather far on the trans side.

The degree of subsequent isomerization of cyclohexanols by nickel must vary with the reaction conditions. Thus, the highly hindered *cis*-2-*tert*-butylcyclohexanol is the main product in the hydrogenation of 2-*tert*-butylphenol with nickel at 200°C. (table 3). There is no evidence that all of the *trans*-2- and -4-substituted cyclohexanols are products of isomerization subsequent to complete hydrogenation.

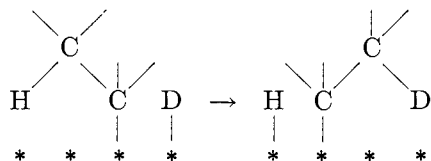
VI. STEREOCHEMISTRY OF ISOTOPIC EXCHANGE

Isotopic exchange between hydrocarbons and deuterium occurs on the surface of a number of transition metals. More than one hydrogen atom is usually exchanged during a single period of adsorption of a hydrocarbon molecule. With acyclic hydrocarbons not possessing a quaternary carbon atom—for example, heptane, hexane, 3-methylhexane, and 2,3-dimethylbutane—the initial product of the exchange reaction contains all exchanged species from the monodeutero to the perdeutero (46, 174), as shown for the last two hydrocarbons in figure 1. Palladium catalysts give similar patterns, but extensive multiple exchange is somewhat more prevalent (48).

The exchange reaction has been investigated on conventional nickel and palladium catalysts (46, 48, 49, 174) and on evaporated films of these and other metals (9, 10, 125, 174). There is little difference between the results obtained on conventional nickel and palladium catalysts and those obtained on evaporated films of the same metals (49, 174).

The reaction seems to involve the following steps: (1) Initial dissociative adsorption of the hydrocarbon, most likely with cleavage of one C—H bond or possibly with the concerted cleavage of two. (2) The propagation step: migration of the position of attachment of the hydrocarbon molecule with accompanying isotopic exchange. (3) Desorption.

Step 2 may be represented thus (assuming monoadsorbed alkane to be formed initially):



Iteration of step 2 permits the exchange of all hydrogen atoms on such a molecule as 3-methylhexane. However, the propagation reaction is blocked by a quaternary carbon atom. Thus, $C_7H_{11}D_5$ is the most multiply exchanged species in the initial products of the exchange of 3,3-dimethylpentane (figure 1) (46, 48, 174). This corresponds to the exchange of one ethyl side chain.

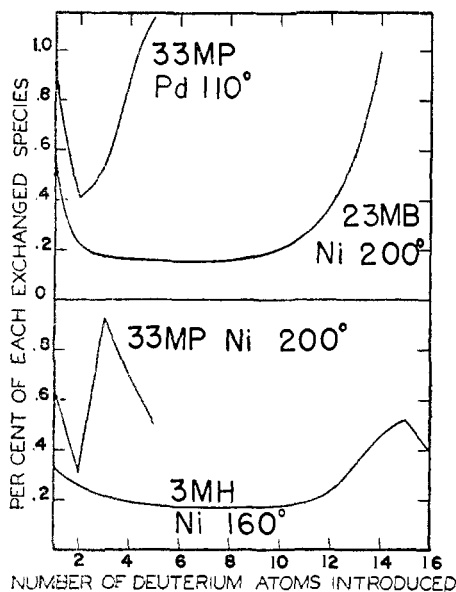


FIG. 1

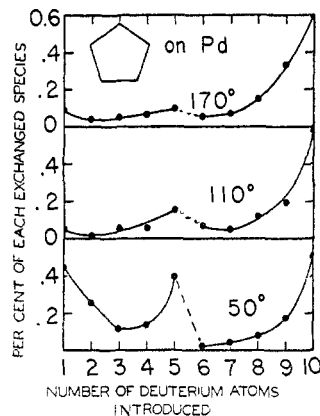


FIG. 2

FIG. 1. Initial isotopic exchange patterns of hydrocarbons on nickel and palladium
 FIG. 2. Initial isotopic exchange patterns of cyclopentane on palladium on γ -alumina

Two types of information bear on the stereochemistry of step 2: that obtained by examination of the exchange of (+)-3-methylhexane and that of cyclic hydrocarbons. The former has been studied on a variety of nickel catalysts including evaporated nickel films (46, 49, 174) and palladium catalysts and film (48). It appears that at temperatures greater than about 90°C., racemization ensues whenever the hydrogen atom at the tertiary position is exchanged. This heterogeneous catalytic racemization is related to the epimerizations of dialkylcyclohexanes reported earlier (210). *cis*-1,2-Dimethylcyclohexane and *cis*-1,4-dimethylcyclohexane are converted into the *trans* forms upon passage over nickel in a stream of hydrogen at 175°C. *cis*-1,3,5-Trimethylcyclohexane and *trans*-1,3,5-trimethylcyclohexane (54) and *cis*-pinane and *trans*-pinane (55) are similarly interisomerized on nickel at 175°C., as are the *cis* and *trans* isomers of 1,2,3-trimethylcyclopentane on platinumized charcoal at 310°C. (124). At least at lower temperatures (below about 200°C.) no other isomerization than racemization and epimerization occurs.

Anderson and Kemball (10) discovered that only half of the hydrogen atoms on cyclopentane and cyclohexane exchange readily during one period of adsorption upon certain evaporated metal films at about 0°C. However, at 150–200°C. all of the hydrogen atoms exchange readily on nickel (174) and palladium (48) catalysts. The effect of temperature upon the exchange reaction between cyclopentane and deuterium on palladium is shown in figure 2 (48). At 50°C. a marked discontinuity separates the concentrations of $C_5H_5D_5$ and $C_5H_4D_6$. With increasing temperature, the relative concentration of perdeuterocyclopentane

increases and the discontinuity diminishes. Above about 150°C. the discontinuity nearly disappears into the experimental error. The curve for the palladium catalyst at 50°C. is very similar to that for evaporated palladium film at 25°C. (10).

The propagation reaction, step 2, primarily proceeds to an adjacent position on the same side of the cyclopentane ring. However, an additional reaction permits the propagation reaction to proceed to the opposite side of the ring. This reaction is the same as or closely related to that which leads to racemization with (+)-3-methylhexane.

With cyclohexane the discontinuity separates $C_6H_6D_6$ and $C_6H_5D_7$. The discontinuity is somewhat smaller and disappears at lower temperatures (48). Nickel catalysts give similar results (49).

On palladium (48) cycloheptane shows slight discontinuities between $C_7H_7D_7$ and $C_7H_6D_8$ at temperatures of 60–80°C., while cyclooctane shows no discontinuity. Bicyclo[2.2.1]heptane exchanges but two hydrogen atoms per adsorption step at temperatures from 75° to 175°C. Presumably the two hydrogen atoms are those on ethylene bridges.

Simultaneous isotopic exchange and racemization have also been observed in the interaction of lactic acid and deuterium oxide on platinum-*asbestos* at 130°C. (25). Exchange seems to lead largely to perdeuterolactic acid and at a rate which is but one-half that of racemization. The authors assume that exchange of the hydrogen atom at the α -position involves inversion. The methyl ether of lactic acid does not react. The mechanism advanced by the authors suffers from two possible difficulties: the nature of binding to the platinum surface is not specified and application of the principle of microscopic reversibility occasions trouble since the assumed adsorption seems to involve one process and desorption a different one.

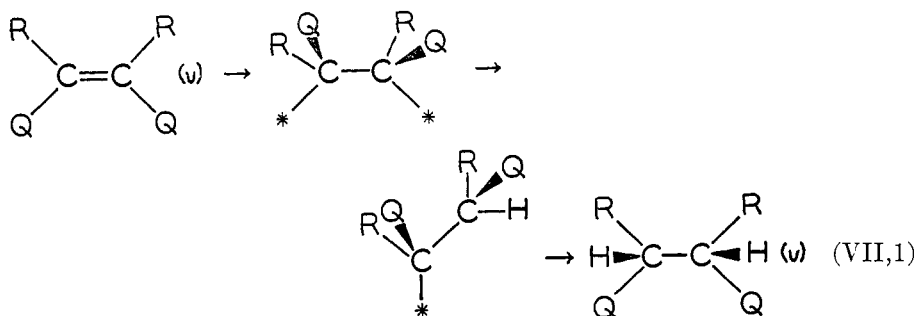
VII. MECHANISM OF THE INTERACTION OF HYDROGEN AND HYDROCARBONS

At present, any consideration of the mechanism of heterogeneous catalysis can lead only to rather tentative conclusions. However, such mechanistic considerations are important to the development of the science, provided, of course, that one does not convert tentative mechanisms into dogma. In spite of the relatively small amount of attention which it has received, stereochemistry makes definite contributions to such considerations of mechanism.

At lower temperatures the addition of hydrogen to a double or triple bond primarily involves *cis* addition. It is the occurrence of some *trans* addition which is of most mechanistic interest, since nearly all proposed mechanisms of hydrogenation lead to pure *cis* addition. Thus, simultaneous addition of a hydrogen molecule from the vapor phase or from an adsorbed state to adsorbed olefin would give *cis* addition, as would simultaneous addition of two hydrogen atoms (85). Successive addition of two hydrogen atoms from the adsorbed state to adsorbed olefin would give *cis* addition (100). Hydrogenation consequent to collision of an olefin molecule from the vapor phase with two adsorbed hydrogen atoms (24, 119) would lead to *cis* addition.

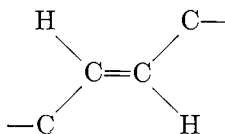
Most recent workers have recognized the probable complexity of reactions between hydrocarbons and hydrogen (or deuterium) on metallic surfaces even when they have disagreed upon details. In addition to a basic process leading to pure *cis* addition in hydrogenation there are probably one or more others which lead to net *trans* addition, to double-bond migration, to multiple isotopic exchange during hydrogenation with deuterium, to *cis-trans* isomerization, and to racemization during isotopic exchange of alkanes. Partial reversal of most of the possible mechanisms of olefin hydrogenation would result in isotopic exchange between the alkane and deuterium. Common steps in the two reactions seem inevitable.

For the basic process the most widely supported mechanism will be used; viz, the associative mechanism (*v* = vapor):



Pure *cis* addition results if the hydrogen atoms add to the plane of the olefin molecule from that side facing the catalyst (as shown) or from that side facing away from the catalyst. Most workers seem implicitly to accept the first possibility. It has been supported explicitly on considerations of steric hindrance (138), but this evidence refers primarily to derivatives of phenanthrene which might not be applicable to a simple double bond. The second possibility has been occasionally proposed (22).

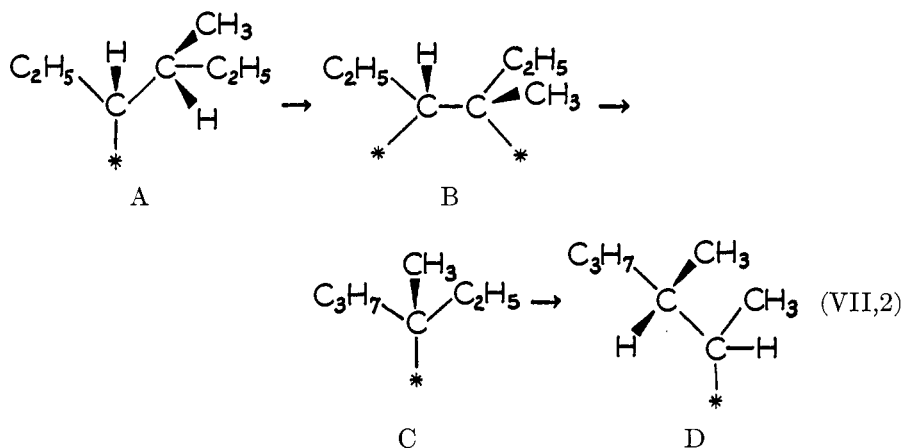
trans-Cyclononene exists in but one relatively unstrained conformation. The carbon atoms of the double bond and the atoms attached to them must lie in a plane:



The two exterior carbon atoms are joined by the chain $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, which passes either behind or in front of the plane, completely blocking one side of the double bond. In *cis*-cyclononene both sides of the double bond are accessible. The ready hydrogenation of both *cis*- and *trans*-cyclononene (30) indicates that hydrogen addition occurs on that side of the plane of the olefin which faces

the catalyst, and it also suggests that a mechanism which involves collision of a nonadsorbed hydrogen molecule with adsorbed olefin is unlikely.

Reversal of the second step in equation VII,1 would permit double-bond migration during hydrogenation, extensive isotopic exchange during hydrogenation with deuterium, and isotopic exchange between alkanes and deuterium. For example,



In naming these adsorbed species the carbon-surface bonds will be treated as substituents in the parent hydrocarbons. Thus, the half-hydrogenated state will be named a monoadsorbed alkane. Specifically, species A above is 3-mono-adsorbed 4-methylhexane. Adsorbed olefin (or two-point adsorption (9)) will be called generically *a, b*- or *vic*-diadsorbed alkane. Specifically, 2,3-diadsorbed 3-methylhexane must intervene between C and D.

Each monoadsorbed alkane may either revert to diadsorbed alkane or undergo desorption. Thus, if A was an initial half-hydrogenated state of 3-methyl-4-hexene, desorption of B would give 3-methyl-3-hexene, that is, double-bond migration during hydrogenation. In the presence of deuterium, each rupture of a C—* bond would introduce a deuterium atom with consequent appearance of more than two deuterium atoms in the final alkane (49, 194, 198). If the species A is the product of dissociative adsorption of 3-methylhexane, iteration of the above steps permits any degree of exchange of the alkane, although one must explicitly assume that ready rotation about carbon-carbon bonds is possible. Equation VII,2 constitutes a detailed mechanism of step 2 of Section VI. Similar extensions of the associative mechanism have often been made in the past.

However, the stereochemistry of *vic*-diadsorbed alkane has rarely been treated. As applied to the simplest case, CH_2-CH_2 , do both C—* bonds lie in the same

plane (eclipsed conformation) or does one C—* bond lie between the C—* and a C—H bond on the other carbon atom (staggered conformation)? In free mole-

cules such as ethane the eclipsed conformation is of higher energy (for a review of this matter see references 20 and 74). Diagrams of diadsorbed alkane have often shown an eclipsed conformation, but the consequences of such stereochemistry have not been discussed. *A priori*, it is hard to decide between the two possibilities, although energetics might be taken to favor the staggered possibility.

Owing to the racemization which accompanies the isotopic exchange of (+)-3-methylhexane, at one point it was suggested (174) that diadsorbed alkane (125) was not a suitable intermediate for isotopic exchange. However, the discovery of the hindrance to the exchange of more than five hydrogen atoms in cyclopentane at low temperatures (10) suggests that exchange proceeds via eclipsed *vic*-diadsorbed alkane as in sequence VII,2 and that some additional process leads to racemization and complete exchange. Eclipsed 1,2-diadsorbed cyclopentane would permit the exchange of only one of the two sets of five *cis* hydrogen atoms. Also, the nearly planar geometry of the cyclopentane molecule makes any other type of diadsorbed cyclopentane difficult.

The principle of economy of hypotheses suggests that one assume that *vic*-diadsorbed alkane occurs only in the eclipsed conformation, particularly since there is no large variation in rates of exchange or in the character of multiple exchange in a large variety of hydrocarbons (48, 174). The assumed conformation is shown for ethylene in figure 3. The diagram is left ambiguous as to whether binding is to one specific surface atom or to several as in a surface alloy or interstitial carbide.

No rigorous proof of the absence of staggered *vic*-diadsorbed alkane is available, but that assumption gives some order to a variety of experimental observations. In particular, results with bicycloheptane afford strong support. In this molecule there are four pairs of rigidly eclipsed hydrogen atoms on the ethylene bridges. Any one of these pairs could exchange via eclipsed 2,3-diadsorbed bicycloheptane, but the exchange could not be propagated via the bridgehead hydrogen atoms because these are rigidly held in nearly staggered positions to the hydrogen atoms on the three adjacent methylene groups. Figure 4 shows this stereochemistry.

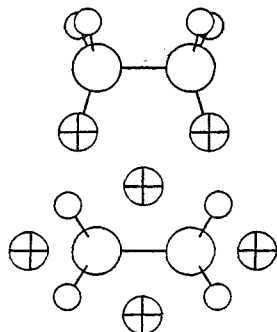


FIG. 3

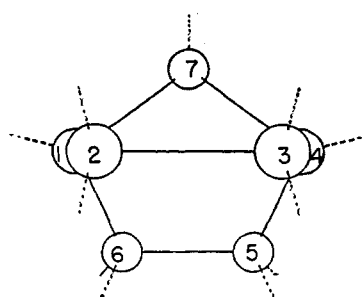


FIG. 4

FIG. 3. Eclipsed two-point adsorption

FIG. 4. Bicycloheptane

One must now assume that 1,2-diadsorbed cyclohexane involves the flexible (or boat) conformation. Here, exchange would be restricted to one of the sets of six cis hydrogen atoms.

However, in a very large ring, since either cis or trans hydrogen atoms can be brought into eclipsed conformations, no discontinuity in concentration should follow the species with half of the hydrogen atoms exchanged. In cyclooctane trans hydrogen atoms are as readily eclipsed as cis. Molecular models indicate that this is so or nearly so for cycloheptane. In cyclohexane it is, of course, impossible for trans pairs of hydrogen atoms to be eclipsed. The lack of discontinuity following half-exchange of cyclooctane, the very slight one for cycloheptane, and the substantial one for cyclohexane (48) (Section VI) accord with the model.

For easier visualization the above discussion has been put in the form of conformations of carbon-hydrogen bonds in the free cycloalkane. Actually, it is the analogous carbon-surface bonds which would be involved. A survey of a problem involving rather similar stereochemistry, that of 1,2 ring fusions, is presented in reference 108.

An eclipsed conformation must be assumed in any transition state leading to diadsorbed alkane. This is *a priori* plausible in the transition state between nonadsorbed olefin and diadsorbed alkane if one is to obtain any contribution from the olefin form to the resonance hybrid in the transition state. However, since cyclooctane very readily exchanges all hydrogen atoms and since *trans*-cyclooctene is highly strained (211), unlike cyclooctane with a pair of trans eclipsed hydrogen atoms, *trans*-1,2-diadsorbed cyclooctane and the transition state joining this with monoadsorbed cyclooctane must resemble cyclooctane in geometry.

The isotopic exchange of (+)-3-methylhexane by sequence VII,2 would be unaccompanied by racemization whereas, in fact, racemization seems virtually complete (Section VI). Casual examination might suggest that mere adsorption of (+)-3-methylhexane to form 3-monoadsorbed 3-methylhexane would lead to racemization (85) or that mere migration of the half-hydrogenated state on the

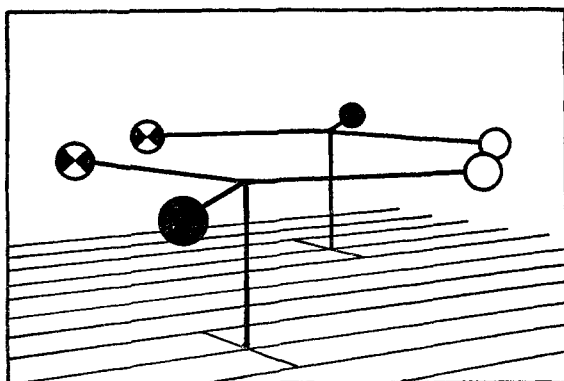
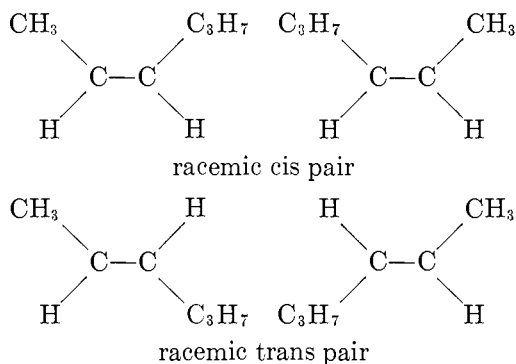


FIG. 5. Stereochemistry of adsorbed trisubstituted methyl. The essential stereochemistry is independent of whether the binding to the surface is covalent or ionic.

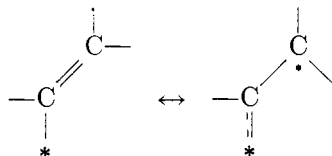
catalyst surface would lead to some trans addition during olefin hydrogenation (100). This is not so (46).

As shown schematically in figure 5, racemic 3-methylhexane so adsorbed exists in two enantiomeric forms. Similarly, the conventional adsorption of 2-hexene could lead to four 2,3-diadsorbed forms, a cis and a trans *dl* set. Viewed from above the catalyst surface and with the carbon-catalyst bond extending into the paper, and not shown, the four forms are:



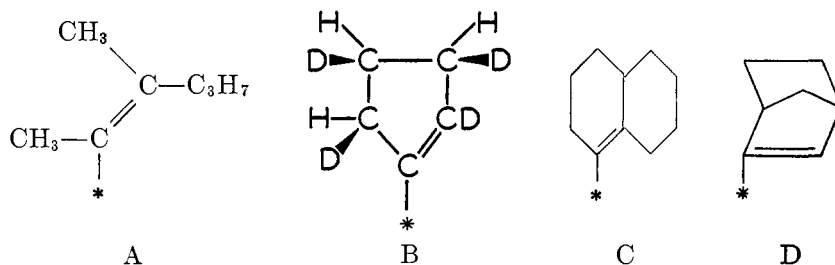
The activation energy for interconversion of the two forms in figure 5 by a process which involved raising the adsorbed radical from the surface and turning it over would appear to be large. One needs, rather, some process which involves a symmetric intermediate capable of reaction to form either stereoisomer or one needs an odd number of reactions involving inversion of configuration. The requirement of microscopic reversibility inhibits the ready design of mechanisms which apply the second concept (46). For example, in adsorption and then desorption of (+)-3-methylhexane, if the carbon-hydrogen bond is broken with retention of configuration, it will be re-formed with retention; if broken with inversion, it will be re-formed with inversion. In both cases, overall retention ensues. The same considerations apply to "racemizing" the half-hydrogenated state to obtain trans addition in the hydrogenation of olefins.

Racemization of (+)-3-methylhexane and complete exchange of cyclopentanes and cyclohexanes requires an additional species the formation of which involves a somewhat higher activation energy than that of *vic*-diadsorbed alkane so that racemization and complete exchange will prevail at higher temperatures. This species must be a carbon atom coordinated to three alkyl groups or hydrogen atoms in one plane (46, 49, 174, 181). On the basis of present data the most satisfactory one appears to be an *a*-monoadsorbed olefin:



Other similar species may be possible (46, 174, 181). Alternatively, though

less probable energetically, one might have the equivalent of a free radical adsorbed perpendicular to the surface (174) or, with greater energetic likelihood, adsorbed at a 45° angle at a step and partially bonded to both surfaces. It seems fruitless to speculate further upon this point, since all have the same stereochemical consequences as the α -monoadsorbed olefin, which is equivalent to dissociatively adsorbed olefin and the half-hydrogenated state in the hydrogenation of acetylenes. It permits racemization during isotopic exchange, complete exchange of cyclopentane, and net trans addition during the hydrogenation of olefins when preceded by migration of the location of diadsorption. This stereochemistry is a consequence of the fact that addition of hydrogen atoms to this species could occur from either side of the double bond. Examples of this species are indicated below as applying (A) to the racemization of 3-methylhexane, (B) to the complete exchange of cyclopentane, and (C) to the formation of *trans*-decalin from 9, 10-octalin.



If one were to attempt to exchange all four hydrogen atoms in an ethylene bridge in bicycloheptane, one would require species D, 2-mono-adsorbed norbornene. The introduction of the double bond into bicycloheptane greatly increases the existing strain. Such a species would form very much less readily than, for example, B. This accords with the observed initial exchange of but two hydrogen atoms in bicycloheptane.

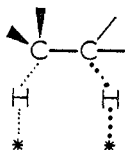
In summary, then, it appears probable that there is a process in which hydrogen atoms add to the side of a double bond facing the catalyst in pure *cis* addition. A related propagation reaction in the isotopic exchange of alkanes proceeds through an intermediate which also occurs in olefin hydrogenation. On the basis of present data, it appears plausible that this intermediate involves an eclipsed conformation. An additional species, dissociatively adsorbed olefin or its equivalent, becomes increasingly common at higher temperatures and leads to racemization and *trans* addition during the hydrogenation of olefins and aromatic hydrocarbons. The specific intermediates which have been proposed above appear plausible and useful but they are not rigorously established.

The *cis-trans* isomerization of olefins and accompanying double-bond migration fit readily into the mechanistic framework in ways which have been proposed before. Return of the half-hydrogenated state to desorbed olefin (i. e., reversal of the first two steps in sequence VII,1) accomplishes either reaction (87). The observation of Taylor and Dibeler (187) that isotopic exchange is slower than the *cis-trans* isomerization of *cis*-2-butene must result from an isotope effect

analogous to that which causes the first observed product of the reaction between ethylene and deuterium to be light ethane (194). Similar isotope effects are involved in the reactions of *trans*-C₂H₂D₂ (87).

The half-hydrogenated state is probably the intermediate involved in net *trans* addition in the formation of olefins from acetylenes, but whether it is formed subsequent to olefin desorption or previous to olefin desorption is not established by presently available data.

An alternative stereochemical mechanism for the hydrogenation of olefins has been proposed by Hadler (101) to explain the stereochemistry of hydrogenating certain steroids. He proposes a transition state,



in which the carbon-hydrogen bonds are assumed to be staggered. This is equivalent to a stereochemical specification of Beeck's (24) mechanism. The olefin is never itself adsorbed.

This proposal is not generally attractive. It could not be applied to hydrogenations of cyclopentene or bicycloheptene. It cannot lead to species with more than two deuterium atoms in hydrogenation with deuterium, to net *trans* addition, to alkane exchange, etc.

In this section an attempt has been made to integrate stereochemistry into mechanistic thinking in heterogeneous catalysis but no attempt has been made to review the development of mechanism in general (references 32 and 81 cover this).

VIII. STERIC HINDRANCE IN THE DETERMINATION OF CONFIGURATION

Consequent to an extensive investigation of derivatives of phenanthrene and of the related diphenic acids, Linstead, Doering, Davis, Levine, and Whetstone developed the importance of steric interaction between substrate and catalyst in determining configuration (138). They assumed that the substrate would be preferentially adsorbed on that side of an aromatic ring from which the least hindrance between catalyst and substrate developed. This concept has been successful in predicting the major product of a number of hydrogenations. Thus, phenanthrene derivatives are hydrogenated predominantly to *cis-syn-cis* perhydro derivatives, although their enthalpies are about 6.4 kcal. greater (121) than those with *trans-anti-trans* configurations.

In some cases, of course, differences in steric hindrance involved in the two modes of adsorption might be small. In such cases nearly equimolecular mixtures should result (140a). It was supposed that minor products might also arise through mechanisms leading to net *trans* addition.

Whether the hydrogenation of cyclohexanone proceeds by *cis* or by *trans* addition of hydrogen is without steric consequences although, at least at low

temperatures, most would assume that it added *cis*. Siegel considers that the hydrogenation of methylcyclohexanones involves such *cis* addition. The configuration of the major product is that which results from the least steric interaction between the catalyst and the reactant molecule in its preferred conformation (180, 181).

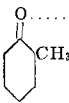
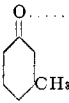
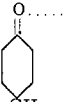
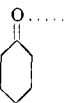
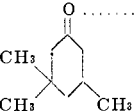



Since both substituents can acquire the equatorial position, *trans*-1,2- and *trans*-1,4- but *cis*-1,3-dimethylcyclohexanes are the more stable species (23). Similar considerations seem to apply to methylcyclohexanols (153). In hydrogenation by platinum under acidic conditions at low temperatures, methylcyclohexanones are assumed to be preferably adsorbed in the conformation in which the methyl group is equatorial and the molecule is oriented with respect to the surface in the less hindered way. Thus, the less stable methylcyclohexanol predominates in the product: *cis*-1,2, *cis*-1,4, but *trans*-1,3 (180). Similar views have also been expressed by Cornubert, Barraud, Cormier, Descharnies, and Eggert (63), who have also extensively reviewed previous work in this field, and by Peppiatt and Wicker (165).

Raney nickel leads to a little more of the more stable form (63). Higher temperatures favor the more stable form. Slow hydrogenation leads to more of the more stable form, and platinum under basic conditions (an inactive catalyst) results in the more stable form. Whether this is consequent to epimerization after reaction (165) or to processes similar to those discussed in the last section is not clear.

Similar considerations should apply to analogs of ketones in which =O is replaced by =CH₂ and =NOH. Similar applications of steric hindrance can also be made to derivatives of cyclohexene (181). A number of examples of these types are given in table 4. It seems probable that the concept of steric hindrance is right in principle, although the table presents some anomalies. However, before much further theoretical advance is likely, one will need a substantial body of results with modern means of analysis over a reasonable range of operating variables. The role of isomerization subsequent to hydrogenation must be determined in all cases.

An alternative interpretation of ketone hydrogenation given by Brewster (42) involves *trans* addition. The catalyst surface donates a hydride ion and the solvent donates a proton. The substrate is never really bonded to the surface by chemical forces. Brewster pictures formation of the less stable alcohol in acidic solution by the transfer of hydride ion to the carbon atom of the C=OH⁺, and formation of the more stable alcohol in basic solution by the addition of first a hydride ion to the oxygen atom of the ketone and then a proton to the resulting carbanion. It is implicitly assumed that the mechanisms of vapor-phase and liquid-phase hydrogenations are different. The proposed mechanism makes definite predictions about the consequences of hydrogenating with deuterium. One should obtain >CDOD with no further introduction of deuterium into the molecule. Sufficiently extensive exchange experiments resembling those of Friedman and Turkevich would be of value (91).

TABLE 4
Stereochemistry of the hydrogenation of cyclic and semicyclic double bonds

Reactant	Catalyst	Solvent	Temperature ^(a)	Pressure	Products ^(b)	Reference
	Platinic oxide	Acetic acid	130	Low	30% trans	(203)
	Nickel	Methanol		7 atm.	30% trans	(203)
	Raney nickel			High	43% trans	(118)
	Platinic oxide	Acetic acid	140	Low	27% trans	(203)
	Platinic oxide	Acetic acid		Low	69% trans	(144)
	Nickel	Methanol		7 atm.	77% trans	(164)
	Raney nickel	Ethanol		High	77% trans	(144)
	Nickel			7 atm.	44% trans	(164)
	Platinic oxide	Acetic acid	130	Low	53% trans	(203)
	Platinic oxide	Methanol		Low	74% trans	(203)
	Raney nickel			High	41% trans	(118)
 C ₆ H ₁₀ (t)	Platinic oxide	Ethanol	120	High	90% trans	(62)
	Raney nickel	Ethanol		High	Heavily cis	(62)
	Copper chromite	Ethanol		High	40% trans ^(c)	(62)
	Platinic oxide	Acetic acid		Low	83% trans	(203)
	Platinic oxide	Methanol		Low	91% trans	(203)
	Nickel	Methanol		7 atm.	88% trans	(203)
 COOC ₂ H ₅	Platinic oxide	Ethanol		5 atm.	11% trans	(162)
 CH ₃	Platinic oxide			Low	50% trans	(113)
 =NOH CH ₃	Platinic oxide	Acetic acid		Low	cis ^(d)	(11)
	Platinic oxide	Cyclohexane		Low	15% trans	(11)
2-Methylmethylenecyclohexane	Platinic oxide	Acetic acid		2 atm.	35% trans	(181)
3-Methylmethylenecyclohexane	Platinic oxide	Acetic acid		2 atm.	32% trans	(181)
4-Methylmethylenecyclohexane	Platinic oxide	Acetic acid		2 atm.	47% trans	(181)
2,3-Dimethylcyclohexene	Platinic oxide	Acetic acid		2 atm.	30% trans	(181)
2,4-Dimethylcyclohexene	Platinic oxide	Acetic acid		2 atm.	32% trans	(181)
1,3-Dimethylcyclohexene	Platinic oxide	Acetic acid		2 atm.	21% trans	(181)
1,4-Dimethylcyclohexene	Platinic oxide	Acetic acid		2 atm.	48% trans	(181)

^(a) Room temperature if no entry.

^(b) Remainder cis. Analysis of the methylcyclohexanones was by refractive index or density. This procedure may be precise but it is subject to gross interference from by-products. Analysis of most of the other types was by separation procedure, which is not very precise but is not subject to similar gross interference. The best results are probably those of the last set (181), in which analysis was by both distillation and infrared absorption.

^(c) The actual compound hydrogenated had a double bond conjugated with the keto group.

^(d) Pure cis isomer reported for active catalyst; a little trans isomer for an inactive catalyst; 15 per cent trans isomer when run in cyclohexane, in which hydrogenation is slow.

IX. APPLICATIONS OF OPTICAL ACTIVITY TO HETEROGENEOUS CATALYSIS

A. Optically active catalysts

The surfaces of enzymes are, of course, asymmetric or "optically active." Thus, enzymes usually discriminate between optical isomers and produce optically active products where the possibility exists. Synthetic "optically active" catalysts consisting of metal deposited on "optically active" substrates have been prepared.

Catalysts consisting of metal films on one of the forms of optically active quartz were first made by Schwab, Rost, and Rudolph (177) by evaporating a slurry of quartz powder (particle size about 0.5 mm.) in solutions of cupric nitrate, nickel nitrate, or ammonium chloroplatinate. The dried material was reduced at 200°C. On nickel at 550°C. 2-butanol decomposed both by dehydration and dehydrogenation. With (+)-quartz, the (-)-alcohol decomposed slightly more rapidly and rotations of the residual alcohol reached about 0.1° (2 dm.), which is an optical purity of about 0.5 per cent, and then declined as a racemization reaction became more important with time. Similar results were obtained in oxidizing the alcohol with oxygen on platinized quartz.

In these experiments the quantity of metallic salt had been adjusted to correspond in quantity to a unimolecular layer. With more salt, the catalyst was less selective; hence the authors concluded that the optical specificity was confined to the boundary zone between covered and uncovered quartz.

Similar results have been reported more recently for copper films on quartz (128, 188). There is no optical selectivity if the quartz is completely covered. Selectivity appears upon removal of some of the metal by grinding.

Other metals and alumina (188, 190) have been investigated, either sputtered on quartz or deposited by the method of Schwab. In the dehydrogenation of 2-butanol, the rotations of residual alcohol reached 0.1 to 0.2° (2 dm.). The sign of rotation of the residual alcohol depended only upon the quartz support and not upon the metal (188).

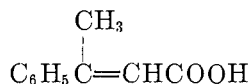
Similar slight rotations have been developed by these catalysts in the isomerization of propylene oxide to propylene glycol (188, 190), in the hydrogenation of substituted ethylenes at low pressures (188, 190) and at high pressures (167), and in cyanoethylation reactions on quartz coated with alkali metal alkoxides (189).

The optical activity of quartz depends upon a helical arrangement of the silica lattice. Optical stereoisomers are adsorbed to slightly different degrees upon a powder of one form of quartz. This has been shown by several groups, all with inorganic coordination compounds (123, 132, 178, 192). It has been possible to effect the complete resolution of *p*-phenylene-bis-iminocamphor by chromatography on a different optically active surface, that of lactose (103). It is probable that the stereoisomeric selectivity of metals on quartz results from different degrees of adsorption on the quartz surface followed by migration to the metal surface.

Very much more substantial asymmetric synthesis results from the use of a catalyst prepared by the reduction of palladium chloride adsorbed on silk

fibroin (2). The hydrogenation of diethyl α -acetoximinoglutarate led to glutamic acid of an optical purity of about 7 per cent. Phenylalanine was prepared from the analogous compound in 25 per cent optical purity. This catalyst would be of considerable value should it effect hydrogenations in general with this degree of specificity.

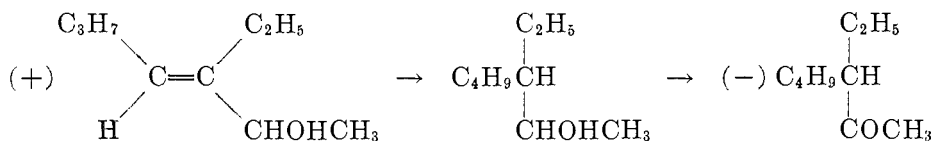
In hydrogenating the menthyl ester of β -methylcinnamic acid,



on platinum black, (+)- β -phenylbutyric acid has been obtained in optical purity as high as 20 per cent (197). This asymmetric synthesis does not involve any optical activity of the catalyst but depends upon interactions between the asymmetric menthyl group, the groups attached to the double bond, and the surface.

The reduction of the hydrocinchonine salt of the acid upon platinum also results in substantial asymmetric synthesis, 9 per cent of optical purity (141). One might consider platinum with the optically active hydrocinchonine adsorbed on it as constituting an optically active hydrogenation catalyst.

Another example of asymmetric synthesis has been reported which is equivalent to that of the menthyl ester. The reduction on Raney nickel at about 100°C. and 7 atm. of hydrogen of (+)-3-ethylhept-3-en-2-ol gives 3-ethylheptan-2-ol in which a new "asymmetric center" has been generated at the 3-position. If the alcohol is oxidized with chromic anhydride to the ketone, the original optical center is destroyed and the degree of asymmetric induction at the 3-position may be determined (13).



The optical purity of the final product is reported to reach 75 per cent. The authors (13) interpret this in terms of steric interaction with the surface of the catalyst (Section VIII).

The same principle is involved in the stereochemistry of the formation of high-molecular-weight polypropylenes on catalysts of the Ziegler type (reference 152 is a leading one to this work of Natta). Presumably the chain-initiating step produces an asymmetric species. On an optically inactive catalyst, one would get equal concentrations of the two enantiomeric species. The addition of a propylene molecule generates a new optical center. In general, one would not expect the two possible forms of the new center to be formed in exactly equal amounts. In practice, the specificity can be very high and isotactic polymers can be formed (152). (An isotactic polymer is one in which all of the optical centers have the same configuration.) If the isotactic polypropylene molecule is

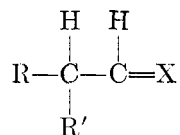
extended to the linear (zigzag) conformation, all of the methyl groups are on the same side.

In principle one should have two kinds of isotactic polypropylene molecules, a (+)-isotactic polymer and a (-)-isotactic polymer. In practice, these would differ only as to the ends occupied by the initiator and the terminator, and one may doubt whether detectable optical rotation would be exhibited by the pure (+) form (152). Somewhat similar stereochemical factors are involved in the polymerization of propylene oxide on powdered potassium hydroxide. The addition process proceeds stereospecifically. *dl*-Propylene oxide gives random configurations (an atactic polymer), whereas *l*-propylene oxide gives an isotactic polymer which is measurably optically active because, so to speak, the oxygen atoms in the chain give a clear direction to the chain (170).

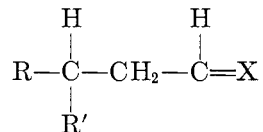
It is also possible to isolate an isotactic polypropylene from propylene polymerized by chromium oxide on a silica-alumina support (60). The factors discussed above also apply to the polymerization reaction on this rather more conventional heterogeneous catalyst.

B. Miscellaneous catalytic reactions

Many optically active compounds have been hydrogenated at room temperatures to yield optically active products, although in many instances the rotations of the optically pure reactant and product are not known accurately enough to assess the exact loss of optical purity, if any. Thus, in a species such as



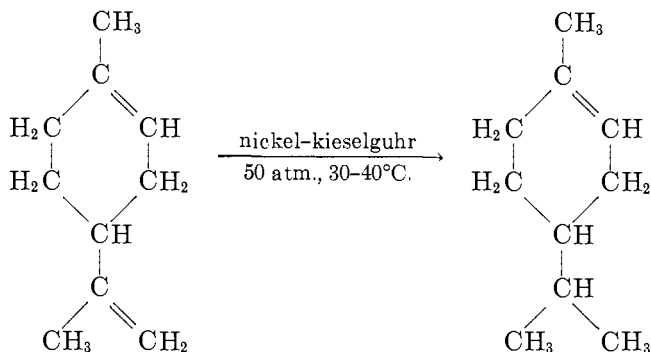
one is not apt to get much racemization at room temperatures and with an insulating methylene group one appears to get even less.



Here, C=X represents any kind of an unsaturated group. The stereochemical point at issue is not the stereochemistry of addition to the double bond but the stereochemical consequences of such addition to other parts of the molecule. Examples follow.

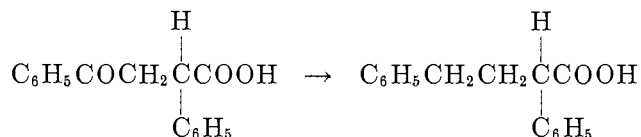
The hydrogenations of butylvinylcarbinol (126) with colloidal platinum in acetic acid and of methylvinylcarbinol (150) with platinum oxide yield 3-heptanol and 2-butanol with little or no loss in optical purity.

One of the double bonds of limonene may be hydrogenated to yield a menthene without material loss of optical purity (166).



Mere migration of the remaining double bond one step counterclockwise would result in racemization.

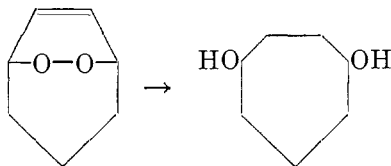
The following reaction on palladium-charcoal under acidic conditions involves little or no racemization (18).



The reduction of a variety of phenyl-substituted acids, alcohols, and hydrocarbons to the cyclohexyl equivalents with platinum oxide in acetic acid proceeds with little loss of optical purity (135).

Hydrogenation of 2-nitrooctane or 1-phenylnitroethane on platinum oxide in acetic acid yields the amine with a loss of optical purity of 15–20 per cent (130).

The following reaction on a platinum catalyst



gives an 83 per cent yield of the cis diol. The remainder is largely the trans diol (62a).

Sugars can be reduced to corresponding polyhydroxy compounds on Raney nickel at room temperature (159) or at about 100°C. (38, 207) with little if any epimerization.

Hydrogenation of (+)-3-methyl-4-hexene with Raney nickel at high pressures of hydrogen and at not over 60°C. (98) or at atmospheric pressures and at 45°C. on nickel-kieselguhr (46) results in not more than a few per cent loss in optical activity. Hydrogenation of 3-phenyl-1-butene results in slight losses of optical purity: palladium-calcium carbonate, 11 per cent; Raney nickel, 2 per cent; platinum oxide, 3.5 per cent (64). Neither 3-methylhexane nor 2-phenylbutane

would be racemized after formation under these conditions but, in view of the multiple exchange which accompanies hydrogenation with deuterium, if hydrogenation and exchange have similar intermediates, why does one not observe considerably more racemization (see Section VII)? The lack of racemization appears to result in part from the temperatures being lower than those in exchange experiments, with consequent declines in the relative rates of the propagation reaction and that leading to racemization during exchange, and in part from inhibition of the propagation reaction by high concentrations of olefin (49).

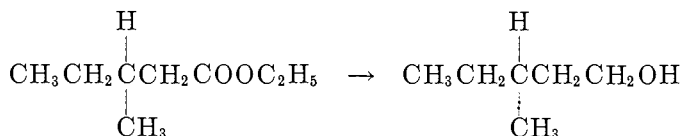
Similarly, in the case of the reactions described earlier in this subsection, if migration of the point of attachment to the catalyst occurs, it must mainly be of the type which involves retention of configuration as in the exchange of hydrocarbons—cyclopentane, for example—at low temperatures.

At higher temperatures one might expect more loss of optical purity by analogy with the results in hydrogenation and exchange. In general this is observed, although it would be hard to predict, *a priori*, the temperature at which such loss of optical purity would become substantial.

For example, the hydrogenation of optically active 2-amino-2-phenylacetic acid with large amounts of Raney nickel at 40°C. gives an aminoalcohol of high rotation (158). Similar results are reported for large amounts of copper chromite at 150°C. and 130 atm. (179), but complete racemization is reported under similar conditions at 175°C. (59).

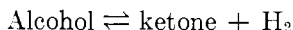
Hydrogenation of the diethyl ester of *d*-tartaric acid with copper chromite at 165°C. and 150 atm. gives a 65 per cent yield of *d*-erythritol. The remainder is largely *meso*-erythritol (191).

In the hydrogenation of esters of optically active acids on copper chromite at 250°C. (40) both the alcohol in the product and the recovered ester are extensively racemized in those cases in which the asymmetric carbon atom adjoins the carboxyl group. Less racemization occurs if the asymmetric carbon atom is insulated by a methylene group:



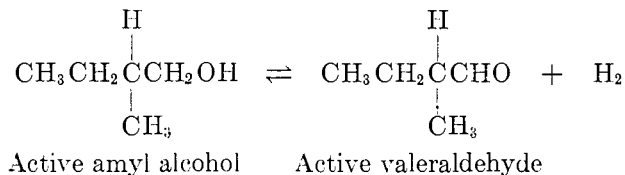
The grouping RCHOHR' is subject to heterogeneous catalytic racemization or epimerization. Optically active secondary butyl alcohol is racemized upon passage over copper (44, 45), zinc chromite (44, 45), and chromium oxide (44) at temperatures of 130–200°C. The interconversion of the *cis*- and *trans*-3,3,5-trimethylcyclohexanols has been studied recently under batch conditions (164, 165, 203). On very large quantities of reduced nickel oxide, in the presence of hydrogen the reaction proceeds to equilibrium (about 73 per cent *cis*) even at room temperatures in less than a day. With conventional quantities of catalyst, higher temperatures are required. Reduced platinum oxide also catalyzes the reaction but its activity is very much reduced by extraction with acid. It was

suggested that epimerization may proceed by the following reversible reaction,



Dehydrogenation accompanied the racemization of secondary butyl alcohol in the flow experiments described above, but it was possible to show that racemization was much faster than the reverse of the dehydrogenation reaction (45).

The interconversion of active valeraldehyde and active amyl alcohol



on Raney nickel at 128°C. results in little loss of optical purity. At temperatures of about 190°C. rather considerable loss in optical purity ensues (16). Racemization of the alcohol seems to occur faster than dehydrogenation. Adsorbed carbinol must exist, in part, in the form of a symmetric intermediate at higher temperatures, and proposals as to such a form have been made (16, 44, 45). However, there is not much data which permits one to decide among various possibilities. Studies of simultaneous racemization and isotopic exchange would be desirable.

Racemization during the reduction of acids on copper chromite is probably related to these racemizations of carbinols, as are the epimerizations at ring junctions adjoining oxime and carbonyl groups which occur in the presence of palladium-charcoal at 190-300°C. (14, 15).

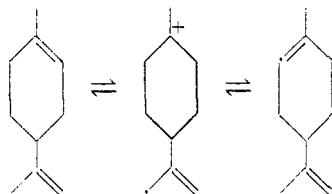
Racemization of 2-phenylbutane on activated charcoal has been reported (76). For example, if the hydrocarbon adsorbed on charcoal is heated at 200°C. for 1 hr., it is 15 per cent racemized; for 5 hr., 47 per cent. Similar results are obtained with optically active 3-methylhexane (120). Surprisingly, *cis*-decalin is not converted to *trans*-decalin under these conditions (120), but the formation of naphthalene may have interfered.

C. Reactions on acidic catalysts

With the possible exception of the last example in the previous subsection, this paper has dealt so far with the stereochemistry of reactions on hydrogenation catalysts. No data seem to deal with catalysis in oxidation reactions. The following reaction might involve ionic intermediates or perhaps S_N2 displacement. Optically active α -phenethyl bromide ($\text{C}_6\text{H}_5\text{CHBrCH}_3$) in solution in carbon tetrachloride saturated with hydrogen bromide is racemized on contact with silver bromide, charcoal, or powdered glass. The catalytic effectiveness decreases in the order listed (12).

Several examples of racemization reactions on acidic catalysts very probably involve carbonium-ion intermediates. Limonene is racemized upon heating with

acidic clays at temperatures of 100°C. and above (176). Migration of the double bond as shown

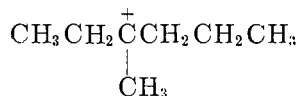


would lead to inversion of configuration. Such isomerization via a tertiary carbonium ion on an acidic catalyst would be expected.

Limonene is also racemized on an activated (acid-washed) clay and on an acidic titania (175). Camphene is likewise racemized under these conditions (125–160°C.), perhaps via tricyclene as an intermediate (175).

The interaction of (+)-3-methylhexane and water on silica-alumina catalysts has been studied in more detail (47). Above 200°C. a nearly equilibrium mixture of (\pm)-3-methylhexane, 2-methylhexane, 2,4-dimethylpentane, and (\pm)-2,3-dimethylpentane is desorbed from the surface. In the presence of heavy water, each reacting molecule appears to be multiply exchanged.

The reaction appears to involve initial formation of the carbonium ion.



which isomerizes to other carbonium ions which then undergo hydride-ion transfer to form isomerized hydrocarbon and new chain-carrying carbonium ions. At 200°C. racemic 3-methylhexane could result from equilibration with the ion of the 2-methylhexane structure, since that ion is incapable of optical activity. However, as the temperature is lowered, the formation of dimethylpentane drops off relatively and then that of 2-methylhexane and, at 56°C., one deals with a nearly pure racemization reaction. This behavior resembles that in the interaction of (+)-3-methylhexane and sulfuric acid (50).

The formation of alkyl carbonium ions in the vapor phase is very endothermal. To occur as intermediates in chemical reactions they must be strongly solvated or, in heterogeneous reactions, they must strongly interact with the surface. The methylethylpropylmethyl carbonium ion from 3-methylhexane is, therefore, capable of existence in two enantiomorphic forms, as shown in figure 5. Mere formation of this adsorbed carbonium ion from (+)-3-methylhexane does not necessarily lead to racemization. Some symmetric intermediate or transition state must exist, but its nature is uncertain at present.

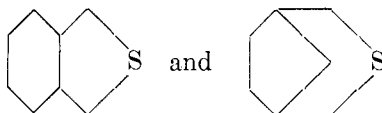
D. Heterogeneous catalytic hydrogenolysis

One would not expect hydrogenolysis at lower temperatures to effect much racemization if the group which is removed is not attached to an asymmetric carbon atom. An example of such a reaction was provided in the last section.

i.e., the conversion of a carbonyl adjacent to a benzene ring into a methylene group. Other examples exist. Cleavage by Raney nickel of the tosyl group in 2-*sec*-butyl-1-tosylbenzene affords 2-phenylbutane with negligible loss in optical purity (102). Similarly, the desulfurization of derivatives of mercaptoamino acids (derivatives of cystine, for example) leads to optically pure amino acids (89, 90).

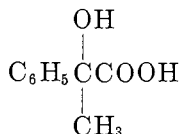
The hydrogenolysis of *N*-benzyl-1-amino-2-propanol with palladium on charcoal gave 1-amino-2-propanol of high rotation, but the data given do not permit conclusions about the degree of racemization if any (61). The hydrogenolysis of 2-bromo-*cis*-decalin with Raney nickel and hydrogen at room temperatures gave pure *cis*-decalin (70).

In the last example, lack of epimerization rather than lack of racemization diagnoses the stereochemistry. Two other examples involve the desulfurization of



with Raney nickel in refluxing ethanol. Both *cis*- and *trans*-2-thiahydrindan (the compound at the left) were hydrogenolyzed and each gave the *cis*-(or *trans*-)dimethylcyclohexane without detectable isomerization (28). The second compound gave *cis*-1,3-dimethylcyclopentane at least 95 per cent pure. However, the presence of about 5 per cent of the *trans*-dimethylcyclopentane seemed probable (27).

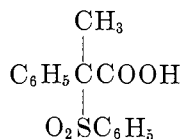
Compounds in which the group being hydrogenolyzed is attached to the asymmetric carbon atom are of greater mechanistic interest. Available examples are derived from atrolactic acid.



The chloro acid prepared by the action of thionyl chloride on atrolactic acid (presumably with retention of configuration) suffers hydrogenolysis upon treatment with hydrogen and palladium-charcoal (157). The resulting α -phenylpropionic acid has the same configuration as the atrolactic acid (43) but the optical purity is low,—12 per cent when hydrogenolysis is conducted in glacial acetic acid and 9 per cent when conducted in ether.

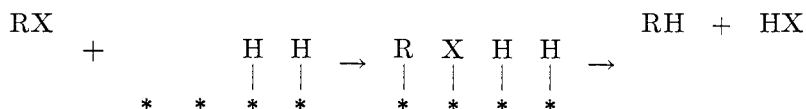
Hydrogenolysis effected by refluxing the reactant with Raney nickel in ethanol is, strictly speaking, not a catalytic reaction since the hydrogen adsorbed in the Raney nickel is consumed. However, one may assume that this reaction is closely related to customary catalytic hydrogenolysis. Bonner has recently investigated the hydrogenolysis of several optically active derivatives of atrolactic acid by this process. The methyl and ethyl esters give phenylpropionic acid with retention of configuration and 15 to 30 per cent loss of optical purity (35, 37).

The methyl ethers of the esters behave similarly (35). The ethyl ester and the amide of the sulfone derived from atrolactic acid,



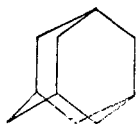
likewise give optically active products with similar loss of optical purity (33). Bonner believed that the reaction involved inversion of configuration, but the assignment of configurational relationships of reactant and product is not secure. Optically inactive products resulted from the reaction of the analogous thio ether (33) and sulfoxide (34).

Several authors have mentioned free radicals as possible intermediates in hydrogenolytic reactions (27, 33). Such intermediates, *per se*, could lead to racemization only if they are "free" free radicals (Section VII). The data now available hardly seem adequate for definitive mechanistic consideration. One would particularly like results on compounds less subject to possible neighboring-group interactions. However, it seems possible to accommodate most of the data into a rather conventional framework.



As written, the reaction would proceed with retention of configuration, but the half-hydrogenated state, R—*, is subject to racemization, as discussed in Section VII. Actually, such side reactions of R—* before final desorption are indicated by the results of isotopic exchange reactions between (+)-phenylpropionamide and deuterated Raney nickel (36). Both exchange and racemization (37) occur.

Bonner and Zderic propose a somewhat similar mechanism but consider that R actually is present as a carbonium ion, R⁺. Much evidence opposes the presence of a carbonium ion on metallic surfaces at lower temperatures: for example, the total absence of any skeletal isomerizations in a variety of hydrocarbon reactions and the relative rates of exchange of various alkanes (46). Nor could carbonium ions be general, since Raney nickel readily removes bromide from the bridgehead positions of adamantane (184). Here, the reaction also of necessity



Adamantane

proceeds with retention of configuration. A mechanism with backside attack would also be difficult in the removal of chlorine atoms from the methylene groups of adamantane (184).

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