Cover Essay

Alkyl and Aryl Derivatives of the Alkali Metals: Useful Synthetic Reagents as Strong Bases and Potent Nucleophiles. 1. Conversion of Organic Halides to Organoalkali-Metal Compounds

I. James Alfred Wanklyn's Synthesis of Alkylsodium and -potassium Complexes, 1858

Edward Frankland had discovered dimethylzinc, the first main-group organometallic compound, in 1849.[1] This discovery was followed soon thereafter by the preparation of alkyl compounds of other main-group metals by Frankland and other chemists in England, Germany, and France: derivatives of mercury, tin, lead, antimony, bismuth, and cadmium by 1856. Notably absent from this list were organic compounds of the alkali metals lithium, sodium, and potassium.[2] Frankland had briefly investigated the sealed-tube reaction of ethyl iodide with potassium in 1847 in his first independent attempt to isolate the ethyl "radical".[1c] The reaction was rather violent, and the gaseous products were not the ones that he had expected; therefore, he changed the metal from potassium to zinc, which ultimately led to his great discovery.

James Alfred Wanklyn (1834−1906)[3] was a protégé of Frankland during his early years (1849−1857) as a student and then as Frankland's assistant at Owens College in Manchester. There he worked on organometallic chemistry until Frankland left for an appointment in London. Wanklyn was the first to prepare ethylsodium and -potassium, albeit as "ate" complexes with diethylzinc. He spent 1857−1859 studying at the University of Heidelberg with Frankland's former teacher, Robert Bunsen of cacodyl fame,[4] and afterward was Lyon Playfair's demonstrator at the University of Edinburgh. From 1863 to 1870 he was professor of chemistry at the London Institution. His further career in chemistry was devoted to analytical chemistry, as a public analyst, and finally as a private analyst. During his career he published nearly 150 papers and gained a reputation for his research on organic synthesis, vapor densities, and qualitative analysis. He fell out with Frankland during a bitter and acrimonious dispute over whose analysis of organic nitrogen in water was the better one. His work on the alkali-metal "ate" complexes of diethyl- and dimethylzinc, begun while he was with Frankland, appears to have been his only independent research in organometallic chemistry.

Wanklyn's first paper, communicated to the Royal Society by Frankland, was published in the *Proceedings of the Royal Society*.[5] Wanklyn had wondered whether the new class of organometallic compounds might not also include such compounds of the alkali metals. However, as he said, there was "a question whether combination between so powerfully electropositive a body as potassium or sodium on one hand, and a hydrocarbon radical on the other, did not involve impossible condition." His first experiments[5b] investigated reactions of ethyl iodide with sodium. In the absence of solvent below 100 °C, no reaction occurred. Ethyl iodide and sodium did react immediately in diethyl ether in the cold and at 100 °C, but there was no indication that ethylsodium had been formed. But Wanklyn noted[5a] "...some months ago I made the observation that potassium and sodium decomposed zinc-ethyl and I found the action to consist in the replacement of a portion of the zinc by the metal employed." This suggested to Wanklyn that reaction of a stoichiometric quantity of sodium with diethylzinc would be of interest. He described the reaction as follows:

> A tube of soft glass was closed at one end and filled with coal gas. In it was placed a single clean piece of sodium; its open extremity was then closed with the finger, and while still filled with coal gas, the tube was contracted about the middle, drawn out and bent twice at right angles; pure zinc-ethyl, in quantity about 10 times the weight of the sodium, was next introduced, and the tube hermetically sealed. So prepared, the apparatus was afterwards placed in cold water, and left therein for several days, being continuously shaken up at intervals.
>
> During this time the following changes were noted in the contents of the tube. The sodium became coated with zinc, and gradually disappeared, whilst the total volume of the solid and liquid contents diminished considerably. The liquid became also viscid, and sometimes separated into two portions non-miscible with each other, becoming, however, homogeneous as the operation advanced. There was no evolution of gas.
>
> After the lapse of some days the apparatus was found to contain metallic zinc and a clear colorless liquid. The former was weighed and found to correspond to the sodium dissolved, one equivalent of zinc being precipitated for each equivalent of sodium dissolved.
>
> The clear liquid was made the subject of special examination. It consisted of zinc-ethyl holding in solution a crystalline compound containing sodium, zinc and ethyl. It was inflammable to the last degree, burning explosively, on exposure to the air, with a yellow flame, and leaving a very alkaline residue. Owing to its extreme tendency to become oxidized, its manipulation presented great difficulties.[6] It was requisite to decant it into bulbs filled with dry hydrogen or coal gas; and since heat produced partial decomposition, the bulbs had to be double, so that the heated bulb might not receive the liquid (Figure 1).[7]

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[1] (a) Frankland, E. *Ann.* **1849**, *71*, 213. (b) Frankland, E., *J. Chem. Soc.* **1850**, *2*, 297. (c) For a historical review, see also: Seyferth, D. *Organometallics* **2001**, *20*, 2940.

[2] Rubidium and cesium were still unknown in 1856; they were first isolated by Robert Bunsen in 1861 and 1860, respectively.

[3] Brock, W. H. In *Dictionary of Scientific Biography*; Gillispie, C. C., Ed.; Charles Scribner's Sons: New York, 1976; Vol. XIV, p 168.

[4] Cacodyl = tetramethyldiarsine. See the essay "Cadet's Fuming Arsenical Liquid and the Cacodyl Compounds of Bunsen": Seyferth, D. *Organometallics* **2001**, *20*, 1488.

[5] (a) Wanklyn, J. A. *Proc. R. Soc.* **1858**, *9*, 341. (b) A full paper in German appeared in the same year: Wanklyn, J. A. *Ann.* **1858**, *108*, 67.

[6] No Schlenk lines or inert-atmosphere boxes in 1858!

10.1021/om058054a CCC: $33.50

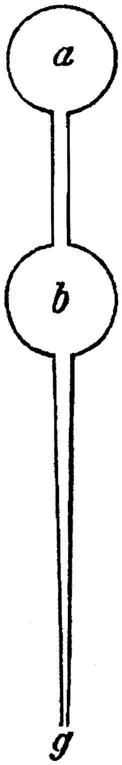

Figure 1. Wanklyn's double-bulb reaction tube (from *Ann.* **1858**, *108,* 67; reproduced by permission of Wiley/VCH).

> The clear liquid deposited large quantities of beautiful crystals when cooled to zero; and when gently warmed in a stream of dry hydrogen gas, so long as zinc-ethyl came off it yielded also a mass of crystals. Some crystals were prepared in the latter manner; they fused at about 27 °C, but once fused they remained fluid at several degrees below that point. Numerous analytical determinations prove that these crystals contain two equivalents of zinc for every equivalent of sodium, and that their formula is
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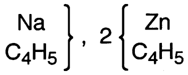
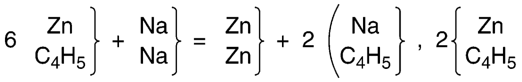
> 
>
> $$\left.\begin{matrix}Na\\C_4H_5\end{matrix}\right\}, 2\left\{\begin{matrix}Zn\\C_4H_5\end{matrix}\right.$$

One must admire the chemists of those days—not only Wanklyn, but also Frankland, Buckton, Bunsen, Löwig, Butlerov, and others—who with very limited means and facilities—no Schlenkware or inert atmosphere boxes, no safe inert gases, no spectroscopy of any kind, no borosilicate glass, only the more difficult to work with soft glass—nevertheless, with superb laboratory expertise, were able to develop organometallic chemistry. In the present case, Wanklyn started out with a reactive solid and a pyrophoric liquid and obtained a pyrophoric product consisting of a pyrophoric liquid and an extremely readily oxidized solid.

Wanklyn wrote the chemical equation describing his reaction as



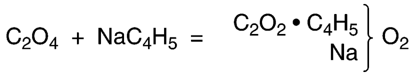
(1)

$$6\left.\begin{matrix}Zn\\C_4H_5\end{matrix}\right\} + \left.\begin{matrix}Na\\Na\end{matrix}\right\} = \left.\begin{matrix}Zn\\Zn\end{matrix}\right\} + 2\left(\begin{matrix}Na\\C_4H_5\end{matrix}\right\}, 2\left\{\begin{matrix}Zn\\C_4H_5\end{matrix}\right. \qquad (1)$$

Note that in 1858 the atomic weight scale of Berzelius, in which C = 6 and O = 8, still was used; thus, C_4H_5 is ethyl (C_2H_5). Wanklyn's elemental analyses for Na and Zn were made difficult by the ready oxidation of his samples. His crystalline product most likely was $NaZn(C_2H_5)_3$. His sodium analysis was satisfactory (12.89 found; 13.11 calcd), but his zinc analysis was way off (28.20 found; 37.25 calcd). (But then, we still have such problems today.)

All attempts to separate the $NaZn(C_2H_5)_3$ into its pure components, C_2H_5Na and $(C_2H_5)_2Zn$, by distillation were unsuccessful. As Wanklyn said, "it would seem that the conjoined zinc-ethyl is necessary to the existence of the sodium ethyl; or more precisely, that some adjunct of a less positive nature than sodium-ethyl is requisite to make the existence of the latter possible." Later workers (vide infra) showed that this is not the case.

Wanklyn's sodium triethylzincate certainly had the reactivity expected for an alkali-metal organic compound. In addition to being extremely readily oxidized in air, its reaction with water was highly exothermic, evolving ethane and leaving hydrated oxides of zinc and sodium as residue. A vigorous, exothermic reaction occurred when dry, gaseous CO_2 was passed over $NaZn(C_2H_5)_3$, producing sodium propionate, $C_2H_5CO_2Na$,[8] whose formation Wanklyn wrote as shown in eq 2. Thus, carbon dioxide cannot be used as a protective gas for $NaZn(C_2H_5)_3$ as it can for diethylzinc. Cyanogen was instantly absorbed in a sample of the zincate in diethylzinc solution, giving a brown solution.



(2)

$$C_2O_4 + NaC_4H_5 = \left.\begin{matrix}C_2O_2\bullet C_4H_5\\Na\end{matrix}\right\} O_2 \qquad (2)$$

A remarkable reaction occurred between $NaZn(C_2H_5)_3$ and carbon monoxide.[9] Wanklyn describes it as follows: carbon monoxide was prepared by heating potassium ferrocyanide with an excess of sulfuric acid and purified by passing it successively through solutions of KOH and sulfuric acid (no convenient gas cylinders in those days). Samples of $NaZn(C_2H_5)_3$ were prepared by heating and shaking 12 g of diethylzinc and 1 g of sodium in a sealed tube. The latter then was opened, and its contents were combined with carbon monoxide in a gas storage vessel (a bit tricky as described). The vessel containing the reactants then was sealed, heated, and shaken in a warm water bath. Within a short time the contents became black. The vessel was cooled, some mercury and water were added, and the mixture was shaken vigorously. The resulting aqueous solution was distilled in a retort. With the water 1 g of an oil distilled as well. The distillation residue was strongly alkaline.

Repetition of this experiment several times gave a larger quantity of the oil. This then was dried and distilled to give two fractions, the first boiling between 100 and 110 °C and the second boiling at 150 °C and higher. The low-boiling component was separated by careful fractional distillation. Combustion analysis led to the empirical formula $C_5H_{10}O$ (although the % H was a bit high; found: C, 68.69; H, 12.39; calcd: C, 69.77; H, 11.63), which Wanklyn thought to be 3-pentanone, $(C_2H_5)_2CO$: i.e., the combination of two ethyl "radicals" and one CO molecule. (By 1866 the atomic scale had been straightened out and the atomic weights of C and O were 12 and 16, respectively, as they are today.) The boiling point and the odor of the lower fraction matched those of authentic $(C_2H_5)_2CO$, as prepared by thermolysis of $Ba(O_2CC_2H_5)_2$ and

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(7) This apparatus operated in the following way: *a* and *b* are two small bulbs connected by a very narrow diameter tube; bulb *b* connects to a narrow diameter tube *g*. To siphon up a sample of the liquid reaction product, the apparatus first is filled with dry coal gas or hydrogen; then bulb *a* is strongly heated, and the tip of tube *g* is immersed into the liquid, which is drawn up into bulb *b* as bulb *a* cools. Both tubes leading to bulb *b* then are cut, and the bulb is sealed. This way, the liquid is never heated.

(8) Wanklyn, J. A. *Ann.* **1858**, *107*, 125.

(9) (a) Wanklyn, J. A. *Philos. Mag.* **1866**, *31*, 505. (b) *Ann.* **1866**, *137*, 256. (c) *Ann.* **1866**, *140*, 211.

by the reaction of diethylzinc with $C_2H_5C(O)Cl$. Wanklyn also carried out an oxidative degradation of his $(C_2H_5)_2CO$ with chromic acid and found the product to be a mixture of $C_2H_5CO_2H$ and CH_3CO_2H. Wanklyn attributed the high % H to the presence of a $(C_2H_5)_2CHOH$ impurity, formed by reduction of the ketone in the workup when water was added to the sodium-containing reaction mixture.

I have described Wanklyn's experiment in some detail because it is a reaction of historical importance, the first carbonylation of an organometallic compound. A study of its mechanism using modern methods would be of great interest.

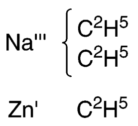
Wanklyn said nothing more about the higher boiling component of his initially formed oil. A reasonable possibility is that it was $(C_2H_5)_3COH$, since Butlerov had developed a route to tertiary alcohols involving the action of 2 molar equiv of a dialkylzinc, R_2Zn, on 1 equiv of an acyl chloride, $RC(O)Cl$.[1c] However, Butlerov's paper was published in *Annalen* in 1867, a year after the appearance of Wanklyn's paper.

Wanklyn prepared $NaZn(CH_3)_3$ in 1859 while he was in Bunsen's laboratory by reaction of dimethylzinc and sodium in diethyl ether.[10] Its reaction with gaseous carbon dioxide, as expected, gave acetic acid after acidification, first identified by smell and taste and subsequently by combustion analysis of its silver salt.

Potassium was found to react more energetically with diethylzinc than did sodium, giving a crystalline product, presumably $KZn(C_2H_5)_3$, that was soluble in diethylzinc.[5b] Wanklyn noted the formation of such a crystalline product in the reaction of lithium with diethylzinc and found that calcium reacts instantly with diethylzinc but that magnesium does not, even at 100 °C.[5b]

This then is the start of organoalkali-metal chemistry: ethyl- and methylsodium, ethylpotassium, and ethyllithium have been prepared. They have not been isolated as such, rather as "ate" complexes with the respective dialkylzinc. We will leave such complexes now, since they represent a minor side branch of organoalkali-metal chemistry. They have had an interesting chemistry in their own right which, in the case of alkali-metal alkylzincates, has been described in a previous cover essay.[1c] These, however, are only one type of a much larger family of "ate" complexes involving the alkali and alkaline-earth metals and organometallic Lewis acids. Some of these have found extensive use in organometallic and organic synthesis: e.g., $MAlR_4$ ($M = Li, Na; R = CH_3, C_2H_5$), $LiB(C_2H_5)_3H$, $KB(iBu)_3H$, etc.

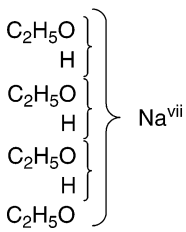
While sodium triethylzincate is now a well-understood compound, this was not the case in Wanklyn's time. In an 1869 paper[11] Wanklyn wrote it as shown in **1** and assigned to sodium



$$\begin{array}{ll} Na''' & \left\{ \begin{array}{l} C^2H^5 \\ C^2H^5 \end{array} \right. \\ Zn' & C^2H^5 \end{array}$$

1

a valence of 3. He also studied the reaction of sodium with ethanol, obtaining, apparently, an ethanol solvate of sodium ethoxide, $NaOC_2H_5{\cdot}3C_2H_5OH$. This he wrote as shown in **2**,



$$\left. \begin{array}{r} C_2H_5O \\ H \\ C_2H_5O \\ H \\ C_2H_5O \\ H \\ C_2H_5O \end{array} \right\} Na^{vii}$$

2

assigning to sodium an "atomicity", i.e., valence, of 7.[12] Wanklyn apparently was not a convert to Frankland's "doctrine of atomicity",[1c] believing that elements could have variable valencies in their organometallic compounds, depending on the compound involved. Wanklyn presented this work at a meeting of the Chemical Society, and the discussion that followed its presentation was published as an attachment to ref 12. The audience was not convinced. Although these examples were "off the wall", in terms of the concept of variable valency of metals in organometallic compounds, Wanklyn turned out to be right in assuming that main-group metals could have more than one valency.

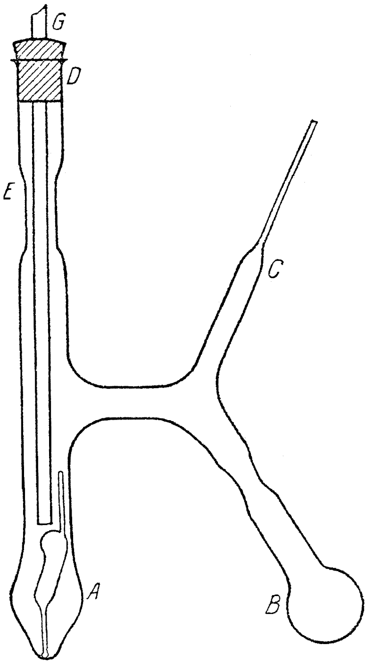


Figure 2. von Grosse's reaction apparatus (from *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 2646; reproduced by permission of Wiley/VCH).

The group 1 series of the $MZnR_3$ complexes was completed in 1926, when Aristid von Grosse reported the preparation of $RbZn(C_2H_5)_3$ and $CsZn(C_2H_5)_3$.[13] The very high reactivity of rubidium and cesium required a special apparatus (Figure 2) constructed of thick-walled glass. The alkali metal (which von Grosse prepared himself) and the diethylzinc (an excess), contained in thin-walled ampules (as shown), were inserted at *A*. *G* is a vertically movable glass rod with a sharp tip. The air was then displaced with purified nitrogen, entering at *C*. The two ampules were smashed with the glass rod. An immediate, exothermic reaction commenced when the alkali metal and diethylzinc came in contact. The metal became covered with zinc of a muddy consistency, and soon two liquid layers formed. In the case of rubidium the reaction mixture was heated at 60 °C for 1 h, while bulb *B* was cooled. Upon completion of the reaction the glass rod was raised to the stopper *D* and the tube was flame-sealed at *E*. The apparatus then was evacuated and flame-sealed at *C*. Subsequently, the contents of *A* were decanted very carefully into bulb *B*. A part of the unreacted diethylzinc was distilled into *A* and used to wash the zinc and glass ampule debris. When bulb *B* was cooled (salt/ice mixture), the $RbZn(C_2H_5)_3$ crystallized. In the $Cs/(C_2H_5)_2Zn$ reaction, two layers were formed as well. The top layer, a mobile liquid, was

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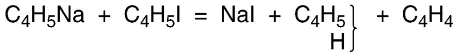
(10) Wanklyn, J. A. *Ann.* **1859**, *111*, 234.
(11) Wanklyn, A. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 64.
(12) Wanklyn, J. A. *J. Chem. Soc.* **1869**, *22*, 199.
(13) von Grosse, A. *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 2646.

composed of mostly diethylzinc. The bottom oil layer was a concentrated solution of $CsZn(C_2H_5)_3$ in diethylzinc.

II. Early Syntheses, without Isolation, of Organosodium Compounds from Organic Halides

In the early days of organometallic chemistry, two syntheses of organoalkali-metal (mostly organosodium) compounds in which they were not actually isolated were discovered: the reaction of sodium with an alkyl or aryl halide and the reaction of sodium with a dialkyl- or diarylmercury compound. Curiously, although by the late 1800s evidence had accumulated that organosodium compounds were intermediates in these reactions, no serious attempts were made to isolate them. Or, if such experiments had been carried out but had been unsuccessful, the experimenters involved, as so often is the case with unsuccessful experiments, did not report them in the literature. The first of these preparative approaches has a long history—it took some 80 years before fairly stable, but highly reactive, suspensions of organosodium and potassium reagents became available. The rest of Part 1 will be devoted to such reactions of organic halides with sodium and potassium and, in section IV, with lithium. The reactions of heavy-metal organometallic compounds, principally diorganomercury compounds, with the alkali metals will be covered in Part 2.

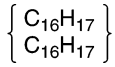
Before Frankland's seminal 1849 discovery of dimethylzinc,[1] he had briefly looked at reactions of sodium and potassium with ethyl iodide in his quest for the ethyl "radical". These reactions were carried out in the absence of solvent. The reaction with sodium was found to proceed readily at 100−130 °C. Frankland had expected to find "ethyl" as the product, but his gaseous products were "Aethylwasserstoff", i.e., ethane, and ethylene. No *n*-butane was found; this is the compound Frankland called "ethyl" (because he had his molecular weights wrong: see footnote 6 in ref 1c), and so he would have searched for it. After Wanklyn's discovery that ethylsodium is stable in diethylzinc solution (because $NaZn(C_2H_5)_3$ is formed, but this was not known at the time), Frankland carried out some experiments in 1859 whose purpose was to explain why he had been unsuccessful in preparing ethylsodium by the $C_2H_5I + Na$ reaction.[14a] Assuming the presence of free ethylsodium in Wanklyn's zincate solutions, Frankland mixed one volume of such a concentrated zincate solution with one volume of ethyl iodide. The result was a vigorous and rapid reaction in which a considerable amount of gas was produced and a precipitate of sodium iodide was formed. The gaseous product was identified as a 1:1 mixture of ethane and ethylene that contained only a trace amount of "ethyl", i.e., *n*-butane. Frankland wrote eq 3. His conclusion was that ethylsodium could not possibly



$$C_4H_5Na + C_4H_5I = NaI + \left.\begin{matrix}C_4H_5\\H\end{matrix}\right\} + C_4H_4 \qquad (3)$$

be prepared by the $C_2H_5I + Na$ reaction, as carried out at 100−130 °C, since it decomposes as it is formed. Wanklyn carried out a similar sealed-tube reaction of methyl iodide with sodium in diethyl ether at 100 °C and obtained ethane, a large amount of methane, and a small amount of ethylene.[14b] As became generally known, reactions of organic halides with sodium occur more readily in ether solution and are facilitated by catalytic amounts of additives such as alcohols and esters. In 1901 Arthur Michael reported that acetonitrile is a particularly effective catalyst.[14c]

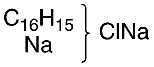
Five years before Frankland's report, Jules Bouis in France published a paper entitled "Sur une nouvelle série de radicaux métalliques", in which he described the action of sodium on capryl chloride (written $C_{16}H_{17}Cl$ in 1854; now $n\text{-}C_6H_{13}CH(Cl)CH_3$, again because C = 6 and O = 8 in 1854).[15] In the cold a liquid product of composition "$C_{16}H_{17}$" was formed. Bouis said that it could be considered to be the "radical", which he wrote as **3**, i.e., as the double formula, since Frankland's



$$\left\{\begin{matrix}C_{16}H_{17}\\C_{16}H_{17}\end{matrix}\right\}$$

3

C_2H_5 had turned out to be C_4H_{10} (but still believed to be a radical by Frankland) or, alternatively, as a mixture of "capryl hydride", $C_{16}H_{18}$, and caprylene, $C_{16}H_{16}$. No experimental data such as boiling point or vapor density were given; thus, we cannot even guess what the products were. If it was the hydrocarbon dimer, this would be the first reported example of the sodium-induced coupling of an organic halide. The capryl chloride/sodium reaction proceeded differently when the mixture was heated. The sodium became "swollen" and violet in color. On being heated to higher temperature the color disappeared, hydrogen was evolved, and the solid reaction mass was transformed into NaCl. The distilled volatile material was treated with sodium, and this procedure was repeated until the added sodium no longer developed a blue coloration. The final distillate was reported to be pure caprylene. The species responsible for the blue/violet color, Bouis suggested, was the complex **4**. Similar chemistry was observed with *n*-amyl chloride and acetyl chloride and with alkyl bromides and iodides. Bouis reported that potassium could be used in place of sodium. In that case the color of the solid phase produced was termed "magnificent", but the reaction was so violent that he could not control it and isolate any products. Bouis' paper ended with a remarkable caveat:



$$\left.\begin{matrix}C_{16}H_{15}\\Na\end{matrix}\right\}ClNa$$

4

> The experiments that I report in this Note seem to me of a nature that would be of interest to chemists: but I give these conclusions with some reservations because I have not been able to obtain the products sufficiently pure for good analyses.

In 1854 Adolphe Wurtz[16] (Figure 3) also had been studying the reactions of sodium with alkyl halides in a much more thorough investigation. The long paper reporting this work[17]

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(14) (a) Frankland, E. *Ann.* **1859**, *110*, 107. (b) Buckeisen, R.; Wanklyn, J. A. *Ann.* **1860**, *116*, 329. (c) Michael, A. *Am. Chem. J.* **1901**, *26*, 419.

(15) Bouis, J. *Compt. Rend.* **1854**, *39*, 288. See also *Ann.* **1854**, *92*, 395.

(16) Charles-Adolphe Wurtz (1817−1884). Son of a Lutheran pastor in Wolfsheim in Alsace, France. Medical studies at University of Strasbourg, M.D. 1834. Study of chemistry and research with Justus Liebig at University of Giessen. Moved to Paris in 1844, in laboratory of Dumas in Faculty of Medicine. Succeeded Dumas as lecturer in organic chemistry in 1849, as professor in 1853, as dean in 1866. Chair of organic chemistry at the Sorbonne, 1874. Very influential in the development of 19th century chemistry; opposed the dualistic approach of Berzelius, supporter of Dumas, Laurent, and Gerhardt; of the concepts of valency and chemical types. Discoverer of primary amines, the first diol (ethylene glycol), ethylene oxide. Vapor density measurement of molecular weights. Brief biography: Brooke, J. H. In *Dictionary of Scientific Biography*; Gillispie, C. C., Ed.; Charles Scribner's Sons: New York, 1976; Vol. XIV, p 529. Friedel, C. *Bull. Soc. Chim.* **1885**, *43*, i−lxxx. Rocke, A. J. *Nationalizing Science: Adolphe Wurtz and the Battle for French Chemistry*; MIT Press: Cambridge, MA, 2001.

Figure 3. Charles Adolphe Wurtz (reproduced courtesy of the Library and Information Centre, Royal Society of Chemistry).

bore the title “Sur une nouvelle série de radicaux organiques”. Wurtz sought to come to grips with the ideas Frankland and Kolbe had developed about the nature of organic “radicals”,[1c] Frankland having prepared what he thought was the “ethyl radical”. Despite its anomalously high boiling point and unexpectedly low reactivity he had insisted, on the basis of its vapor density, that it was C_4H_5. Laurent and Gerhardt quickly disputed this, pointing out that Frankland had misinterpreted his vapor densities and that the molecular weights should be doubled. Supporters of the radical theory then wrote the doubled formulas, but not as the corresponding saturated hydrocarbon. Instead, they wrote them as “radical dimers”, e.g., **5**. It was

$$\left\{\begin{matrix} C_nH_{2n+1} \\ C_nH_{2n+1} \end{matrix}\right\} \quad \underline{5} \qquad\qquad \left\{\begin{matrix} C_nH_{2n+1} \\ C_mH_{2m+1} \end{matrix}\right\} \quad \underline{6}$$

Wurtz’s idea to see if he could prepare mixed radical dimers of type **6**. To investigate this question, Wurtz employed the sodium-induced reactions of mixtures of alkyl halides. To start, Wurtz carried out the reaction of 13−14 g of sodium with 100 g of *n*-butyl iodide, with cooling, to develop the appropriate procedure. The sodium began to swell, and slowly the blue color that Bouis had noticed developed. The mixture then was heated (à l’aide d’une lampe à esprit-de-vin). When the liquid boiled, the blue color disappeared and a white solid of sodium iodide impregnated with liquid remained. The collected volatile products consisted of *n*-butane and butene. The flask containing the NaI and the less volatile products was heated in an oil bath to 150 °C. The expected “butyl” distilled and was redistilled twice to give a liquid with boiling point 105−108 °C, pure “butyl”, according to Wurtz. If it was the dimer (of type **5**, $n = 4$), Wurtz expected it to react with HCl as shown in eq 4. It did

$$\left\{\begin{matrix} C_8H_9 \\ C_8H_9 \end{matrix}\right\} + HCl = Cl,C_8H_9 + C_8H_9,H \qquad (4)$$

not do so; it was inert to attack by HCl at ordinary temperatures. Reaction with Cl_2 gave substitution products of the dimer and HCl. The amyl “radical”, $(C_{10}H_{11})_2$, was prepared in the same way from *n*-amyl iodide in analytical purity (calcd C, 84.50; H, 15.50; found C, 84.20; H, 15.65), bp 158°C. It also was very unreactive, reacting only slowly with fuming H_2SO_4 and with $HNO_3{\cdot}H_2O$.

Now came the critical experiment. Reaction of a mixture of 40 g of *n*-butyl iodide and 34 g of ethyl iodide with 11 g of sodium was carried out using this procedure, with heating required in this case. Distillation of the liquid portion yielded a major fraction boiling at 60−65 °C and another fraction at 100−110 °C which was “butyl”. Refractionation of the lower boiling fraction gave analytically pure (calcd C, 83.72; H, 16.28; found C, 83.48; H, 16.50) “ethyl-butyl” (**7**), with bp 62 °C and vapor density 3.053 (calcd 2.972). The lower boiling “ethyl dimer” must have been missed. Ethyl-amyl (**8**) was formed in a similar reaction of a mixture of ethyl iodide and amyl iodide with sodium, again as the major product, with bp 88 °C and vapor density 3.522 (calcd 3.455). Also prepared in this study was the “radical” *n*-butyl-amyl, $(C_8H_9{-}C_{10}H_{11})_2$. In this case, the distillation showed the presence of $(C_8H_9)_2$ and $(C_{10}H_{11})_2$ as well as $(C_8H_9{-}C_{10}H_{11})$, which made the isolation of the pure mixed “radical” difficult.

$$\left.\begin{matrix} C_4H_5 \\ C_8H_9 \end{matrix}\right\} \quad \underline{7} \qquad\qquad \left.\begin{matrix} C_4H_5 \\ C_{10}H_{11} \end{matrix}\right\} \quad \underline{8}$$

Wurtz believed that the existence of organic “radicals” as “normal” as well as “mixed” dimers fit well into the scheme of things, and their existence was considered reasonable on the basis of the Dumas theory of types. The “radicals” were thus included in Dumas’ MM type to which H_2, HCl, $(CN)_2$, alkyl chlorides, alkanes (as alkyl hydrides), and the alkali metals (believed to be M_2 dimers) belonged. The observation that reaction of the “butyl” dimer with chlorine gave substitution products rather than 2 equiv of butyl chloride did not appear to bother Wurtz, and the idea that the “dimer” could be a monomer with the same molecular weight appears not to have come to mind.

The sodium-induced coupling of two alkyl halides, either both the same or two different ones, came to be known as the Wurtz reaction or the Wurtz synthesis.

The Wurtz reaction and its variation, the Wurtz−Fittig reaction, to be discussed below, eventually provided the death knell of the radical theory. Experiments by Schorlemmer in England and Fittig in Germany eventually showed that such sodium-induced coupling reactions actually were those shown in eqs 5 and 6.

$$2\,RX + 2\,Na \longrightarrow R{-}R + 2\,NaX \qquad (5)$$

$$RX + R'X + 2\,Na \longrightarrow R{-}R' + R{-}R + R'{-}R' + 2\,NaX \qquad (6)$$

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(17) Wurtz, A. *Ann. Chim. Phys. Paris* **1855**, *44*, 275. (In the French literature of that time, compound formulas were written with superscript, rather than subscript, numbers; e.g., C^2H^5Cl, rather than C_2H_5Cl.)

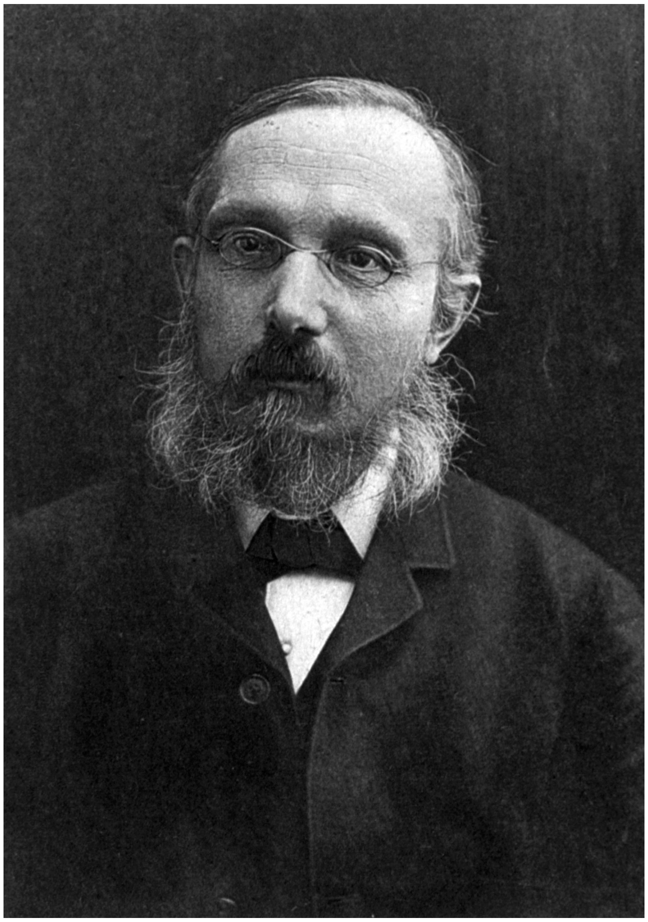
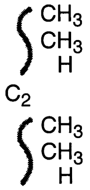


Figure 4. Carl Schorlemmer (reproduced courtesy of the Library and Information Centre, Royal Society of Chemistry).

The coupling of two different alkyl halides by this procedure is not a very useful synthetic reaction, since three products (and, in addition, some side products of elimination and reduction common to all Wurtz reactions) are formed. Such mixtures usually are difficult to separate into the pure components by distillation. The coupling reaction involving a single alkyl halide (eq 5) is in principle synthetically more useful, but the side reactions mentioned above intrude. However, such reactions have found successful application in alkane synthesis, as a few examples show.

In 1867 Carl Schorlemmer[18] (Figure 4) investigated the reaction of isopropyl iodide with sodium in anhydrous diethyl ether.[19] An exothermic reaction accompanied by gas evolution occurred. The gaseous products were identified as propene and propane; the liquid product was "diisopropyl", $(CH_3)_3CHCH(CH_3)_2$, which Schorlemmer wrote as **9**. *n*-Octane was prepared



$$C_2\begin{cases}\left\{\begin{matrix}CH_3\\CH_3\\H\end{matrix}\right.\\\left\{\begin{matrix}CH_3\\CH_3\\H\end{matrix}\right.\end{cases}$$

9

a few years later by the action of sodium on *n*-butyl iodide.[20] The preparation of *n*-octane in large amounts in 65−70% yield by the reaction of *n*-butyl bromide with sodium in diethyl ether was studied years later in great detail by American workers[21] in order to optimize the reaction conditions. Krafft[22] used the respective alkyl iodide/sodium reactions to prepare n-$C_{20}H_{42}$, n-$C_{18}H_{38}$, n-$C_{16}H_{34}$, and n-$C_{14}H_{30}$. There are other examples, but these should suffice.

An earlier paper by Schorlemmer is of special interest,[23] in that it came close to discrediting the radical theory. Pointing out that two C_nH_{2n+2} series of hydrocarbons seemed to exist which differed in the method of their preparation, the "alkyl hydrides" and the "radicals", he noted that among their physical properties only their boiling points appeared to differ. Members of both series reacted with gaseous chlorine to give substitution products, as Wurtz had found. The chlorinated derivatives, however, had not been compared, and this Schorlemmer set out to do. Using a 1:1 mixture of ethyl iodide and amyl iodide in a reaction with sodium in diethyl ether, he prepared "ethyl-amyl", the assumed radical, **7**, $C_2H_5{-}C_5H_{11}$. The assumed dimeric radical "amyl", $C_5H_{11}{-}C_5H_{11}$, also was isolated, but "ethyl", $C_2H_5{-}C_2H_5$, was not. Then Schorlemmer chlorinated "ethyl-amyl" in the presence of a small amount of iodine. The reaction was stopped before all of the "ethyl-amyl" had reacted in order to favor monosubstitution. The product, ethyl-amyl chloride, was isolated by fractional distillation and compared with the heptyl chloride that Schorlemmer had prepared earlier[24] by chlorination of "heptyl hydride". The two C_7H_{15} chlorides were identical both in physical properties, including boiling point, and in chemical properties, e.g., conversion to the same heptyl mercaptan. The "amyl radical dimer", bp 158 °C, also was chlorinated, giving a monochloride, $C_{10}H_{21}Cl$, with bp ~200 °C. These boiling points were compared with those of two hydrocarbons of the same $C_{10}H_{22}$ composition and of the derived chlorides which had been prepared by other workers: Wurtz's "diamyl hydride", bp 155−157 °C, and its monochlorination product, bp 190−200 °C, and a hydrocarbon isolated from American petroleum, bp 160−162 °C, and the product of its monochlorination by Cahours and Pelouze, bp 204−206 °C. Schorlemmer concluded: "I believe that these two hydrocarbons are identical to the amyl of bp 158°; and in any case, the three chlorides derived from them are identical." Schorlemmer did worry about the differences in boiling points and suggested causes such as the presence of impurities and the difficulty of obtaining pure compounds in the fractional distillation of higher boiling mixtures. Thus, some

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[18] Carl Schorlemmer (1834−1892). Birth and schooling in Darmstadt, Germany. Early employment as apprentice and assistant pharmacist in Umstadt (Hessen) and Heidelberg, Germany. In Heidelberg, he attended Robert Bunsen's chemistry lectures and began studies in chemistry. After a semester's study at the University of Giessen, in 1858 he went to Manchester in England on the advice of a friend. There he became private assistant to Henry Roscoe (who had been a student of Bunsen) at Owens College. He was appointed assistant instructor at Owens College in 1861, lecturer in 1872, and professor of organic chemistry in 1874. Before 1874, his research was focused on the synthesis and study of hydrocarbons which were isolated from coal tar and American petroleum. An important finding, which contributed to the demise of the radical theory, was that Frankland's "methyl" radical really was ethane. Other research was concerned with the plant dye aurin, thiosulfuric acid, and the chemical constitution of bleaching powder. Schorlemmer was a close friend and also the science advisor of Friedrich Engels and Karl Marx and became their follower, joining the International Workingmen's Association and the German Social Democratic Party. As the first Marxist chemist, he was revered in the late German Democratic Republic and the Technische Hochschule für Chemie "Carl Schorlemmer" in Merseburg in the GDR was named in his honor. Brief biographies: Heinig, K. In *Dictionary of Scientific Biography*; Gillispie, C. C., Ed.; Charles Scribner's Sons: New York, 1975; Vol. XII, p 208. *J. Chem. Soc. Trans.* **1893**, *63*, 756 (obituary with complete bibliography).

[19] Schorlemmer, C. *Ann.* **1867**, *144*, 184.

[20] Schorlemmer, C. *Ann.* **1872**, *161*, 280.

[21] Lewis, H. F.; Henricks, R.; Yohe, G. R. *J. Am. Chem. Soc.* **1928**, *50*, 1993.

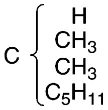
[22] Krafft, F. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2219.

[23] Schorlemmer, C. *Ann.* **1864**, *129*, 243.

[24] Schorlemmer, C. *Ann.* **1863**, *128*, 103.

doubt remained, and instead of concluding that the "radical dimer" and the "alkyl hydride" of the same composition and molecular weight are in *all* respects identical, thus rendering the radical theory superfluous, Schorlemmer ended by saying "From the results of the work described above I believe I can conclude that between the alkyl hydrides and the so-called radicals there is no chemical difference and they are only physical isomers." A very cautious man!

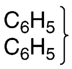
In 1858, Kekulé recognized the tetraatomicity (or tetravalence) of carbon and introduced the concept of linking carbon atoms to one another (and to atoms of other elements), thus providing the basis for the structural theory of organic chemistry.[25] This new approach gained gradual acceptance, and in Schorlemmer's 1867 paper[19] there is no mention of "radicals", only of hydrocarbon compounds. When he described the reaction of a mixture of isopropyl iodide and amyl iodide with sodium in diethyl ether, he reported the three products as diisopropyl, amyl-isopropyl and diamyl. Schorlemmer wrote amyl-isopropyl as **10** and said it could be called dimethyl-amyl-methane.



$$C\left\{\begin{array}{l}H\\CH_3\\CH_3\\C_5H_{11}\end{array}\right.$$

10

A more useful modification of the Wurtz synthesis that involves the reaction of a mixture of an alkyl and an aryl halide with sodium, which gives the alkyl-substituted aromatic compound generally in good yield and in good selectivity, came from the laboratory of Rudolf Fittig[26] (Figure 5) at the University of Göttingen. In 1862 Fittig reported his work on bromobenzene, a compound that he had found to be rather unreactive.[27] Thus, it could be heated, without reaction, with concentrated aqueous KOH for days. Nor did bromobenzene react with solutions of KCN (sealed tube at 100 °C) or potassium acetate under the same conditions. The one reaction that did proceed readily was that with sodium. In the absence of solvent the reaction was rather exothermic, but it was more moderate when carried out in diethyl ether using sodium in small pieces in excess. Here also the sodium became covered with a blue-black material, which caused it to sink to the bottom of the flask. An exotherm caused the ether to reflux, and the reaction proceeded rapidly. On its completion, evaporation of the ether left a yellow oil, distillation of which gave a colorless, crystalline solid, mp 70.5 °C. Its combustion analysis (C, 93.24; H, 6.55) was in good agreement with the empirical formula C_6H_5 or, as Fittig assumed it to be, $C_{12}H_{10}$ (without any molecular weight data since it was a solid). He believed that he had prepared the dimeric radical **11** and said he would call it "phenyl". Thus, the Wurtz reaction also was applicable to aromatic halides. Fittig had prepared biphenyl but at this point did not know it.

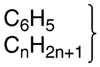


$$\left.\begin{array}{l}C_6H_5\\C_6H_5\end{array}\right\}$$

11

Figure 5. Rudolph Fittig (photo courtesy of University of Pennsylvania Library, Edgar Fahs Smith Collection).

Further work by Tollens and Fittig brought clarification and, in principle, an end to the idea that "radical dimers" were the products of the Wurtz reaction.[28] Fittig had become suspicious about his "phenyl", since in none of its reactions that worked was a six-carbon product formed; it seemed as if the two C_6H_5 groups in **10** were so tightly bound to each other that they could not be separated again. To gain more information on this question, mixtures of bromobenzene and an alkyl iodide were treated with sodium. The idea was to prepare mixed "radical dimers", **12**, and to see if they were different from or identical with known alkylbenzenes. A 1:1 mixture of bromobenzene and methyl iodide and an excess of small sodium pieces did not react at room temperature, but when the reaction was carried out in the presence of an equal volume of diethyl ether, a mild exotherm was observed so that external cooling was required. Distillation of the volatiles gave first the ether solvent, no benzene, and a liquid boiling at 108−116 °C. Treatment of the latter with more sodium and redistillation yielded a liquid of constant boiling point, 111 °C, in considerable quantity. Its C, H analysis indicated the empirical formula C_7H_8. In both its physical and chemical properties this product was identical with coal tar derived toluene. Among its conversions that Tollens and Fittig studied were its nitration to nitrotoluene and reduction of the latter to toluidine, its oxidation to benzoic acid, and its sulfonation with fuming sulfuric acid. The proof that the mixed



$$\left.\begin{array}{l}C_6H_5\\C_nH_{2n+1}\end{array}\right\}$$

12

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(25) Kekulé, A. *Ann.* **1858**, *106*, 129.

(26) Rudolph Fittig (1835−1910). Born in Hamburg, Germany. During studies at University of Göttingen, 1856, developed an interest in chemistry. Assistant to Heinrich Limpricht and Friedrich Wöhler. Doctorate in 1858. Privatdozent at Göttington, 1860; Professor (Extraordinarius), 1866. Professor at University of Tübington, 1870−1876, at University of Strasbourg, 1876−1902. Research on preparative organic chemistry, aromatic compounds: work on mesitylene, naphthalene, fluorene; discoverer of phenanthrene in coal tar. Work on unsaturated acids and lactones. Brief biographies: Leicester, H. M. in *Dictionary of Scientific Biography*; Gillispie, C. C., Ed.; Charles Scribner's Sons: New York, 1976; Vol. V, p 12. Fichter, F. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1339.

(27) Fittig, R. *Ann.* **1862**, *121*, 361.

(28) Tollens, B.; Fittig, R. (a) *Ann.* **1864**, *129*, 369. (b) *Ann.* **1864**, *131*, 303.

"phenylmethyl radical" was identical with toluene was indisputable, and thus, one would think, the "dimer radical" theory was history. Tollens and Fittig prepared ethylbenzene and *n*-amylbenzene by the same procedure. All the physical and chemical properties of these products were consistent with those expected for alkylbenzenes, "homologues of benzene", as Fittig called them: i.e., compounds of type RC_6H_5. However, Fittig was cautious. After all, there was only one example of the identity of an assumed "mixed radical dimer" with a known compound, and for the alkylbenzenes with alkyl groups larger than methyl, the authentic compounds often still were unknown. In the case of the "aryl alkyl radical dimers", because of the possibility of isomers of the same empirical formula, equating the dimers with hydrocarbons of the same composition and molecular weight was not exactly straightforward. Thus, Fittig tried to compare his ethyl-phenyl with xylene from coal tar and found that their boiling points differed by 7 °C. Even in the case of the methyl-phenyl/toluene comparison, Fittig was not 100% sure, since there was no agreement in the literature concerning the boiling point of toluene. Therefore, Fittig at this point, like Schorlemmer, was reluctant to state with 100% certainty that the "alkyl−aryl radical dimers" and the alkylbenzenes were identical.

Continuing these studies, Fittig found that reaction of a mixture of bromotoluene and methyl iodide with sodium gave methyltoluene, a product that was different from ethylbenzene but that Fittig said was identical with xylene.[29] Reaction of a mixture of bromotoluene and ethyl iodide with sodium gave ethyltoluene, which was different from the other known C_9H_{12} benzene derivatives. August Kekulé, who at the time was engaged in his investigations of aromatic compounds,[30] appreciated Fittig's work. Describing the Tollens and Fittig experiments, he said, "The beautiful experiments that led Fittig to the synthesis of hydrocarbons that are homologous with benzene are still fresh in the memories of chemists."

Expanding his studies of alkylbenzenes, Fittig and his students prepared a trimethylbenzene, which he called methylxylene, and ethylxylene,[31] amylbenzene, amyltoluene and amylxylene,[32] propylbenzene and propyltoluene,[33] the first tetramethylbenzene (which Fittig called durene),[34a] and ethyl- and diethylbenzene.[34b] In the last paper, Fittig finally put the "radical" theory to rest, saying that the reactivity of the products indicated that they were real compounds: i.e., alkyl derivatives of benzene, RC_6H_5. No reactions could be found that involved the separated R group alone or the separated C_6H_5 group alone. Also, Fittig's "phenyl radical dimer" underwent no reactions in which a product containing a single C_6 ring was formed; the two C_6H_5 groups were tightly bonded together. These views concerning the earlier assumed "radical dimers" were accepted by other chemists. Although Kekulé had published his paper on the structure of benzene and on the substitution patterns of di- and polysubstituted benzenes in 1866,[30] Fittig at that time had no way of knowing, for instance, what isomer his methyltoluene was: ortho, meta, or para.

Other contemporary chemists had trouble obtaining good product yields using the Tollens/Fittig procedure. In a paper devoted to the synthesis of ethylbenzene and diethylbenzene,[34b] Fittig and König provided detailed experimental directions, stressing that good alkylbenzene yields were obtained only when scrupulously dried diethyl ether was used as solvent. This they accomplished by predrying commercial ether over calcium chloride and distilling it directly into the reaction flask. Carefully cleaned sodium (50% excess) was cut into thin pieces and added to the ether. The flask was placed in a cold water bath and topped with a Liebig condenser. Upon addition of the sodium, hydrogen was evolved as it reacted with residual water. Ice was added to the water bath, and then the alkyl halide (iodide or bromide) (25% excess)/aryl bromide mixture was added. In most cases, the reaction commenced shortly after the halide addition, as indicated by the sodium slices becoming dark in color and sinking to the bottom of the flask. Occasionally the reaction was slow to start. In those cases, heating was to be avoided, since an uncontrollable reaction usually resulted. Once started, the exothermic reaction proceeded quickly, requiring that external cooling be continued. Upon completion of the reaction the ether was distilled using a warm water bath and the product using (carefully) an open flame.

Since the aryl halide generally reacts more rapidly with sodium than does the alkyl halide, the Fittig reaction was a very useful variation of the Wurtz reaction in that it allowed the clean synthesis of alkylbenzenes and biphenyl derivatives, generally in reasonable yield (eqs 7 and 8), and it came to be called the Wurtz-Fittig reaction. Such reactions were used by later workers to good advantage in organic synthesis. For example, Krafft and Göttig at the University of Heidelberg,[35] in reactions of mixtures of cetyl iodide, $n\text{-}C_{16}H_{33}I$, and bromobenzene (and various methylated bromobenzenes) with sodium, prepared *n*-cetylbenzene, *o*-, *m*-, and *p*-methylcetylbenzene, 1,3,4-dimethylcetylbenzene, and 1,3,5,6-trimethylcetylbenzene. No solvent was used. *p*-Bromotoluene and *m*-bromotoluene reacted reasonably well, but the reactions of the more hindered *o*-bromotoluene and the more highly methylated bromobenzenes stopped at the stage of the formation of the deep blue crust on the sodium. Heating to 140 °C or higher led to formation of the desired cetyl-substituted products, but only in low yield. Fittig's biaryl synthesis was found by later workers to be complicated by the formation of byproducts, for the most part due to nuclear metalation of the biphenyl product by as yet unreacted phenylsodium or of methyl substituents, if such were present on the benzene ring.[36]

$$\mathrm{RX + ArX + 2\,Na \longrightarrow R{-}Ar + 2\,NaX} \tag{7}$$

$$\mathrm{2\,ArX + 2\,Na \longrightarrow Ar{-}Ar + 2\,NaX} \tag{8}$$

The "heteroatom Wurtz-Fittig reaction" in later years proved useful in the synthesis of completely alkylated and arylated organometallic compounds of the group 14 and 15 elements, especially of tetraalkyl- and tetraarylsilanes.[37] Thus, reaction of chlorobenzene, silicon tetrachloride, and sodium in diethyl ether produced tetraphenylsilane.

Now the Wurtz and the Wurtz−Fittig reactions are "history" in the colloquial sense. It's not that carbon−carbon coupling reactions are not important. Quite the contrary, as Frisch and

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(29) (a) Fittig, R. *Ann.* **1865**, *133*, 47. (b) Glinzer, E.; Fittig, R. *Ann.* **1865**, *136*, 303. (c) Later work (Fittig, R. *Z. Chem. (Neue Folge)* **1867**, *3*, 523) showed some differences between some derivativs of methyltoluene and xylene; thus, it appeared that methyltoluene and coal tar xylene were isomeric, not identical.

(30) Kekulé, A. *Ann.* **1866**, *137*, 129 (section IV of the 66 page paper, pp 188−189).

(31) Fittig, R. *Z. Chem. (Neue Folge)* **1865**, *1*, 572.

(32) Bigot, C.; Fittig, R. *Ann.* **1867**, *141*, 160.

(33) Fittig, R.; Schaeffer, C.; König, J. *Ann.* **1869**, *149*, 324.

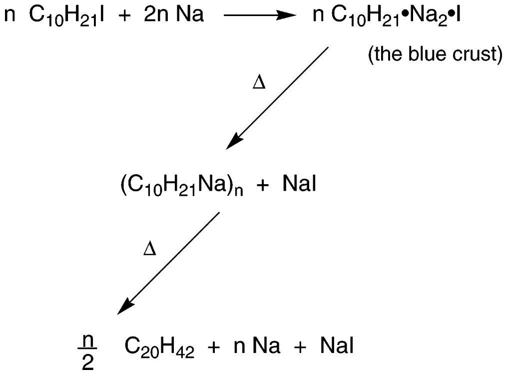
(34) (a) Fittig, R. *Z. Chem. (Neue Folge)* **1870**, *6*, 161. (b) Fittig, R.; König, J. *Ann.* **1867**, *144*, 277.

(35) Krafft, F.; Göttig, J. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 3180.

(36) (a) Weiler, M. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 115. (b) Bachmann, W. E.; Clarke, H. T. *J. Am. Chem. Soc.* **1927**, *49*, 2089.

(37) (a) Jones, R. G.; Gilman, H. *Chem. Rev.* **1954**, *54*, 835. (b) Eaborn, C. *Organosilicon Compounds*, Butterworths: London, 1960; pp 26−31.

Scheme 1



Beller said in a recent review:[38] "C−C coupling reactions are among the most important transformations in organic synthesis as they make it possible to build up complex structures from readily available components in diverse ways." The reason the Wurtz and Wurtz−Fittig reactions no longer find much, if any, applications in organic synthesis is found in Frisch and Beller's next sentence: "As a result of the development of a large number of metal-catalyzed coupling reactions of various C−X-containing compounds (X = Cl, Br, I, OTf, OMes, N_3^+, etc.) over the last three decades, efficient methods are now available for the direct formation of bonds between sp^3-, sp^2- and sp-hybridized carbon atoms." Catalysis of such cross-coupling reactions by, for the most part, transition-metal complexes, notably those of palladium and nickel, has put sodium chemistry on the shelf.[39]

However, the Wurtz and Wurtz−Fittig reactions are only the beginning of organoalkali-metal chemistry, and there is much more to this story.

It was Krafft and Göttig who ventured the first suggestion concerning the course of the Wurtz reaction.[35] Their starting point was what they described as the "deep blue, heavy, crystalline crust" which formed on the surface of the sodium in the case of those aryl bromides which did not react at room temperature. Such crusts disappeared and were replaced by white sodium halide only when heat was applied. (Such intermediacy of a colored coating on the sodium pieces had been noted by essentially all previous workers in the case of both alkyl and aryl halides.) Krafft and Göttig, citing as analogy Frankland's ethylzinc compounds (eqs 9 and 10), suggested that organosodium compounds were formed as intermediates (Scheme 1). In analogy to the thermal decomposition of diethylzinc (eq 11), the alkylsodium compound then decomposed to the Wurtz product.

$$C_2H_5I + Zn \longrightarrow C_2H_5ZnI \qquad (9)$$

$$2\,C_2H_5ZnI \longrightarrow (C_2H_5)Zn + ZnI_2 \qquad (10)$$

$$(C_2H_5)Zn \xrightarrow{\Delta} C_4H_{10} + Zn \qquad (11)$$

The nature of the blue crystalline crust on the sodium that is formed during the interaction of an organic halide with a sodium surface still is somewhat of a mystery today. Such blue species also occur in reactions of chlorosilanes with sodium and potassium, and Richard Jones and co-workers have studied them using UV/vis and EPR spectroscopy.[40] It was concluded that "the blue color (which was found to be air-stable) is due to colloidal alkali metal particles formed during the reaction contained in a matrix composed of an intimate mixture of polymer and alkali metal halide." However, since the reaction mixture containing such blue-crusted solids in the case of organic halides undergoes such an exothermic reaction when heated, it may be more reasonable that an organosodium intermediate is a component of the matrix rather than the coupled product.

In both the Wurtz and Wurtz−Fittig reactions, byproducts are formed, and in some cases only low product yields were obtained. Assuming this to be due to the fact that a heterogeneous reaction is involved, Müller and Röscheisen[41a] solubilized the sodium as its tetraphenylethylene adduct (eq 12). Initially, a stoichiometric amount of tetraphenylethylene was used in reactions of sodium with benzyl halides in THF. Dropwise addition of the red sodium tetraphenylethylenide solution to the benzyl halide solution resulted in instantaneous discharge of the color, and bibenzyl was obtained in 70−82% yield. Due to its high molecular weight, the use of stoichiometric amounts of tetraphenylethylene was not practical, but it was found that the use of only a catalytic amount (5 mol %) of tetraphenylethylene with high-speed stirring under nitrogen gave good coupling product yields with benzylic and allylic halides. In an improvement of this approach, Japanese workers[41b] used catalytic amounts of tetrakis(*p*-(dimethylamino)phenyl)ethylene in place of tetraphenylethylene. This allowed easy removal of the catalyst from the reaction solution as its hydrochloride. Optimum yields were obtained when liquid Na/K alloy was used in place of sodium and the reaction temperature was lowered to −40 °C.

$$(C_6H_5)_2C{=}C(C_6H_5)_2 + 2\,Na \xrightarrow{THF} 2\,Na\,(THF)_n^+ + [(C_6H_5)_2C_2(C_6H_5)_2]^{2-} \qquad (12)$$

Almost all workers who have considered the course of the Wurtz and Wurtz−Fittig reactions have concluded that it is a two-step process, the first step of which is the formation of an organosodium compound (eq 13). In situ trapping experiments gave organosodium-derived products, not surprisingly, often in low yield.

$$RX + 2\,Na \longrightarrow RNa + NaX \qquad (13)$$

(R = alkyl or aryl)

As early as 1866, Kekulé had reported a preparation of benzoic acid which involved carrying out the reaction of bromobenzene with sodium in benzene under an atmosphere of carbon dioxide.[30] Remarkably, better yields of benzoic acid were obtained when moist, rather than dry, carbon dioxide was used. Similar reactions with Fittig's bromotoluene and bromoxylene gave the respective carboxylic acids. Kekulé began his discussion of this new benzoic acid synthesis by referring to Wanklyn's $NaZn(C_2H_5)_3/CO_2$ reaction; thus, he could have been thinking in terms of a phenylsodium intermediate, although he did not say so.

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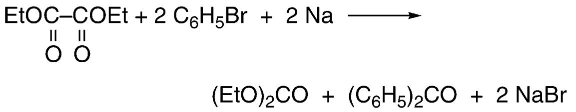
[38] Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 624.

[39] For reviews see: (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (c) Reference 38. (d) Rouhi, A. M. *Chem. Eng. News* **2004**, *82* (Sept. 26), 49.

[40] Benfield, R. E.; Cragg, R. H.; Jones, R. G.; Swain, A. C. *Nature* **1991**, *353*, 340.

[41] (a) Müller, E.; Röscheisen, G. *Chem. Ber.* **1957**, *90*, 543. (b) Miyahara, Y.; Shiraishi, T.; Inazu, T.; Yoshino, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 953.

In later years, Frey treated a mixture of diethyl oxalate and bromobenzene in anhydrous ether with sodium (with cooling). After ~14 days at room temperature, hydrolytic workup gave, with some difficulty, triphenylcarbinol in low yield.[42a] Its formation was rationalized as shown in eqs 14 and 15. An



$$\mathrm{EtOC{-}COEt} + 2\ \mathrm{C_6H_5Br} + 2\ \mathrm{Na} \longrightarrow (\mathrm{EtO})_2\mathrm{CO} + (\mathrm{C_6H_5})_2\mathrm{CO} + 2\ \mathrm{NaBr} \qquad (14)$$

$$(\mathrm{C_6H_5})_2\mathrm{CO} + \mathrm{C_6H_5Br} + \mathrm{Na} \longrightarrow \xrightarrow{\mathrm{H_2O}} (\mathrm{C_6H_5})_3\mathrm{COH} + \mathrm{NaBr} \qquad (15)$$

improved triphenylcarbinol synthesis was developed 45 years later by Morton using the reactions of in situ generated phenylsodium (from chloro-, bromo-, and iodobenzene in diethyl ether and sodium sand or wire) with ethyl or methyl benzoate. During the initial stages, cooling was necessary, but then the reaction was continued at room temperature during the 2 day reaction time. Triphenylcarbinol yields of 70−98% were obtained.[42b]

Paul Schorigin at the Imperial Technische Hochschule in Moscow carried out similar experiments in which he trapped in situ generated alkylsodium intermediates with ethyl benzoate (eq 16).[43] Starting with benzophenone as the reactant, Schorigin

$$\mathrm{C_6H_5CO_2Et} + 2\ i\text{-}\mathrm{C_5H_{11}Br} + 4\ \mathrm{Na} \xrightarrow{\mathrm{Et_2O}} \xrightarrow{\mathrm{H_2O}} \mathrm{C_6H_5}(i\text{-}\mathrm{C_5H_{11}})_2\mathrm{COH} + \mathrm{EtOH} + 2\ \mathrm{NaBr} + 2\ \mathrm{NaOH} \qquad (16)$$

trapped ethylsodium to give ethyldiphenylcarbinol, and with acetophenone he intercepted isoamylsodium.[44] An attempt to trap in situ generated isobutylsodium with a stream of dry carbon dioxide in diethyl ether solution gave only a very low yield of the expected acid, i-$C_4H_9CO_2H$. Of special interest is that when this reaction was carried out in benzene solution, the acid that Schorigin isolated, again in low yield, was benzoic acid. This appears to be the first example of the metalation of an aromatic hydrocarbon by an alkali-metal alkyl[44] (eq 17). A more effective

$$i\text{-}\mathrm{C_4H_9Br} + 2\ \mathrm{Na} \longrightarrow \mathrm{NaBr} + i\text{-}\mathrm{C_4H_9Na} \xrightarrow{\mathrm{C_6H_6}} \mathrm{C_6H_5Na} + i\text{-}\mathrm{C_4H_{10}} \qquad (17)$$

procedure for the *in situ* trapping of organosodium intermediates by reaction with carbon dioxide was developed later by Morton and co-workers.[45] Good yields of aromatic carboxylic acids (67−95%) were obtained when the reaction of the respective aromatic chloride (C_6H_5Cl, *m*- and *p*-$CH_3C_6H_4Cl$, *p*-$C_6H_5C_6H_4Cl$, *p*-ClC_6H_4CHO), sodium sand, and carbon dioxide was carried out in benzene at 110−120 °C under a CO_2 pressure of 200−400 psi in a high-pressure apparatus. The *n*-amyl chloride/Na/CO_2 reaction had to be performed in ligroin, since metalation of benzene by the more reactive amylsodium was competitive with the $C_5H_{11}Na/CO_2$ reaction. In addition to the expected caproic acid, *n*-butylmalonic acid was formed in substantial yield. Formation of the two acids also occurred when the trapping reaction was carried out with CO_2 at atmospheric pressure. Initially, the formation of *n*-butylmalonic acid was puzzling to Morton, and the possible formation of a 1,1-disodium intermediate, $C_5H_{10}Na_2$, was discussed. However, eventually it was realized that the *n*-amylsodium, as it was being formed, had two possible reactions that it could undergo: reaction with CO_2 and the α-metalation of the CO_2 reaction product, $C_5H_{11}CO_2Na$, to give $C_4H_9CH(Na)CO_2Na$, whose reaction with CO_2 would give the sodium salt of *n*-butylmalonic acid. Under the reaction conditions, these two processes apparently were competitive.

Some other trapping reactions are of interest. A reaction of ethyl bromide and 35 g of sodium in 150 mL of ether under a stream of carbon monoxide at room temperature was carried out by Schlubach and Goes over a period of 10 days, the C_2H_5Br (330 g) being added in 2 mL portions during this time. Low yields of $(C_2H_5)_2C{=}O$ and $(C_2H_5)_3COH$ were isolated.[46] Thus, the higher-boiling product in Wanklyn's $NaZn(C_2H_5)_3 + CO$ experiment[9] must have been triethylcarbinol. Schlubach and Goes also carried out the reaction of bromobenzene and sodium in benzene, with slow, portionwise addition of the bromobenzene over 4 days, under a stream of carbon monoxide. Workup gave four products: biphenyl, benzoic acid, and the carbonylation products, benzophenone and triphenylcarbinol.

Such trapping reactions were important, because they demonstrated that organosodium compounds were intermediates in the Wurtz and Wurtz−Fittig reactions. They were not synthetically useful, especially since the more easily prepared, soluble, and easy-to-handle Grignard reagents had become available in 1900.

It is not clear, even today, exactly how the organosodium compound is formed when an organic halide and metallic sodium react. The problem is that this interaction is a heterogeneous process: the sodium is insoluble in hydrocarbon solvents, as are the organosodium and the sodium halide products. To make matters even more difficult, the organosodium compounds are very highly reactive toward oxygen and moisture and react with diethyl ether (eq 18).[47]

$$\mathrm{C_2H_5Na} + (\mathrm{CH_3CH_2})_2\mathrm{O} \longrightarrow \mathrm{C_2H_5ONa} + \mathrm{C_2H_6} + \mathrm{C_2H_4} \qquad (18)$$

Many workers over the years have suggested that the Wurtz and Wurtz−Fittig reactions are free radical processes. However, both proceed in two steps and the various experimental approaches used to study the Wurtz reaction could not distinguish whether formation of the alkylsodium compound (eq 13) or its subsequent reaction with the alkyl halide (eq 19) (or both) was the free radical process.

$$\mathrm{RNa} + \mathrm{RX} \longrightarrow \mathrm{R{-}R} + \mathrm{NaX} \qquad (19)$$

It is difficult to conceive of a nonradical process, one that does not involve initial electron transfer from the sodium to the alkyl halide, for the RX + Na reaction, but one was proposed in 1899 which is a mechanistic curiosity. Around the end of the 19th century, John Ulric Nef, a distinguished American organic chemist who spent the major part of his career (1892−1915) at the University of Chicago, was engaged in studies of the chemistry of divalent carbon compounds (isocyanides, fulminates, and prussic acid, also in a search for methylene). He did not believe that carbon possessed a constant valency of 4, which certainly is correct, but took his enthusiasm for divalent

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(42) (a) Frey, H. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 2514. (b) Morton, A. A.; Stevens, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 2244.

(43) Schorigin, P. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3111.

(44) Schorigin, P. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 2711.

(45) Morton, A. A.; LeFevre, W. J.; Heckenbleikner, I. *J. Am. Chem. Soc.* **1936**, *58*, 754.

(46) Schlubach, H. H.; Goes, E. C. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 2889.

(47) Schorigin, P. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1931.

Scheme 2

$$\mathrm{CH_3CH_2X + NaOC_2H_5 \longrightarrow C_2H_5OC_2H_5 + NaX}$$

Nef's mechanism:

$$\mathrm{CH_3CH_2X \rightleftharpoons CH_3CH{=} + HX} \quad \text{(methylene formation)}$$

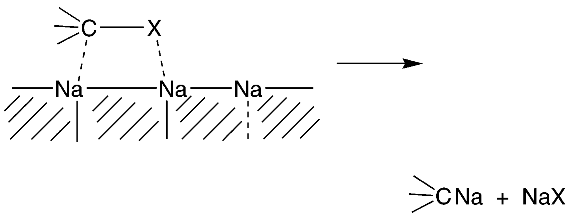
$$\mathrm{HX + NaOC_2H_5 \longrightarrow C_2H_5OH + NaX}$$

$$\mathrm{CH_3CH{=} + C_2H_5OH \longrightarrow C_2H_5OC_2H_5}$$

carbon to extremes. In an article summarizing his views,[48] he stated that "methylene chemistry plays an important role in many of the simplest reactions of organic chemistry, reactions which have hitherto been explained on the basis of substitution." An application of his methylene mechanism to the Williamson synthesis is shown in Scheme 2.

The reaction of bromobenzene with sodium also was rationalized in terms of a divalent carbon intermediate, whose reaction with sodium gives phenylsodium: "Phenylsodium must be formed from bromobenzene via an intermediate dissociation to HBr and phenylene and subsequent addition of the metal to the latter."[49] Nef wrote no equations or formulas, so one must guess as to what he meant. Scheme 3 shows a fanciful interpretation. The "phenylene" is shown with two "free affinity units", as Nef called them (or as "dehydrobenzene", aka benzyne).

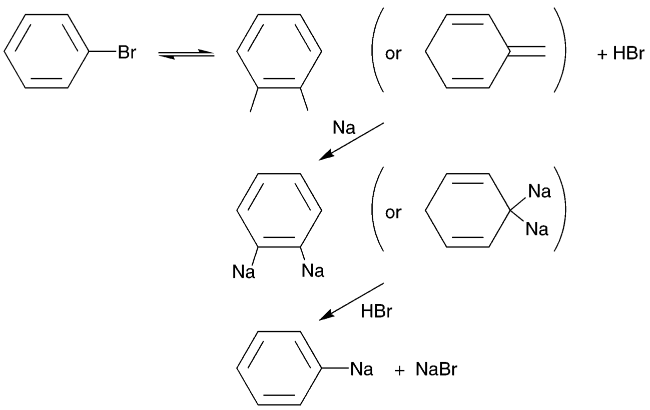
Another suggested mode for the formation of organoalkali-metal compounds in the heterogeneous reaction of an organic halide with an alkali metal was published by Ziegler and Schäfer in 1930.[50] It was pointed out that in the solid alkali-metal lattices the metal−metal distances are on the order of 3−4 Å (Li, 2.7 Å; Na, 3.5 Å; K, 4.2 Å), while C−halogen distances are around 2 Å (C−Cl, ~1.8 Å; C−Br, ~1.9 Å; C−I, 2.1 Å), so that a direct reaction via a four-center interaction (eq 20) could lead to formation of the organoalkali-metal compound. Ziegler thought that this was a fine idea ("Irgendeine gedankliche Schwierigkeit besteht tatsächlich nicht").



(20)

Since it had been shown, as noted above, that the reactions of alkyl and aryl halides with sodium proceed by way of an organosodium intermediate, it was surprising that no serious attempts had been made to find conditions under which stable (or relatively stable) solutions or, at least, suspensions of organosodium reagents could be prepared by the RX/Na reaction. This took some years, probably because most of the Grignard reagents, available after 1900, could be prepared quite readily from the organic halide in ether medium (in which they were soluble and stable). The Grignard reagents showed good nucleophilic reactivity and, as an added bonus, they were not strong bases, thus avoiding side reactions that might complicate their synthetic applications. Nevertheless, the Grignard reagents had some drawbacks, especially if they were to be used on a large scale: magnesium was relatively expensive compared to sodium and, while the reaction of magnesium worked well with alkyl and aryl bromides and iodides in diethyl ether, it proceeded much less well with the cheaper alkyl and aryl chlorides. Furthermore, Grignard chemistry was best carried out in the then available, volatile, and flammable diethyl ether, which additionally was dangerous because light-induced autoxidation formed explosive hydroperoxides. Thus, industrial, more than academic, researchers were interested in developing organosodium compounds as useful reagents for organic synthesis.

Scheme 3



III. Synthesis of Suspensions and Solutions of Organosodium and Potassium Reagents

A. Arylsodium and -potassium Reagents: Bockmühl and Ehrhart at I.G. Farben, 1931. It was Max Bockmühl and Gustav Ehrhart, chemists working in the laboratories of the I.G. Farbenindustrie A.G. in Frankfurt am Main-Höchst, Germany, who made the breakthrough when they found that phenylsodium could be prepared by reaction of sodium wire with chlorobenzene in benzene or benzene/ligroin solution in the absence of atmospheric moisture at temperatures of 15−30 °C. Such $C_6H_5Na/NaCl$ suspensions were stable, and the electrophile then could be added in a subsequent step. A series of German and British patents[51,52] and a U.S. patent[53] provided detailed experimental procedures for the preparation of phenylsodium, as well as for *p*- and *m*-tolylsodium and (*p*-(dimethylamino)phenyl)sodium, from the respective aryl chloride and for the reactions of these reagents with gaseous carbon dioxide, sulfur dioxide, aliphatic and aromatic nitriles, phenyl isocyanate, and 2-(dimethylamino)ethyl chloride to give the expected products. The product yields were reported as being good to excellent. For instance, in the reaction of phenylsodium with CO_2, yields of benzoic acid of 95−98% were recorded. Many of these reactions also were carried out using the in situ variation, in which phenylsodium was generated in the presence of the reactive electrophile. Here also, high product yields were obtained.

Ziegler, in a 1936 review on the significance of organoalkali-metal compounds in organic synthesis,[54] reported that the

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(48) Nef, J. U. *J. Am. Chem. Soc.* **1904**, *26*, 1549. For a rather harsh critical discussion of Nef's ideas, including his view of the Wurtz reaction, see ref 14c. The last sentence of Michael's paper is "The criticism of Nef's views may be left at this point, but it certainly does not seem unreasonable to expect from a chemist, who proposes to revolutionize the present theories, a more thorough knowledge of facts and a better acquaintance with these theories."

(49) Nef, J. U. *Liebigs Ann. Chem.* **1899**, *308*, 264 (footnote 42, p 291).

(50) Ziegler, K.; Schäfer, O. *Liebigs Ann. Chem.* **1930**, *479*, 150.

(51) Bockmühl, M.; Ehrhart, G. (a) Reichspatent 622 875, 12/7/1935. (b) Reichspatent 644 486, 5/4/1937. (c) Reichspatent 633 083, 7/27/1936. (d) Reichspatent 671 098, 1/31/1939. All four patent applications were made during 1931.

(52) (a) Brit. Patent 401,312, 10/30/1933. (b) Brit. Patent 378,743, 8/18/1932. (c) Brit. Patent 412,049, 6/21/1934.

(53) Bockmühl, M.; Ehrhart, G. U.S. Patent 2,012,372, 8/27/1935.

experiments in the I.G. Farbenindustrie patents were reproducible and described his observations of the C_6H_5Cl/Na reaction in great detail, describing the phenylsodium/NaCl mixture as a gray powder that was insoluble and had to be used as such in further reactions.

A detailed study of the preparation of phenylsodium was reported in 1954 by Nobis and Meermeier of the National Distillers Chemical Co., whose goal was a commercial synthesis of phenylacetic acid[55] and the preparation of organic derivatives of other metals and metalloids.[56] In this work, phenylsodium was generated using the reaction of a freshly prepared sodium dispersion[57] with chlorobenzene in toluene at 25−30 °C. The reaction was rapid, and C_6H_5Na yields were nearly quantitative.[58] Other solvents (benzene, octane, pentane) also could be used.[55] When a toluene suspension of phenylsodium was heated at reflux for 2 h, metalation of toluene by the organosodium reagent occurred and red benzylsodium, $C_6H_5CH_2Na$, was formed (eq 21), the subsequent reaction of which with gaseous CO_2 gave, after hydrolysis, the desired phenylacetic acid. Best results were obtained when the benzylsodium suspension was poured onto solid CO_2, but this was not practical in the plant. When the CO_2 reaction was carried out slowly above 30 °C, phenylacetic acid was obtained in only 35% yield and phenylmalonic acid was the major product (70% yield). A few years later, workers at the Pharmaceutic Research Laboratory of Farbwerke Hoechst A.G. developed a continuous process for the preparation of phenylsodium.[59]

$$C_6H_5Na + C_6H_5CH_3 \longrightarrow C_6H_5CH_2Na + C_6H_6 \qquad (21)$$

Phenylpotassium was prepared in 82% yield in similar manner by reaction of chlorobenzene with a potassium sand slurry in toluene by Gilman et al. in 1940.[60] Gau[61] used a potassium dispersion[62] with chlorobenzene at 20 °C in methylcyclohexane to prepare phenylpotassium in essentially quantitative yield. Like phenylsodium, the C_6H_5K/KCl suspension prepared in this manner was useful for the metalation of methyl-substituted benzenes.

A most intriguing discovery—that phenylsodium, which had been found to metalate diethyl ether and be destroyed in the process, becomes soluble in and stabilized toward reaction with diethyl ether by the presence of 1 molar equiv of phenyllithium—was reported by Georg Wittig, Ludwig, and Polster in 1955.[63] To prepare this complex, a solution of 1 molar equiv of phenyllithium in diethyl ether was shaken in a Schlenk tube under nitrogen with $^1/_2$ molar equiv of diphenylmercury and an excess of sodium wire. A rapid reaction of the $(C_6H_5)_2Hg$ with the sodium produced phenylsodium and sodium amalgam.[64] After filtration of the reaction mixture and concentration of the filtrate, large crystals of the monoetherate of the 1:1 adduct, $C_6H_5Li{\cdot}C_6H_5Na{\cdot}Et_2O$, formed. This complex, which Wittig formulated as an "ate" complex, $Na[(C_6H_5)_2Li]$, is soluble in diethyl ether, and such solutions are stable for several days at room temperature. The $Na[(C_6H_5)_2Li]$ is much more reactive than phenyllithium alone, and the phenylsodium component reacted selectively and rapidly with *n*-butyl iodide and with triphenylmethane before the phenyllithium part began to react. In further work, Wittig and co-workers made the astounding discovery that phenyllithium could stabilize up to 24 molar equiv of phenylsodium, giving an insoluble solid mass that did not attack diethyl ether. Wittig's explanation for this remarkable observation was that the ether-soluble $Na[(C_6H_5)_2Li]$ with its "latent Na^+ ion" that was present in the large excess of phenylsodium had what he termed "a salting out effect", making the resulting insoluble mass unavailable for reaction with the ether. However, such $C_6H_5Li{\cdot}nC_6H_5Na$ reaction masses nevertheless reacted with benzophenone to give, after hydrolytic workup, triphenylcarbinol in ∼90% yield based on the PhNa content.

The use of the $(C_6H_5)_2Hg$/Na reaction to prepare C_6H_5Na makes this chemistry less attractive, but the authors noted that the 1:1 complex also could be prepared by mixing an ether solution of phenyllithium with a benzene suspension of phenylsodium that had been prepared by the I.G. Farben procedure.

Wittig and Bickelhaupt[65] explored complexes of this type more broadly and found that such $RLi{\cdot}RM$ (M = alkali metal) complexes were not always stable. The *n*-butyl complex, $(C_4H_9Li{\cdot}C_4H_9Na)$, was stable only for a short time and could not be isolated. The equilibrium between $Na[(CH_3)_2Li]$ and its components greatly favored the latter, so that the ether solution contained methyllithium and only very little methylsodium. The solid phase, which contained the methylsodium, was stable toward diethyl ether. It must have contained some $Na[(CH_3)_2Li]$, Wittig concluded, since lithium-free methylsodium did attack ether. $K[(C_6H_5)_2Li]$ and $Cs[(C_6H_5)_2Li]$ also were prepared, but these were very insoluble, in contrast to $Na[(C_6H_5)_2Li]$. An alternate constitution of the 1:1 C_6H_5Na/C_6H_5Li complex in terms of phenyl bridging between the two metal atoms was considered, but the "ate" complex formulation was preferred. These presumed "ate" complexes remained mysterious curiosities for 30 years, receiving no further attention until Schümann and Erwin Weiss were able to prepare, crystallize, and structurally characterize by X-ray crystallography a yellow, pyrophoric complex of composition $3C_6H_5Na{\cdot}C_6H_5Li{\cdot}3(CH_3)_2NCH_2CH_2N(CH_3)_2$ ($(CH_3)_2NCH_2CH_2N(CH_3)_2$ = TMEDA) (Figure 6).[66] This compound is indeed an "ate" complex, $3[Na(TMEDA)]^+[(C_6H_5)_4Li]^{3-}$. The lithium atom is pseudotetrahedrally coordinated by four phenyl groups. TMEDA molecules are chelate-bonded to each sodium ion, which in turn bonds to the ipso carbon atom of two phenyl

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(54) Ziegler, K. *Angew. Chem.* **1936**, *40*, 455.

(55) Nobis, J. F.; Moormeier, L. F. *Ind. Eng. Chem.* **1954**, *46*, 539.

(56) Nobis, J. F.; Moormeier, L. F.; Robinson, R. E. In *Metal-Organic Compounds*; Advances in Chemistry Series 23; American Chemical Society: Washington, DC, 1959; pp 63−68.

(57) Frampton, O.; Nobis, J. F. *Ind. Eng. Chem.* **1953**, *45*, 404.

(58) The chlorobenzene/sodium reaction could be tricky, as the directions for carrying it out as given in ref 55 indicate: "Initiation of reaction usually occurs 1 to 5 min after addition of the first 10 to 25 ml. of the chlorobenzene-toluene mixture and is characterized by an increasingly rapid temperature rise, plus the appearance of the black phenylsodium particles. In no case should additional chlorobenzene be added until the initial exothermic reaction has occurred and been brought under control. As the temperature approaches 30° to 40°C., a cooling bath (around −20°C.) should be raised around the reaction flask. The internal temperature should never be allowed to exceed 40°C. In cases where no reaction is observed for 20 min, 2 to 4 ml. of amyl alcohol may be added to initiate reaction. Cooling is needed immediately after this addition, since the reaction may start rapidly. If, inadvertently, large amounts of unreacted chlorobenzene and sodium are brought together without reaction, the flask should be cooled rapidly to a low temperature. The reaction mixture may be then rendered comparatively safe by dilution with several volumes of mineral oil or kerosene and the resulting mixture should be taken promptly to a burning area for disposal."

(59) Ruschig, H.; Fugmann, R.; Meixner, W. *Angew. Chem.* **1958**, *70*, 71.

(60) Gilman, H.; Pacevitz, H. A.; Baine, O. *J. Am. Chem. Soc.* **1940**, *62*, 1514.

(61) Gau, G. *J. Organomet. Chem.* **1976**, *121*, 1.

(62) Pratt, M. W. T.; Helsby, R. *Nature* **1959**, *184*, 1694.

(63) Wittig, G.; Ludwig, R.; Polster, R. *Chem. Ber.* **1955**, *88*, 264.

(64) This synthesis of organoalkali-metal compounds by the metal displacement reaction will be considered in detail in part 2.

(65) Wittig, G.; Bickelhaupt, F. *Chem. Ber.* **1958**, *91*, 865.

(66) Schümann, U.; Weiss, E. *Angew. Chem.* **1988**, *100*, 573.

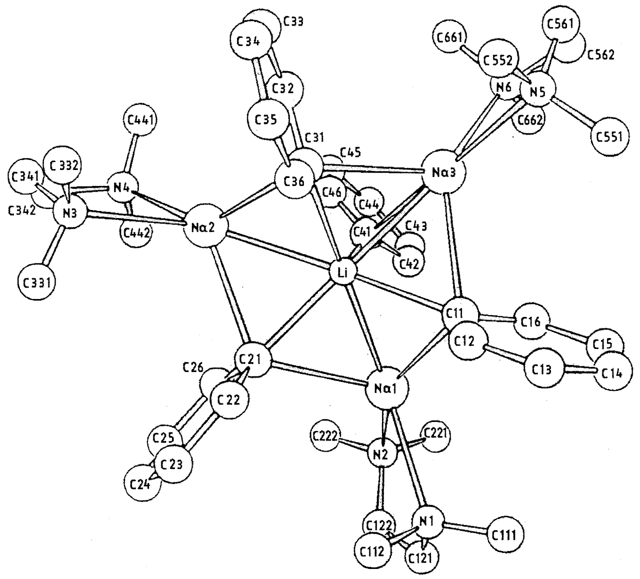


Figure 6. Molecular structure of $3C_6H_5Na{\cdot}C_6H_5Li{\cdot}3(CH_3)_2NCH_2CH_2N(CH_3)_2$ (from *Angew. Chem.* **1988**, *100*, 573; reproduced by permission of Wiley/VCH and Professor Erwin Weiss).

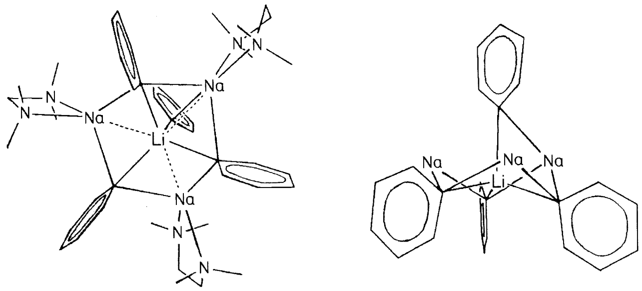
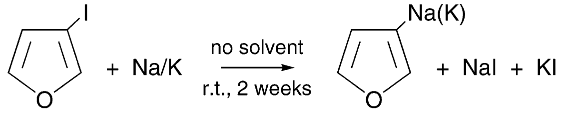


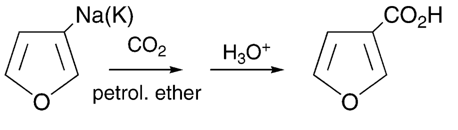
Figure 7. Line drawing showing the sodium, lithium, phenyl bonding in $3C_6H_5Na{\cdot}C_6H_5Li{\cdot}3(CH_3)_2NCH_2CH_2N(CH_3)_2$ (from *Angew. Chem.* **1988**, *100*, 573; reproduced by permission of Wiley/VCH and Professor Erwin Weiss).

groups, as the line drawing in Figure 7 shows. Molecular orbital calculations indicated that the bonding in this complex is mainly ionic, with the negative charge of the anion delocalized in the phenyl groups. A crystalline 1:1 complex could not be isolated.

In what was claimed to be a special case, the preparation of stable samples of 3-furylsodium and -potassium was reported by Gilman and Wright in 1933.[67] The reaction of 3-iodofuran with sodium and with potassium, using no solvent, at room temperature was carried out over a period of 2 weeks (eq 22).



(22)



(23)

Subsequent reaction with CO_2 and hydrolytic workup followed (eq 23). The yields of 3-furoic acid were low, but that the reaction worked in this two-step procedure at all was claimed to be due to the fact that the C−I bond of 3-iodofuran is very unreactive. However, in view of the stability of suspensions of arylsodium compounds in hydrocarbon media, this may not be a special case at all.

Figure 8. Avery A. Morton (courtesy MIT Museum).

B. Alkylsodium and -potassium Reagents in Hydrocarbon Suspension: Avery A. Morton at the Massachusetts Institute of Technology, 1936. The preparation of stable solutions or suspensions of alkylsodium and -potassium reagents was a different matter. In an example in a Bockmühl/Ehrhart patent[52b] the reaction of 11.5 g of sodium wire with 23 g of *n*-butyl chloride in 100 cm^3 of benzene at 0−5 °C under nitrogen is described. After nearly all of the sodium had been consumed, 24 g of $(C_2H_5)_2CHC{\equiv}N$ was added at 0−10 °C, followed by 19 g of allyl chloride after 1 h at room temperature. After a 10 min reflux period, hydrolytic workup, it was said, gave the expected $(C_2H_5)_2(CH_2{=}CHCH_2)CC{\equiv}N$. However, in contrast to all the other examples in refs 51−53, the amount of product obtained was not reported. One is led to suspect that the product yields and the initial *n*-butylsodium yields were rather low.

Ziegler in his review[54] stated, “It is not possible to convert aliphatic chlorine compounds to sodium alkyls in an analogous manner,” i.e., by the procedure which was successful in the case of aryl chlorides. However, he went on to say that this was not a problem, since it had been discovered in his laboratory that alkyl- and aryllithium compounds could be readily prepared by reaction of lithium metal with organic halides[68] (vide infra). Thus, the problem of preparing stable alkylsodium compounds, while interesting and challenging, was not pressing.

It was Avery A. Morton[69] (Figure 8) and his students at the Massachusetts Institute of Technology who, in the same year that Ziegler expressed his doubts, found the reaction conditions under which *n*-alkyl halides would react with sodium and

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(67) Gilman, H.; Wright, G. F. *J. Am. Chem. Soc.* **1933**, *55*, 2893.

(68) Ziegler, K.; Colonius, H. *Liebigs Ann. Chem.* **1930**, *476*, 135.

potassium in alkane medium to give reasonably stable suspensions of *n*-alkylsodium (and -potassium) compounds in high yield with only minimal formation of Wurtz coupling and decomposition products. The experiments leading to this discovery had been meant to provide some understanding of Morton's earlier finding that the alkyl chloride/sodium/CO_2 one-pot procedure gave not only the expected carboxylic acid but also the unexpected alkylmalonic acid.[45] Morton and Heckenbleikner[70] investigated the factors responsible for the formation of the alkylmalonic acid, preparing in this case the needed (in situ) alkylsodium intermediate by the well-known reaction of a dialkylmercurial with sodium sand (a reaction that will be discussed in Part 2 of this essay). The mercury reagents, di-*n*-amyl- and diethylmercury, were prepared by the action of *n*-amyl chloride and ethyl iodide, respectively, on 1−2% sodium amalgam. Two significant observations were made during the course of this work. (1) It was found that the reaction of ethyl iodide and *n*-amyl chloride with sodium amalgam in petroleum ether, when carried out at 35 °C, gave higher R_2Hg yields than when it had been carried out by earlier workers at higher temperatures. (2) The total yield of acids obtained after reaction with CO_2 decreased as the temperature at which the R_2Hg/Na reaction was carried out was increased. These observations suggested to Morton "that a Wurtz synthesis might be stopped at this intermediate point (i.e., at the completion of the RNa generation) if the reaction were carried out at low temperatures in the presence of an excess of sodium."[71] The first experiments showed that this was indeed the case. In an experiment carried out under nitrogen, 20 mL of *n*-amyl chloride in 20 mL of solvent (ligroin or pentane) was added to a suspension of 10 g of sodium sand in 50 mL of the solvent, with stirring at 0−22 °C during 75 min. (Stirring was continued while the low temperature was maintained, with a cold bath if necessary, for 0.5−3 h.) Subsequently, the reaction mixture was treated with gaseous carbon dioxide. Acid hydrolysis gave a mixture of caproic and *n*-butylmalonic acids. The best total acid yield was 57%. No attempts were made to isolate and quantify the Wurtz coupling and decomposition products (*n*-decane, pentane, 1-pentene). With time and effort, Morton and his students considerably improved the procedure. Decisive for obtaining high (80−90%) yields of amylsodium was the efficient agitation of the heterogeneous reaction mixture. Accumulation of the blue (dark) coating on the sodium had to be avoided so that fresh sodium surface always was available for attack by amyl chloride. To accomplish this, special creased flasks ("Morton flasks") and high-speed stirring assemblies were developed which ensured efficient agitation of the reaction mixture.[72] Figure 9 shows a drawing of one such creased flask, and Figure 10 shows such an apparatus for high-speed stirring.[72c]

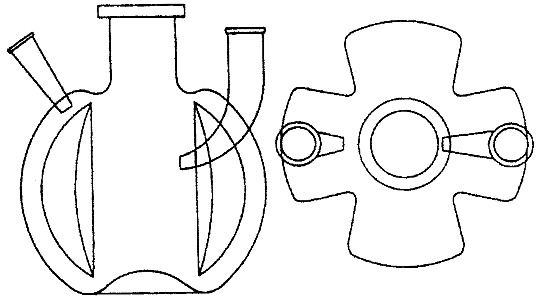

Figure 9. A Morton creased flask (From *Ind. Eng. Chem., Anal. Ed.* **1942**, *14*, 734, American Chemical Society).

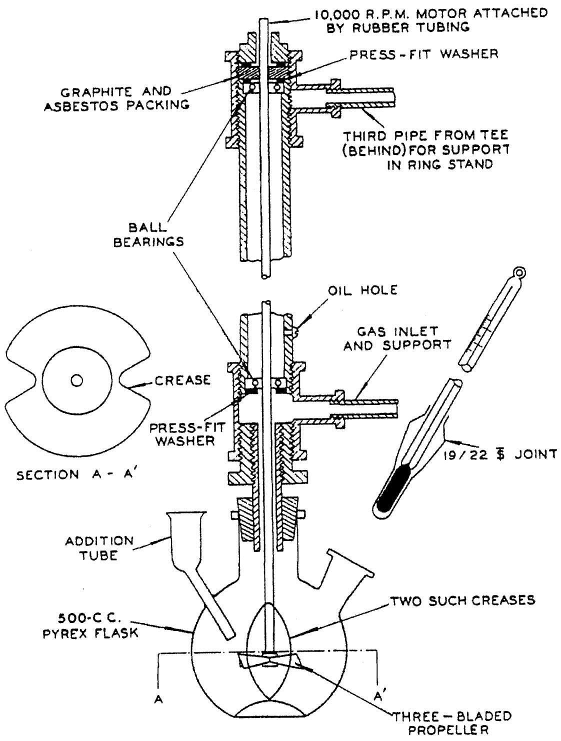

Figure 10. Morton high speed stirring apparatus (From *Ind. Eng. Chem., Anal. Ed.* **1942**, *14*, 734, American Chemical Society).

In the improved procedure using a creased flask and high-speed stirring,[73] the sodium sand was prepared by stirring the sodium in decane at 110−130 °C for 1 min at 10 000 rpm under nitrogen. The decane was replaced by pentane. Dropwise addition of 0.5 mol of purified amyl chloride to 1 mol of sodium sand in pentane at −10 °C (1 L Morton flask, high-speed stirring) followed. After the mixture had been stirred for 1−2 h, it was forced by nitrogen pressure onto solid carbon dioxide.[74]

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(69) Avery A. Morton (1893−1983). b. St. Lawrence, South Dakota. A. B. Cotner College in Nebraska. Graduate studies (University of Chicago, Harvard) interrupted by service in the U.S. Marine Corps during World War I. Studies continued at MIT, Ph.D. 1924 (research supervisor James F. Norris). Appointed to MIT chemistry faculty, remaining an active member until his retirement in 1957. Research in organic and organoalkali-metal chemistry: synthesis, reactivity, applications in catalysis of 1,3-diene polymerization (Alfin catalyst). Morton championed a very controversial view that alkylsodium compound reactions were electrophilic in nature, stating in his 1964 book *Solid Organoalkali Metal Reagents* "that cations which bind organic anions into insoluble aggregates must be the more powerful half of ion-pairs; their bonding power must be satisfied before an anion can function. In short, an organoalkali metal reagent has electrophilic character before nucleophilic activity." (See also: Morton, A. A. *Chem. Rev.* **1944**, *35*, 1−49.) This idea went against the then (and now) commonly accepted view of organoalkali-metal compounds as nucleophilic reagents. Morton defended his ideas tenaciously and aggressively, but, as he admitted in his book, "Chemists have not taken kindly to the new view." Biographical sketch: Claff, C. F., Jr.; Atkinson, E. R. *The Nucleus* **1983** (Oct), 6.

(70) Morton, A. A.; Heckenbleikner, I. *J. Am. Chem. Soc.* **1936**, *58*, 1024.

(71) Morton, A. A.; Heckenbleikner, I. *J. Am. Chem. Soc.* **1936**, *58*, 1697.

(72) (a) Morton, A. A. *Ind. Eng. Chem., Anal. Ed.* **1939**, *11*, 170. (b) Morton, A. A.; Knott, D. M. *Ind. Eng. Chem., Anal. Ed.* **1941**, *13*, 649. (c) Morton, A. A.; Darling, B.; Davidson, J. *Ind. Eng. Chem., Anal. Ed.* **1942**, *14*, 734. (d) Morton, A. A.; Redman, L. M. *Ind. Eng. Chem., Anal. Ed.* **1948**, *40*, 1190.

(73) As described, for instance, in: Morton, A. A.; Marsh, F. D.; Coombs, R. D.; Lyons, A. L.; Penner, S. E.; Ramsden, H. E.; Baker, V. B.; Little, E. L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1950**, *72*, 3785. For a study by microscope of the development of the surface of the sodium particles as the *n*-$C_5H_{11}Cl$ + Na reaction progressed, see: Morton, A. A.; Davidson, J. B.; Newey, H. A. *J. Am. Chem. Soc.* **1942**, *64*, 2240. Secondary alkyl halides appear to be much less reactive because, in contrast to the case of *n*-amyl chloride, the coating on the surface of the sodium particles is reported as "hard and impenetrable".

The yield of caproic acid obtained from the resulting sodium caproate provided a measure of the amylsodium yield.

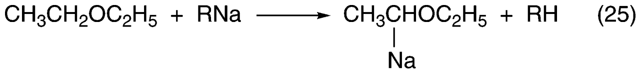
This procedure was reported to work well in the preparation of amylpotassium by reaction of amyl chloride with potassium sand, but the yield, as indicated by the yield of caproic acid after reaction with dry ice, was considerably lower.[75] Others have reported the utility of this alkylpotassium synthesis.[76] However, later work by R. A. Finnegan[77] claimed that the preparation of alkylpotassium compounds (n-C_3H_7K, n-C_4H_9K, n-$C_5H_{11}K$) by the standard n-$C_5H_{11}Na$ procedure was much more complex. Evaporation of the reaction mixtures at reduced pressure and then hydrolysis of the residue and analysis of the resulting volatiles by GC appeared to indicate that predominantly unsaturated organopotassium compounds had been present. The hydrolysis gases contained 55−85% olefins and a small amount of hydrogen in addition to the expected alkane. Several pathways to unsaturated organopotassium compounds were suggested, but these had no experimental support.

The reactions of n-propyl and n-butyl chloride with sodium sand as a preparation of the respective alkylsodium reagents also were investigated by Morton, but not using the optimum procedure. These RCl/Na reactions were sluggish, and the butyric and valeric acid yields obtained on carbonation were not high.[78] Higher alkylsodium compounds also were prepared: n-$C_8H_{17}Na$ and n-$C_{10}H_{21}Na$[79] and n-$C_{12}H_{25}Na$ and n-$C_{16}H_{33}Na$.[76e] Also prepared was n-$C_{12}H_{25}K$.[76e]

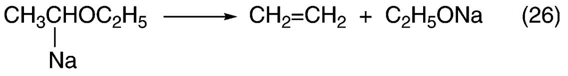
With fairly stable suspensions of alkyl- and arylsodium compounds available, the mechanism of the second step of the Wurtz synthesis could be probed. R. L. Letsinger, one of Morton's students, who had become a faculty member at Northwestern University, studied the reactions of benzylsodium with optically active 2-bromooctane and 2-bromobutane.[80] The expected hydrocarbons, $C_6H_5CH_2CH(CH_3)C_6H_{13}$ and $C_6H_5CH_2CH(CH_3)C_2H_5$, respectively, were obtained in 69% and 80−81% yield. In the reaction with 2-bromobutane, a major portion of the optical reactivity was retained in the hydrocarbon product. It was concluded that an inversion of configuration probably had occurred. When n-butylsodium was used, complete racemization resulted. Extensive racemization also was observed in the reaction of ethylsodium with (−)-2-bromooctane.[81] Since secondary and tertiary alkylsodium compounds are unstable at room temperature with respect to β-elimination of sodium hydride, such studies with optically active alkylsodium reagents were not possible. Therefore, a clear answer concerning the mechanism of the second step of the Wurtz reaction was not obtained in this work. Later work of Garst and Hart[82] provided evidence against an S_N2 mechanism. It was found that the reaction of neopentyl iodide with a sodium mirror in 1,2-dimethoxyethane (DME) at 22 °C gave an 80% yield of the expected hydrocarbon dimer (eq 24). Since bimolecular nucleophilic S_N2-type displacement of halide ion from a neopentyl halide is extremely slow because of the steric hindrance to backside attack at the carbon atom bearing the halogen substituent, an S_N2 process for the reaction in eq 24 was considered to be highly unlikely, and a radical process would be a more likely mechanism. In another experiment, equimolar amounts of neopentyl iodide and n-amyl iodide were allowed to react with a sodium mirror in DME. All three possible products of C−C coupling were formed: n-$C_{10}H_{22}$, $(CH_3)_3CCH_2C_5H_{11}$-n, and $(CH_3)_3CCH_2CH_2C(CH_3)_3$ in a 1.2:1.7:1.1 ratio, which is close to the 1:2:1 statistical ratio. Such a lack of selectivity also was deemed consistent with the operation of a radical mechanism for the second step. It may be noted that neopentylsodium has been prepared in 60−75% yield in pentane by the reaction of neopentyl chloride with a sodium dispersion in the cold.[83]

$$2\,(CH_3)_3CCH_2I + 2\,Na \longrightarrow (CH_3)_3CCH_2CH_2C(CH_3)_3 + 2\,NaI \tag{24}$$

The alkylsodium reagents are strong bases as well as highly reactive nucleophiles. Their ability to deprotonate many classes of organic compounds can be useful as well as detrimental. Thus, they cannot be prepared and used in diethyl ether medium because they deprotonate the carbon atom α to the oxygen atom, which results in fragmentation of the ether (eqs 25 and 26).



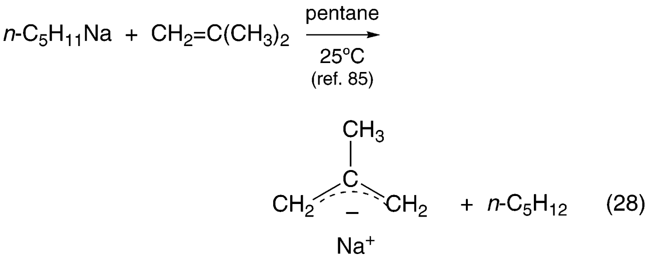
$$CH_3CH_2OC_2H_5 + RNa \longrightarrow \underset{\displaystyle Na}{CH_3CHOC_2H_5} + RH \tag{25}$$



$$\underset{\displaystyle Na}{CH_3CHOC_2H_5} \longrightarrow CH_2{=}CH_2 + C_2H_5ONa \tag{26}$$

Useful applications of the strong basic properties of the alkylsodium and -potassium reagents are found in their use in the synthesis of other organoalkali-metal compounds via deprotonation (e.g., eqs 27 and 28).

$$n\text{-}C_5H_{11}K + C_6H_6 \xrightarrow[\substack{-10°C\\ \text{(ref. 84)}}]{\text{heptane}} C_6H_5K + n\text{-}C_5H_{12} \tag{27}$$



$$n\text{-}C_5H_{11}Na + CH_2{=}C(CH_3)_2 \xrightarrow[\substack{25°C\\ \text{(ref. 85)}}]{\text{pentane}} CH_2{=}C(CH_3){-}CH_2^-\,Na^+ + n\text{-}C_5H_{12} \tag{28}$$

In 1946, Morton published the first of a series of papers on the use of n-amylsodium and other organosodium reagents as initiators of the polymerization of 1,3-dienes.[86,87] Initially, information was sought on intermediates formed in the first stages of the RNa/diene reaction by adding the diene slowly to a very large excess of organosodium reagent. The effect of

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(74) Such reaction with solid rather than with gaseous CO_2 reduced the formation of alkylmalonic acids to a few percent: Gilman, H.; Pacevitz, H. A. *J. Am. Chem. Soc.* **1940**, *62*, 1301.

(75) Morton, A. A.; Brown, M. L.; Holden, M. E. T.; Letsinger, R. L.; Magat, E. E. *J. Am. Chem. Soc.* **1945**, *67*, 2224.

(76) (a) Benkeser, R. A.; Liston, T. V. *J. Am. Chem. Soc.* **1960**, *82*, 3221. (b) Morton, A. A.; Lanpher, E. J. *J. Org. Chem.* **1958**, *23*, 1636, 1639. (c) Morton, A. A.; Wohlers, H. C. *J. Am. Chem. Soc.* **1947**, *69*, 167. (d) Morton, A. A.; Letsinger, R. L. *J. Am. Chem. Soc.* **1947**, *69*, 172. (e) Meals, R. N. *J. Org. Chem.* **1944**, *9*, 211.

(77) Finnegan, R. A. (a) *Tetrahedron Lett.* **1962**, 1303. (b) *Tetrahedron Lett.* **1963**, 851. (c) *Trans. N.Y. Acad. Sci., Ser. II* **1965**, *27*, 730. Finnegan (1932−1986) had obtained his Ph.D. at MIT, working with Morton.

(78) Morton, A. A.; Richardson, G. M.; Hallowell, A. T. *J. Am. Chem. Soc.* **1941**, *63*, 327.

(79) Morton, A. A.; Davidson, J. B.; Best, R. J. *J. Am. Chem. Soc.* **1942**, *64*, 2239.

(80) Letsinger, R. L. *J. Am. Chem. Soc.* **1948**, *70*, 406.

(81) Brink, N.; Lane, J.; Wallis, E. *J. Am. Chem. Soc.* **1943**, *65*, 943.

(82) Garst, J. F.; Hart, P. W. *J. Chem. Soc., Chem. Commun.* **1975**, 215.

(83) Finnegan, R. A. *Chem. Ind. (London)* **1962**, 895.

(84) Morton, A. A.; Lanpher, E. J. *J. Org. Chem.* **1958**, *23*, 1636.

(85) Morton, A. A.; Brown, M. L.; Holden, M. E. T.; Letsinger, R. L.; Magat, E. E. *J. Am. Chem. Soc.* **1945**, *67*, 2224.

(86) Morton, A. A.; Patterson, G. H.; Donovan, J. J.; Little, E. L. *J. Am. Chem. Soc.* **1946**, *68*, 93.

various additives was examined. During the course of these studies, a remarkably effective catalyst system was discovered serendipitously, as Morton reported in 1947:[88]

> The catalyst was discovered by accident in the course of our study on the addition of organosodium compounds to dienes. The effect of diisopropyl ether was being tested in the same way as the effect of a tertiary amine on the addition of amylsodium to butadiene had previously been tested. The reaction took, however, an entirely different course and high polymers resulted in spite of the fact that the diene was added drop by drop to a very large excess of the organoalkali metal reagent. A similar result was obtained with isoprene, although the polymer was stickier than that obtained from butadiene.
>
> The explanation of this unusual effect on the two dienes lay in the formation of two products, sodium isopropoxide and allylsodium, derived from the ether and amylsodium according to the equations

$$C_5H_{11}Na + (CH_3)_2CHOCH(CH_3)_2 \longrightarrow (CH_3)_2CHONa + C_5H_{12} + CH_2{=}CHCH_3 \quad (1)$$

$$C_5H_{11}Na + CH_2{=}CHCH_3 \longrightarrow CH_2CHCH_2Na + C_5H_{12} \quad (2)$$

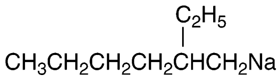
As Morton said, “a rubbler-like polymer was obtained only when sodium isopropoxide and allylsodium were both present and no polymer was obtained if either one was absent.” Thus, the catalyst suspension contained allylsodium, sodium isopropoxide, and sodium chloride (from the preparation of amylsodium from amyl chloride). In further work, isopropyl alcohol was used in place of the ether to generate sodium isopropoxide. This catalyst system was dubbed the “Alfin catalyst” (the “al” from *al*cohol; the “fin” from ole*fin*). Further studies showed the lower $RCH_2CH{=}CH_2$ olefins and the lower $R(CH_3)CHOH$ alcohols to provide the most effective Alfin catalysts. Actually, these catalysts were too effective. As Morton said:[89] “The two additional compounds (i.e., isopropyl alcohol and propene) change a slow-acting process which can be interrupted at any stage of chain growth into one which cannot be halted until molecules of around 10^{17} or more in size have formed.” The nature of the Alfin catalyst system was never completely clarified and remained the subject of conjecture, which is not surprising, considering that it was a highly reactive, heterogeneous system. The polybutadiene that was produced using the Alfin catalyst was very difficult to process. It did not soften on the mill the way natural rubber does;[90] therefore, it never was commercialized in the USA.

The polymerization of styrene was 6−10 times faster when the Alfin catalyst was used than with *n*-amylsodium alone, and the Alfin polystyrene had a higher molecular weight.[91] A commercial process was not developed.

Sodium isopropoxide and also potassium isopropoxide were found to have an activating effect on the general reactivity of alkylsodium reagents. They made the already very basic *n*-amylsodium a superbase. Sodium isopropoxide not only accelerated the metalation of olefins by *n*-amylsodium[92] but also made possible the direct metalation of ethylene to vinylsodium.[93] Sodium and potassium alkoxides also facilitated the mono- and dimetalation of benzene, thiophene, and *tert*-butyl-, *sec*-butyl-, and isopropylbenzene.[94] The potassium alkoxide/*n*-$C_5H_{11}Na$ combinations gave the higher metalation product yields. Also, Morton and Eisenmann found that the metalation of alkylbenzenes, RC_6H_5 (R = Me_2CH, Me_3C, *n*-C_4H_9), was considerably accelerated when a ca. 2:1 molar mixture of *n*-amylsodium and sodium 2-methyl-2-heptoxide was used rather than *n*-amylsodium alone.[95]

The presence of sodium and, especially, potassium alkoxides increased the coupling product yields obtained in some Wurtz reactions.[96] Thus, the reaction of *n*-amylsodium with *n*-amyl chloride in toluene, which generated benzylsodium as the active reagent by initial rapid metalation of toluene, gave *n*-hexylbenzene (16%) and *n*-decane (25%). When this reaction was carried out in the presence of sodium 2-methyl-2-heptoxide, these yields were 55% and 7%, respectively. When potassium isopropoxide was the additive, the yield of *n*-hexylbenzene was 76% and no decane was produced. As Morton said, “this increase can be attributed to an improved conversion of amylsodium to benzylsodium”: i.e., here also the superbase reactivity of the *n*-$C_5H_{11}Na$/ROM systems is involved, although the alkoxide also may be involved in the coupling reaction.

An important, more recent advance in the direct preparation of alkylsodium compounds by the reaction of alkyl chlorides with sodium was the finding, claimed in a 1981 European patent by Eidt and Malpass of Texas Alkyls, Inc., in Deer Park, TX, that (2-ethylhexyl)sodium (**13**) is soluble in hydrocarbon medium.[97] In the one example described in detail in the patent, 0.5 mol of 2-ethylhexyl chloride (49.4 wt % solution in isopentane) was added during the course of 3 h to a suspension of 1.1 mol of sodium powder (particle diameter ∼10 μm) in 447 g of isopentane in a 1 L creased flask with vigorous stirring under a purified nitrogen atmosphere. An exothermic reaction ensued, which was controlled by external cooling in the range of 18−27 °C. The resulting reaction mixture contained a purple-black solid. This was filtered at 10 °C under nitrogen pressure to give a clear, pale orange filtrate. Acid−base titration of a sample of the latter indicated that (2-ethylhexyl)sodium was present in 79% yield. The purple-black solid presumably contained the hydrocarbon-insoluble sodium chloride and the excess of sodium. Unfortunately, the patent provided no further details about the presumed (2-ethylhexyl)sodium: its thermal



$CH_3CH_2CH_2CH_2CH(C_2H_5)CH_2Na$

13

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(87) That an organoalkali-metal compound can initiate the polymerization of 1,3-dienes and styrene was discovered by Ziegler, who used cumylpotassium: (a) Ziegler, K.; Crössmann, F.; Kleiner, H.; Schäfer, O. *Liebigs Ann. Chem.* **1929**, *473*, 1 (p 31). (b) Ziegler, K.; Bähr, K. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 253. (c) Ziegler, K.; Kleiner, H. *Liebigs Ann. Chem.* **1929**, *473*, 57.

(88) Morton, A. A.; Magat, E. E.; Letsinger, R. L. *J. Am. Chem. Soc.* **1947**, *69*, 950.

(89) Morton, A. A. In *Advances in Catalysis*; Farkas, A., Ed.; Academic Press: New York, 1957; Vol. IX, p 743.

(90) Morton, A. A. *Ind. Eng. Chem.* **1950**, *42*, 1488.

(91) Morton, A. A.; Grovenstein, E. *J. Am. Chem. Soc.* **1952**, *74*, 5434.

(92) Morton, A. A.; Holden, M. E. T. *J. Am. Chem. Soc.* **1947**, *69*, 1675.

(93) Morton, A. A.; Marsh, F. D.; Coombs, R. D.; Lyons, A. L.; Penner, S. E.; Ramsden, H. E.; Baker, V. B.; Little, E. L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1950**, *72*, 3785. Parsons et al., who used this procedure with some modification, reported vinylsodium yields of 43-45%: Parsons, T. D.; Silverman, M. B.; Ritter, D. M. *J. Am. Chem. Soc.* **1957**, *79*, 5091.

(94) (a) Morton, A. A.; Claff, C. E., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 4935. (b) Morton, A. A.; Claff, C. E., Jr.; Collins, F. W. *J. Org. Chem.* **1955**, *20*, 428.

(95) Morton, A. A.; Eisenmann, J. L. *J. Org. Chem.* **1958**, *23*, 1469.

(96) Morton, A. A.; Brachman, A. E. *J. Am. Chem. Soc.* **1951**, *73*, 4363.

(97) Eidt, S. H.; Malpass, D. B. Eur. Patent EP 0041306, Dec 9, 1981; *Chem. Abstr.* **1981**, *96*, 123007.

stability, its solution molecular weight, and its reactions with electrophiles and with Lewis acids and bases. It was only in 1995 that Russian workers followed up on this interesting alkylsodium compound.[98,99] Solutions of (2-ethylhexyl)sodium in heptane, prepared by the reaction of the chloride with a 10–25 μm sodium dispersion, were found to be quite stable at room temperature, decomposing only during the course of several weeks to give a dark red color at the top of the solution and a precipitate.[98] Examination of the resulting supernatant solution by proton NMR spectroscopy showed signals due to allylic and olefinic protons. Thus, decomposition by β-elimination to olefin and sodium hydride seemed indicated. Heating the heptane solution to 70 °C accelerated this decomposition. An intriguing observation was made when the 2-ethylhexyl chloride/Na reaction was carried out using sodium in the form of purified balls instead of a dispersion. In this case, elemental analysis showed sodium and ionic chloride to be present in a $\sim$2:1 ratio in the heptane solution, presumably in the form of a soluble RNa/NaCl complex. This species and the essentially Cl-free (2-ethylhexyl)sodium/heptane solution showed dramatically different ^{21}Na NMR spectra: the latter a very broad signal centered at δ 27 ppm and the former a sharp singlet at δ 8.1 ppm (vs external 10% aqueous NaCl).[99] (2-Ethylhexyl)sodium was used as an initiator in the anionic polymerization of 1,3-butadiene and isoprene in heptane at 30 °C.[98] While the preparation of (2-ethylhexyl)sodium as a hydrocarbon-soluble species certainly was interesting, a different, more general preparation of homogeneous hydrocarbon solutions of alkylsodium and -potassium reagents had been discovered 15 years earlier, as will be described in Part 2 of this essay.

IV. Development of the Organolithium Reagents: Karl Ziegler, Georg Wittig, and Henry Gilman

One might have expected a priori that the organic compounds of lithium would be different in their physical and chemical properties and structures from those of their more electropositive congeners, Na, K, Rb, and Cs. The small size of Li$^+$ compared to those of the other alkali-metal cations results in a much greater polarizing power for Li$^+$: i.e., a greater ionic potential, $\phi = Z/r$, where Z is the ionic charge (+1 in the case of the alkali metals) and r is the ionic radius in Å units.[100] The respective ionic potentials are as follows, for the metals with which we are concerned: Li$^+$, 1.66; Na$^+$, 1.04; K$^+$, 0.76. Thus, one would expect organolithium compounds to be more covalent (less ionic) than those of sodium and potassium and much more soluble in organic solvents. This turned out to be the case. Although organolithium compounds are less reactive than the analogous organic compounds of sodium and potassium, they are soluble in organic solvents (the alkyllithiums, with the exception of methyllithium, in hydrocarbons, the aryllithiums in ethers), less prone (with some exceptions) to attack diethyl ether, and, in general, easier to handle. As a result, they, together with the analogous Grignard reagents, have become the reagents of choice for use in organic and organometallic synthesis when organometallic nucleophiles are needed.

It was three giants of 20th century organometallic chemistry who led the way in the development of organolithium chemistry: Karl Ziegler[101] (Figure 11), Georg Wittig[102] (Figure 12), and Henry Gilman[103] (Figure 13). We have already encountered their names in the foregoing discussion of organosodium and -potassium compounds, and all three contributed broadly to organometallic chemistry.

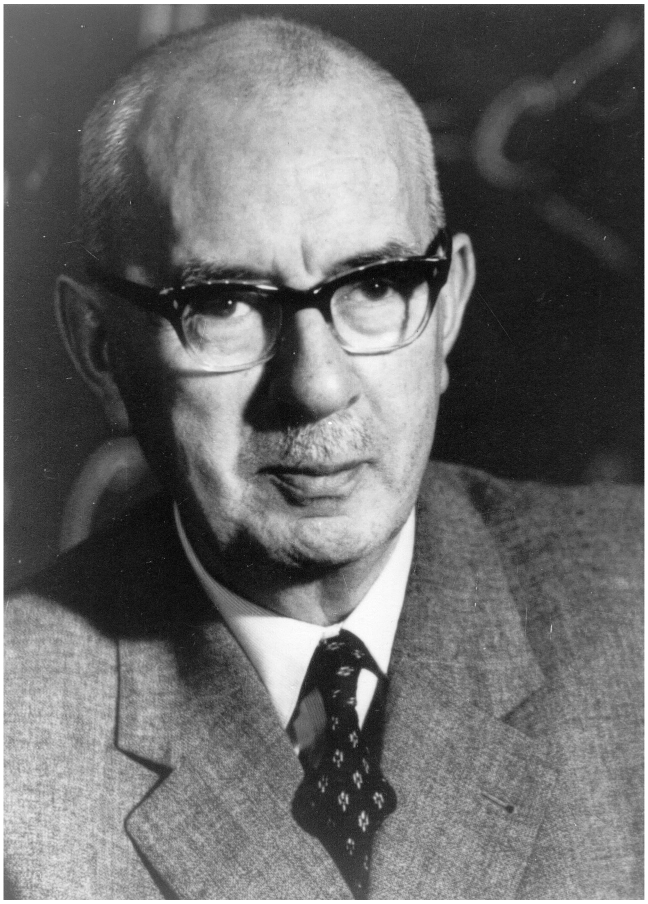

Figure 11. Karl Ziegler (reproduced courtesy of the Archives, Deutsche Akademie der Naturforscher Leopoldina, Erna Lämmel, Director).

A. Synthesis of Organolithium Compounds by the Reaction of Metallic Lithium with Organic Halides: Karl Ziegler, 1930. The first study of the reaction of metallic lithium with organic halides was reported by Spencer and Price in 1910.[104]

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[98] Arest-Yakubovich, A. A.; Pakuro, N. I.; Zolotareva, I. V.; Kristal'nyi, E. V.; Basova, R. V. *Polym. Int.* **1995**, *37*, 165.

[99] Pakuro, N. I.; Arest-Yakubovich, A. A.; Shcheglova, L. V.; Petrovsky, P. V.; Cheklaeva, L. A. *Russ. Chem. Bull.* **1996**, *45*, 838; *Izv. Akad. Nauk, Ser. Khim.* **1996**, 883.

[100] Cartledge, G. H. *J. Am. Chem. Soc.* **1928**, *50*, 2855.

[101] Karl Ziegler (1898–1973). Entered University of Marburg in 1916, completed his Ph.D. studies (with Karl von Auwers) in 1920. Habilitation in Marburg in 1923 with research on homolytic cleavage of C–C bonds and persistent free radicals. First work on organoalkali-metal compounds (preparation of $C_6H_5(CH_3)_2CK$ by cleavage of $C_6H_5(CH_3)_2COCH_3$ by K). Associate professor, University of Heidelberg, 1927–1936. Continuation of free radical and organoalkali-metal research. Study of mechanism of butadiene polymerization by metallic sodium; reactions of organoalkali-metal compounds with olefins and dienes; synthesis of RLi compounds by RX/Li reactions. Application of high-dilution technique to synthesis of medium- and large-ring compounds. 1936–1943 Professor of Chemistry and Director of the Chemistry Institute, University of Halle. Continuation of organoalkali-metal and free radical chemistry; *N*-bromosuccinimide as allylic bromination agent. 1943 Director of the Kaiser-Wilhelm-Institut für Kohlenforschung (now Max-Planck-Institut für Kohlenforschung), Mülheim (Ruhr), Germany. Organolithium research leads, by way of study of $LiAlH_4$ addition to olefins, to organoaluminum chemistry: trialkylaluminum/ethylene chain growth ("Aufbau") reaction; trialkylaluminum/α-olefin dimerization. "Ziegler catalysts" ($R_3Al/TiCl_4$ or $TiCl_3$) for polymerization of ethylene to poly(ethylene) of suitably high molecular weight. Preparation of trialkylaluminum compounds by the olefin/Al/H_2 process. Large-scale industrial commercialization of this technology. 1963 Nobel Prize in Chemistry (shared with Guilio Natta) for ethylene polymerization by "Ziegler catalysts". See: (a) Wilke, G. *Liebigs Ann. Chem.* **1975**, *805*, 833 (obituary with complete publication list). (b) Hafner, K. *Nachr. Chem. Technol. Lab.* **1999**, *47*, 23. (c) Eisch, J. J. *J. Chem. Educ.* **1983**, *60*, 1009.

Figure 12. Georg Wittig (reproduced courtesy of the Archives, Deutsche Akademie der Naturforscher Leopoldina, Erna Lämmel, Director).

No solvent was used. Equimolar quantities of organic halides and the lithium (in small pieces) were heated at reflux in a quartz flask for 3−20 h. Atmospheric moisture appears not to have been excluded; no mention is made of a protective atmosphere. Methyl iodide and bromobenzene, which did not react with lithium under these conditions, were heated with lithium in a sealed tube at 250 °C for 6 h. In all cases the products were described as "white, crystalline, deliquescent solids" that reacted exothermally with water. They were presumed to be mixtures of the respective organolithium product and lithium halide. Table 1 shows some results. Of course, the reaction conditions—no solvent, unnecessarily high temperatures—were rather extreme and the 1:1 RX/Li stoichiometry should have been 1:2 (although the authors correctly wrote the equation as $RX + 2Li = RLi + LiX$). The reaction of lithium and iodobenzene also was carried out in diethyl ether solution, and biphenyl, in "small quantity", was reported to be the sole product. The formation of phenyllithium appears to have been missed. After this inauspicious start, no further work appears to have been done on the RX/Li reaction for over 20 years. Ziegler and Colonius[68] repeated the experiments of Spencer and Price and found, not surprisingly, that under their conditions not even trace amounts of organolithium compounds were formed.

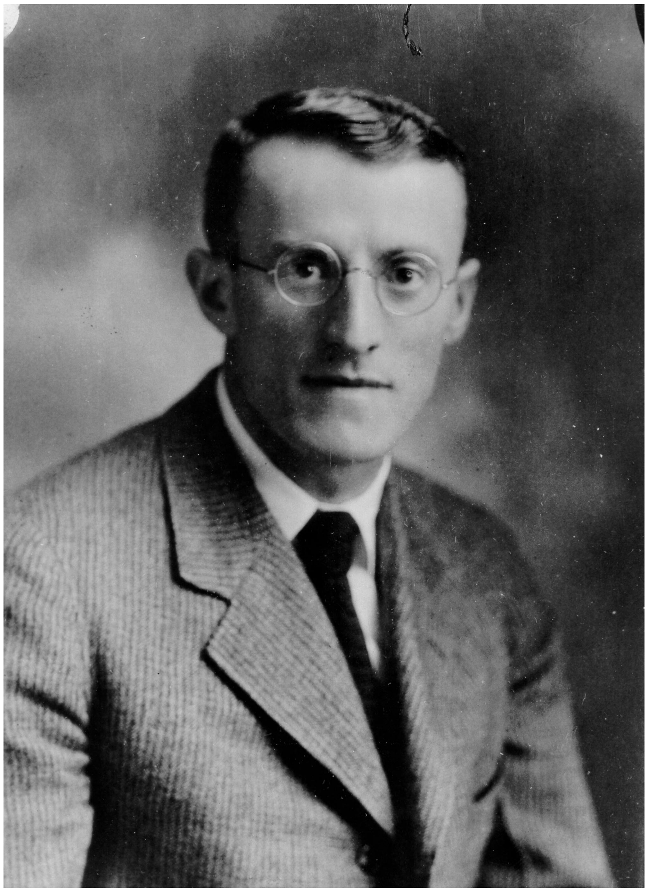

Figure 13. Henry Gilman (photo courtesy of Iowa State University, Chemistry Department).

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(102) Georg Wittig (1897−1987). Born in Berlin. 1916, enrolled at University of Tübingen for study of chemistry. 1916−1918, Army service; up ranks to lieutenant. 1918−1919, prisoner of war. 1919−1923, Chemistry student at University of Marburg, Ph.D. (with Karl von Auwers), 1923, Habilitation in Marburg, 1926, on benzo-γ-pyrones. Friendship with Karl Ziegler. 1926−1932, Privatdozent and Oberassistent in Marburg. 1932−1937, assistant professor (ausserplanmässiger Professor), Chemistry Institute, Technische Hochschule Braunschweig. Research in organic chemistry. Discovery of the lithium−hydrogen and lithium−halogen exchange reactions. 1937−1944, Associate Professor (Professor extraordinarius), Chemistry Institute, University of Freiburg. 1944, to University of Tübingen as Professor and Director of the Chemistry Institute (as successor to Wilhelm Schlenk, whom we will meet in Part 2). Move to the University of Heidelberg, again as Professor and Director of the Chemistry Institute, 1956. Emeritus, 1967. Highlights of his contributions 1944−1967: generation of benzyne via *o*-lithiation of fluorobenzene; Wittig rearrangement of ethers, trimethylammonium methylide; development of "ate" complexes; pentaphenyl compounds of P, As, Sb, and Bi, pentamethyl compounds of As and Sb; tetraphenyltellurium and triphenyliodine; triphenylphosphinemethylene and the Wittig olefin synthesis; directed aldol condensations. The Wittig olefin synthesis was his crowning achievement, which was recognized with the award of the Nobel Prize in Chemistry (shared with H. C. Brown) in 1979. See: (a) Tochtermann, W. *Liebigs Ann. Chem. Recl.* **1997**, I−XXI (obituary with complete publication list). (b) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2001**, *40*, 1411.

(103) Henry Gilman (1893−1986). Born in Boston, Mass. B.S., Harvard University, 1915. Undergraduate research with Roger Adams; Ph.D., Harvard University, 1918 (with E. P. Kohler). 1919, Assistant Professor at the Iowa State College of Agriculture and Mechanic Arts (later Iowa State University) in charge of organic chemistry, where he stayed until his retirement in 1963. Continued research until 1975. Early research on Grignard reagent chemistry and heterocyclic chemistry. Subsequent research focus on main-group organometallic chemistry: broader studies of the chemistry of the Grignard reagents and diorganomagnesium compounds, alkyl- and aryllithium reagents as major research areas, but also research on the organometallic chemistry of periodic groups 1 (the heavier alkali metals), 2 (esp. Be), 13, 14, 15, 11 (including R_2CuLi cuprates, called Gilman reagents), and 12. Major effort in organosilicon chemistry after 1945 (silylmetallics, e.g., Ph_3SiK; perhaloorganosilicon compounds). Recognized as "Father of Organometallic Chemistry in the United States". See: (a) Eaborn, C. *Biogr. Mem. Fellows R. Soc.* **1990**, *36*, 153 (also published as *Biogr. Mem.* (*Nat. Acad. Sci. U.S.A.)* **1996**, *70*, 83). (b) Eisch, J. J. *Organometallics* **2002**, *21*, 5439. (c) Ingham, R. K. *J. Organomet. Chem.* **1982**, *225*, ix. (d) Eisch, J. J. *J. Organomet. Chem.* **1988**, *338*, 281.

Table 1. Spencer and Price's Reported Results of Reactions of Organic Halides with Lithium (after Hydrolytic Workup)[a]

reacting substance	heating time and temp	hydrolysis products
iodobenzene	1 h at 188 °C	70% benzene and diphenyl
bromobenzene	in sealed tube at 150 °C for 8.5 h	benzene and diphenyl
p-bromotoluene	1.5 h at 184 °C	24% toluene
p-chlorotoluene	4.5 h at 150 °C	7% toluene; *p*-ditolyl
m-chloroaniline	0.5 h at 230 °C	80% aniline; *m*-diaminodiphenyl, traces of carbylamine
p-chloroaniline	1.5 h at 230 °C	68% aniline, traces of carbylamine
p-bromoacetanilide	2 h at 210 °C	40% aniline, 12% acetanilide
p-chlorophenol	several min at 217 °C	14% phenol
α-chloronaphthalene	17.5 h at 263 °C	naphthalene; α-dinaphthyl
methyl iodide	in a sealed tube for 4.5 h at 200 °C	27% ethane, 33% methane mixed with 40% hydrogen
n-propyl iodide	1.5 h at 46.5 °C	*n*-hexane; *n*-propane
sec-octyl iodide	20 h at 220 °C	9% octane; 17% hexadecane, mp 20 °C

[a] From ref 93; reproduced by permission of the Royal Society of Chemistry.

The preparation and isolation of alkyl- and aryllithium compounds by the metal displacement reaction, the reaction of metallic lithium with a dialkyl- and diarylmercury compound, respectively, had been reported by Schlenk and Holtz in 1917.[105] This route, however, did not gain general application and did not lead to broad development of organolithium chemistry, since it required the prior preparation of the diorganomercurials, many of which are toxic. The discovery by Ziegler and Colonius that organolithium compounds could be prepared readily by reaction of metallic lithium with organic halides, bromides, and, especially, chlorides, in benzene, was the needed breakthrough.[68] This RLi synthesis had several important advantages over the Morton RNa preparation: most of the alkyllithium compounds are soluble in benzene, aliphatic hydrocarbons, and ethers and the aryllithiums in ether. The RX/Li reaction, with some exceptions, is not complicated by Wurtz-type R−R formation. The stability of most organolithium reagents toward diethyl ether is better than that of the analogous organosodium reagents, which can only be prepared and used in hydrocarbon medium. Experiments carried out under nitrogen with *n*-butyl halides provided some information about the RX/Li reaction. The course of the reaction was followed by hydrolysis of the reaction solution and titration of the LiOH formed ($RLi + H_2O \rightarrow RH + LiOH$). The reaction of *n*-$C_4H_9I$ with lithium in diethyl ether did not result in formation of any *n*-C_4H_9Li, although the Li wire was in large part consumed. It was assumed that the Wurtz reaction (to give *n*-octane) had occurred. With *n*-butyl bromide in ether, *n*-C_4H_9Li was formed in ~15% yield. *n*-Butyl chloride reacted with lithium in ether to give *n*-C_4H_9Li in ~55% yield after 20 h. In reactions carried out in benzene, a 45% yield of *n*-C_4H_9Li was obtained when *n*-butyl bromide was used. With *n*-C_4H_9Cl, a 67% yield of the lithium reagent was realized. Further examination of reaction variables showed that an excess of lithium was not necessary, that fine lithium shavings worked better than lithium wire, that reaction temperatures of 50−60 °C result in a rapid rate, and that agitation (shaking) of the reaction mixture is required. In the preparation of phenyllithium, the use of iodo- and bromobenzene gave good results, but chlorobenzene was not very reactive. Since phenyllithium is not soluble in benzene, hydrocarbon solvents were not examined. Phenyllithium is a weaker base than the alkyllithiums; thus, diethyl ether could be used as the solvent for the $C_6H_5Br(I)/Li$ reactions, which started out quite vigorously and required external cooling. Phenyllithium yields of ~75% were obtained.

Ziegler and Colonius[68] carried out their reactions in Schlenk tubes ("Stickstoffröhren"). Gilman and his students[106,107] provided an improved procedure similar to that used for Grignard reagent preparations, in which they used a standard three-necked, round-bottomed flask equipped with a mercury-seal mechanical stirrer, a dropping funnel, and a spiral condenser topped with nitrogen inlet and outlet tubes. This simplified procedure then was used to prepare many alkyl- and aryllithium reagents in diethyl ether solution (e.g., Table 2[106b]). Further work showed that secondary alkyl- and *tert*-butyllithium reagents also could be prepared in high yield, but this required the use of alkane solvents. Preparative details for the synthesis of *n*-butyllithium in 80−85% yield in diethyl ether at −10 °C were published by Gilman some years later.[108]

Table 2. Synthesis of Organolithium Reagents by the Reaction of Organic Halides with Metal Lithium (in Fine Pieces) in Diethyl Ether[a]

organic halide, RX	RLi yield, %	organic halide, RX	RLi yield, %
1,4,2-$(CH_3)[(CH_3)_2CH]C_6H_3Br$	74	CH_3I	74
o-$CH_3OC_6H_4Br$	84	*n*-C_4H_9Cl	76
p-$CH_3OC_6H_4Br$	75	*n*-C_4H_9Br	59
o-$C_2H_5OC_6H_4Br$	73	*n*-$C_{11}H_{12}Br$	39
p-$C_2H_5OC_6H_4Br$	77	cyclo-$C_6H_{11}Cl$	23
p-$(CH_3)_2NC_6H_4Br$	95	C_6H_5Cl	35
α-$C_{10}H_7Br$	79	C_6H_5Br	95
β-$C_{10}H_7Br$	74	C_6H_5I	80
p-$C_6H_5C_6H_4Br$	77	*o*-$CH_3C_6H_4Br$	93
		m-$CH_3C_6H_4Br$	85
		p-$CH_3C_6H_4Br$	98

[a] From ref 95b. Conditions: 0.05 mol of RX in 15 mL of Et_2O added to 0.11 mol of lithium cut into fine pieces in 15 mL of Et_2O over 30−35 min, mild heating (if necessary) applied to maintain a gentle reflux, stirring and refluxing maintained for 1 h.

Lithium metal that contains a small concentration of sodium was found to be more effective than sodium-free lithium in the preparation of organolithium reagents by the RX/Li reaction.[109] Better rates of RLi formation and higher, nearly quantitative, yields resulted. In diethyl ether, a concentration of 0.02% of sodium in the lithium was optimum in the preparation of phenyl- and *n*-butyllithium. In hydrocarbon medium, higher Na concentrations were more effective. Thus, t-BuLi could be prepared in pentane in over 80% yield when lithium containing 2% sodium was used.

As was the case with Na/RX reactions, lithium can be "solubilized" and made more reactive by interaction with a polynuclear hydrocarbon such as a naphthalene or a biphenyl derivative. Transfer of the lithium electron to the LUMO of

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(104) Spencer, J. F.; Price, G. M. *J. Chem. Soc.* **1910**, *97*, 385.

(105) Schlenk, W.; Holtz, J. *Ber. Dtsch. Chem. Ger.* **1917**, *50*, 272.

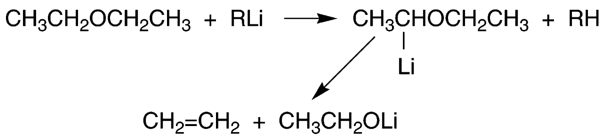
(106) (a) Gilman, H.; Zoellner, E. A.; Selby, W. M. *J. Am. Chem. Soc.* **1932**, *54*, 1957. (b) *J. Am. Chem. Soc.* **1933**, *55*, 1252.

(107) Gilman, H.; Moore, F. W.; Baine, O. *J. Am. Chem. Soc.* **1941**, *63*, 2479.

(108) Gilman, H.; Beel, J. A.; Brannen, C. G.; Bullock, M. W.; Dunn, G. E.; Miller, L. S. *J. Am. Chem. Soc.* **1949**, *71*, 1499.

(109) Kamienski, C. W.; Esmay, D. L. *J. Org. Chem.* **1960**, *25*, 1807.

Scheme 4



the hydrocarbon with formation of the Li^+ salt of the hydrocarbon radical anion or dianion facilitates RLi formation. Thus, Freeman and Hutchinson[110] found that reaction of alkyl halides with an excess of the lithium *p,p*′-di-*tert*-butylbiphenyl radical anion salt in THF at −78 °C gave the RLi reagents in 93−95% yield. Reduction (to RH) was a major competing reaction when Li^+[di-*tert*-butylanthracene]$^-$ was used.

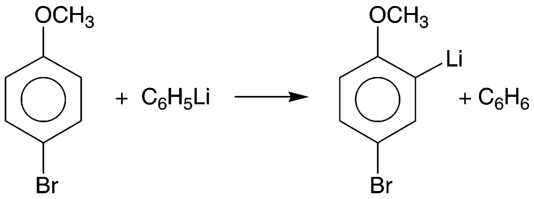
All organolithium reagents, with the exception of methyllithium, react with diethyl ether.[111] The reaction involved, as in the case of sodium alkyls, is α-metalation followed by fragmentation (Scheme 4). The order of decreasing stability in diethyl ether is MeLi > PhLi > n-$C_5H_{11}Li$ > n-C_4H_9Li > C_2H_5Li > n-C_3H_7Li > i-C_4H_9Li > cyclo-$C_6H_{11}Li$ = i-C_3H_7Li = s-C_4H_9Li > t-C_4H_9Li. Organolithium reagents are considerably less stable in tetrahydrofuran.[112] The temperatures at which selected organolithium reagents could be used in THF were found to be as follows: CH_3Li, 0 °C; n-C_4H_9Li, below −35 °C; C_6H_5Li, 0 to −10 °C. Here also α-lithiation of the ether is the first step; the final products are RH, C_2H_4, and $CH_2{=}CHOLi$. In fact, such an RLi/THF reaction is a useful preparation of $CH_2{=}CHOLi$.

B. Synthesis of Organolithium Reagents by the Lithium−Halogen Exchange Reaction. Wittig and Gilman, 1938. A very useful and widely utilized procedure for the preparation of organolithium reagents is the lithium−halogen exchange reaction (called the lithium−halogen interconversion reaction in Gilman's papers) (eq 29). When R = alkyl (e.g., *n*-butyl)

$$\mathrm{RLi} + \mathrm{R'X} \overset{K}{\rightleftharpoons} \mathrm{R'Li} + \mathrm{RX} \qquad (29)$$

and R′ = aryl, the equilibrium lies far to the right; therefore, the reaction is preparatively useful for the synthesis of aryllithium reagents. When R and R′ both are primary alkyl groups, the equilibrium constant is not large and a mixture of the two possible alkyllithiums results. Wurtz-type reactions generally do not occur except in the case of highly reactive halides, such as allylic or benzylic halides, or in the case of unnecessarily long reaction times. The lithium−halogen reaction does not take place with the less reactive alkyl chlorides. Instead, dehydrochlorination (via α-metalation) usually occurs. In the case of aryl halides, the bromides and iodides work best.

The first example of a lithium−halogen exchange reaction was reported by Wittig et al. in 1938.[113] After they had discovered that phenyllithium metalated *p*-bromoanisole (i.e., reacted with lithium−hydrogen exchange) (eq 30) and that 1,4- and 1,3-dimethoxybenzene reacted with phenyllithium in the same manner, they found, to their surprise, that 1,3-dimethoxy-4,6-dibromobenzene reacted quite differently with phenyllithium in diethyl ether at room temperature (eq 31): i.e., lithium−bromine, not lithium−hydrogen, exchange had occurred. Wittig



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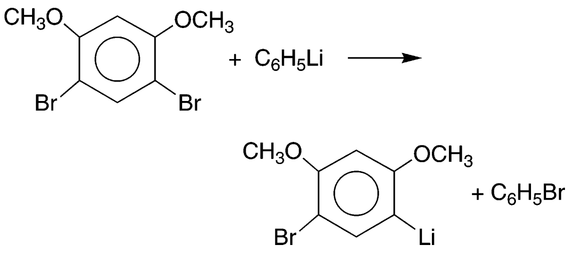
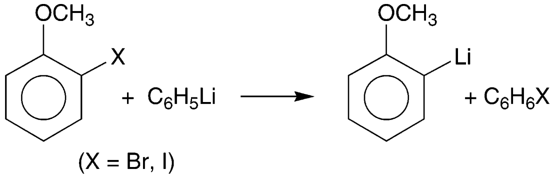
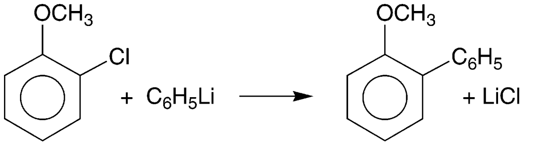


(31)

expressed his surprise about this result, calling the reaction contrary to every chemical intuition ("Es hat sich also die folgende, jedem chemischen Gefühl widerstrebende Reaktion abgespielt"). This chemistry showed very dramatically the much greater reactivity of phenyllithium compared to phenylmagnesium bromide. The Grignard reagent reacted neither with *p*-bromoanisole nor with 1,3-dimethoxy-4,6-dibromobenzene, even after a reaction time of 16 h at 100 °C. Wittig followed up this work with more detailed studies of other haloanisoles and related systems.[114] Of interest is the different reaction course of *o*-chloroanisole compared with those of *o*-bromo- and *o*-iodoanisole (eqs 32 and 33). In the case of *o*-chloroanisole, the reaction was very slow, with a 90% recovery of starting material after 20 h at room temperature and only a 10% yield of methoxybiphenyl. In contrast, the reactions of eq 32 were rapid, requiring 2 min and 1 h, respectively, for *o*-iodoanisole and *o*-bromoanisole at room temperature.



(32)



(33)

During the course of such studies of the reactions of phenyllithium with iodo-, bromo-, chloro-, and fluorobenzene the first example of a reaction that proceeded by the benzyne mechanism was discovered: the *o*-lithiation of fluorobenzene followed by LiF elimination and addition of phenyllithium to the benzyne (Scheme 5).[114c,d]

In a paper received by the *Journal of the American Chemical Society* in October 1938, three months after Wittig's paper had been received by the *Berichte*, Gilman et al. reported their independent discovery of the reaction of *o*-bromoanisole with *n*-butyllithium, which gave *o*-anisyllithium, in agreement with

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[110] Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

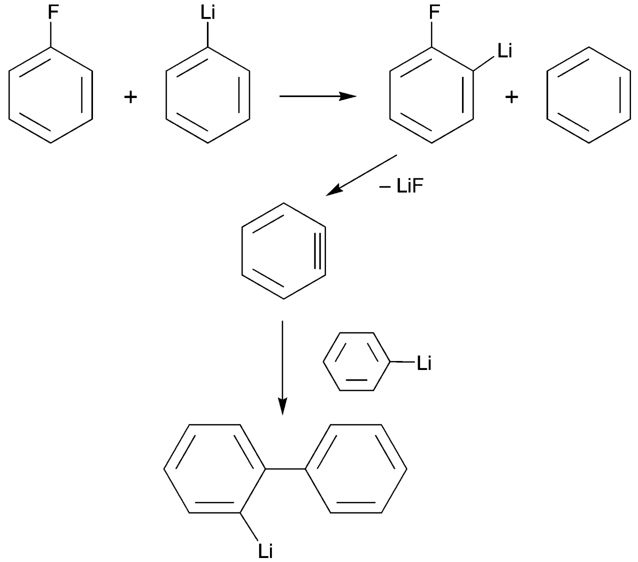
[111] Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, U.K., 1974; pp. 198−199. Methyllithium is stable for weeks in diethyl ether: Ziegler, K.; Zeiser, H. *Liebigs Ann. Chem.* **1931**, *485*, 174.

[112] Gilman, H.; Gaj, B. J. *J. Org. Chem.* **1957**, *22*, 1165.

[113] Wittig, G.; Pockels, U.; Dröge, H. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1903.

[114] (a) Wittig, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1197. (b) Wittig, G.; Pockels, U. *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 89, 884. (c) Wittig, G.; Witt, H. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 1471. (d) Wittig, G.; Pieper, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1193. (e) Wittig, G.; Merkle, W. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1491.

Scheme 5



Wittig's finding, and *n*-butyl bromide.[115] Wittig and Gilman recognized the importance in terms of its potential utility of the lithium−halogen exchange reaction and, to avoid duplication of effort and any disputes, made a gentleman's agreement that Wittig would restrict his continuing investigations to such reactions of aryllithium reagents and that Gilman would carry out his studies with alkyllithiums (ref 114a, footnote 3, p 1198). Gilman had the better of the deal in the long run, for *n*-butyllithium, and also *tert*-butyllithium, turned out to be more versatile than phenyllithium and hence became the reagents of choice for use in the lithium−halogen exchange preparation of a great number of organolithium reagents. Furthermore, all butyllithium isomers (in alkane solution) became commercially available in later years, which greatly facilitated this chemistry. However, phenyllithium served Wittig very well in his subsequent research, and he appreciated its worth and its promise, entitling a review that appeared in *Naturwissenschaften* in 1942, "Phenyllithium, the Key to a New Chemistry of Organometallic Compounds".[116]

Gilman, Langham, and Moore undertook a broader investigation of the lithium−halogen exchange reaction.[117] Solvent effects were examined, and it was found that the reaction proceeds well in petroleum ether, but more slowly than in diethyl ether. Aryl iodides were more reactive than aryl bromides and aryl chlorides, and fluorides in most cases did not undergo lithium−halogen exchange with *n*-butyllithium. With longer reaction times, the Wurtz coupling reaction, which is slower and usually not competitive with the lithium−halogen exchange reaction, appeared and eventually consumed the initially formed products (eqs 34 and 35). The conversion of aryl iodides and bromides

$$C_6H_5Br + n\text{-}C_4H_9Li \longrightarrow C_6H_5Li + n\text{-}C_4H_9Br \qquad (34)$$

$$C_6H_5Li + n\text{-}C_4H_9Br \longrightarrow C_6H_5C_4H_9\text{-}n + LiBr \qquad (35)$$

to the respective aryllithium reagents by reaction with *n*-butyllithium was found to be a more general process, and a vinylic lithium reagent, $C_6H_5CH{=}CHLi$, also was prepared in low yield.

The lithium−halogen exchange reaction, which provides access to many useful aryl, vinylic, and heterocyclic lithium reagents, has received extensive use and study since its discovery and has been the subject of reviews.[118]

As noted earlier, the lithium−halogen exchange reaction is reversible, and in the case of alkyl halide/alkyllithium reactions, the rather small equilibrium constants (e.g., ~2.6 for the C_2H_5I/n-C_3H_7Li reaction in 60% pentane/40% Et_2O at −70 °C and ~7.8 for the n-$C_3H_7I/(CH_3)_2CHCHLi$ reaction in pentane at −23 °C) do not favor a useful preparative reaction.[119] In addition, side reactions, alkyl−alkyl coupling and dehydrohalogenation, can occur, especially on long reaction times in the case of the former reaction.

tert-Butyllithium was found to be especially useful for the preparation of organolithium reagents by lithium−halogen exchange. However, 2 molar equiv of t-C_4H_9Li must be used: one for the exchange and the other to react with and destroy the *tert*-butyl halide produced in the exchange, which otherwise would react with the newly formed organolithium reagent (eqs 36 and 37); thus, as carried out, this is a nonequilibrium process.

$$RX + (CH_3)_3CLi \longrightarrow RLi + (CH_3)_3CX \qquad (36)$$

$$(CH_3)_3CX + (CH_3)_3CLi \longrightarrow (CH_3)_3CH + (CH_3)_2C{=}CH_2 + LiX \qquad (37)$$

This procedure works well in the preparation of aryl- and alkenyllithiums.[120,121] Primary alkyl iodides undergo this reaction with *tert*-butyllithium very well;[121] thus, primary alkyllithium reagents can be prepared cleanly by lithium−halogen exchange. Such reactions with *tert*-butyllithium were not satisfactory in the case of secondary alkyl iodides and primary alkyl bromides.

The general rule in the lithium−halogen exchange equilibria is that the more electronegative of the two organic groups, i.e., the one that can better stabilize a (partial) negative charge, will become preferentially attached to the lithium atom. Thus, there is little difference in the electronegativities of the ethyl and *n*-propyl groups and the equilibrium constant is close to 1. However, the n-C_3F_7 group is very electronegative, and the reaction of methyllithium with n-C_3F_7I in diethyl ether gave n-C_3F_7Li in 75% yield.[122]

The lithium−halogen exchange reaction might well have been discovered 11 years earlier, in 1927, when Marvel, Hager, and Coffman studied reactions of *n*-butyllithium in petroleum ether with various organic halides.[123] The reactions were carried out in the Schlenk-type apparatus shown in Figure 14. A 1 M n-C_4H_9Li solution in pentane was contained in bulb C; bulbs E

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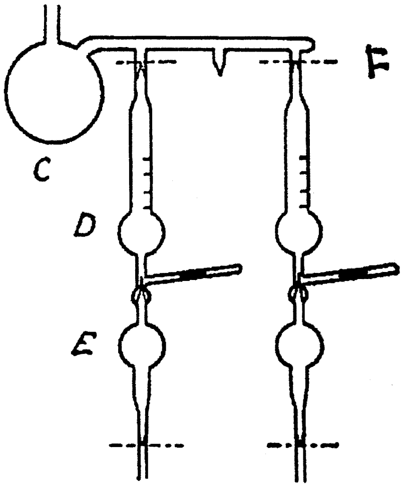

Figure 14. Marvel's Schlenk-type apparatus (from *J. Am. Chem. Soc.* **1927**, *49*, 2323, American Chemical Society).

contained the organic halides, also in pentane. Air was displaced with solvent vapors or by evacuating it under high vacuum. The *n*-C_4H_9Li solution was transferred to the bulbs D, and the D/E systems then were sealed off at F. The glass valve between bulbs D and E was broken, and the *n*-C_4H_9Li and organic halide solutions were slowly mixed. Upon completion of the reaction, the two flasks were opened and the reaction mixtures were poured into ice water. The organic layer was separated and fractionally distilled. In the *n*-butyllithium/*p*-bromotoluene reaction, the product, obtained in 75% yield after 4 days at room temperature, was *p*-*n*-butyltoluene. With *o*- and *m*-bromotoluene under the same conditions, toluene was obtained in >85% yield. The reaction of *n*-butyllithium with *n*-heptyl bromide, which was allowed to proceed for 90 days (summer vacation?) at room temperature, gave *n*-undecane, the coupling product. The reaction times obviously were too long, but the formation of toluene in high yield in the reactions of *o*- and *m*-bromotoluene with *n*-butyllithium, after hydrolytic workup, should have suggested to the authors that *o*- and *m*-tolyllithium had been formed. However, this connection was not made and the lithium–halogen exchange reaction became the discovery of Wittig and Gilman. Had his focus not been otherwise directed, Ziegler also could have been the discoverer of the lithium–halogen exchange reaction in 1929.[124] To determine the concentration of alkyllithium solutions in benzene, he first tried to use a Wurtz reaction with *n*-butyl bromide ($\rightarrow n$-$C_4H_9R + LiBr$), with subsequent determination of inorganic bromide. However, the expected Wurtz reaction was very slow, requiring hours for the first traces of LiBr to appear. At this point, some degree of lithium–halogen exchange between RLi and the added *n*-C_4H_9Br must have taken place. Thus, both RLi and *n*-C_4H_9Li, as well as the two bromides, RBr and *n*-C_4H_9Br, most likely were present. However, the authors had no reason to think of such a possibility and so those reaction mixtures were not examined more closely.

Marvel's paper[123] was entitled "The Mechanism of the Reaction between *n*-Butyllithium and Various Organic Halogen Compounds". On the basis mainly of the reactions of *n*-butyllithium with triphenylmethyl chloride and β-bromostyrene, the authors concluded "there seems to be little doubt that free radicals are first produced when a halogen compound reacts with a lithium alkyl." Much study has been devoted since then to the mechanism of the lithium–halogen exchange reaction, and a discussion of the various proposed mechanisms, usually based on experimental studies, is beyond the scope of this essay. The reader is referred to an excellent 1988 review on this subject by Bailey and Patricia.[118a] As these authors note, the mechanism of the lithium–halogen exchange reaction "remains something of an enigma". That still seems to be the case today, with three different types of mechanisms (including a four-center transition state, another proceeding by an electron transfer (radical) process, and the third involving a nucleophilic mechanism via halogen "ate"-type intermediates) being discussed.

C. Synthetic Applications of Organolithium Reagents. The applications of organolithium reagents in organic and organometallic syntheses are too varied and too numerous to permit their discussion in this essay,[125] and just a few aspects will be mentioned here.

The organolithium compounds, like their organosodium and -potassium analogues, are strong bases, albeit somewhat weaker. For example, benzene is metalated only slowly by *n*-butyllithium in diethyl ether solution.[126] There is a marked effect of donor solvents and Lewis base additives on the basicity of organolithium compounds. Thus, *n*-butyllithium metalates benzene at a moderate rate in THF, and in the presence of an equimolar amount of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) metalation of benzene by *n*-butyllithium occurs rapidly to give a good yield of phenyllithium.[127,128] The use of this additive in the reactions of organolithium reagents has become widespread.[127] (The structures of organolithium compound/Lewis base adducts will be discussed in Part 2.)

In view of the previous discussion of Morton's 1,3-diene polymerization studies, the use of organolithium compounds as initiators of the commercial polymerization of 1,3-dienes and styrene should be noted. Although Ziegler, in his investigations of the addition of organoalkali-metal compounds to activated $C{=}C$ bonds, studied the addition of *n*-butyllithium to 1,1-diphenylethylene (to give $(C_6H_5)_2C(Li)CH_2C_4H_9$-*n*),[129] it was not until 1957 that it was reported that alkyllithium compounds initiated the polymerization of isoprene to give cis polymers with properties resembling those of natural rubber.[130] This generated much research into the scope and mechanism of such polymerization of 1,3-dienes, and the production of synthetic rubber by the organolithium initiation route became an industrial process.[131] *n*-, *sec*-, and *tert*-Butyllithium are effective catalysts, and this is why all three are commercially available today.

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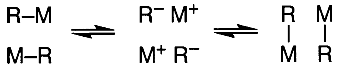
V. Concluding Remarks

This brings us nearly to the end of Part 1. The focus in Part 1 has been on the preparation of alkyl and aryl compounds of the alkali metals by reactions of organic halides with alkali metals or, by halogen−metal exchange, with organoalkali-metal compounds. Other preparative methods will be covered in Part 2.

In the 1950s, the time frame at which Part 1 for the most part ends, essentially nothing certain was known about the structure and bonding of alkali-metal alkyls and aryls in the solid state and in solution. The alkyl- and arylsodium and alkyl- and arylpotassium compounds were a complete mystery. The sodium alkyls, up to octylsodium, were completely insoluble in all "inert" organic solvents such as the alkanes and benzene. They decomposed without melting when heated, and they were reported to be amorphous. Sidgwick, in his 1950 treatise,[132] characterized the alkali-metal alkyls as "covalent and associated" and said that the alkyls of sodium and the heavier alkali metals are more highly associated than those of lithium. However, he wondered what is the nature of such association was, saying:

> Now in all these metallic alkyls there are no unshared valency electrons, so that an attachment by coordination is impossible, and there is no other obvious method. The problem is at present unsolved, and as long as we do not know why any of these compounds are associated it is useless to ask why some are more associated than others. The cause of the association may possibly be a high dipole moment of the M−C link (dipolar association), or some resonance scheme, for example:



This then was the state of knowledge around 1950. In the case of the alkyl- and aryllithium compounds there were grounds for hope. The alkyllithiums, except for methyllithium, are soluble in alkanes and benzene and the aryllithiums in diethyl ether. Ethyllithium and *n*-butyllithium could be distilled very slowly under high vacuum at 80−100 °C; thus, the vapor state was accessible for study. Ethyllithium had been obtained as pyrophoric crystals, with mp 95 °C, from benzene.[133]

Since the organolithium compounds were soluble in organic solvents, some information about their constitution in solution could be obtained. Wittig and co-workers[134] studied the molecular weights of some organolithium reagents ebullioscopically in diethyl ether using a specially constructed apparatus from which air and moisture could be excluded. The molecular weight of phenyllithium (formula weight 84) was somewhat concentration dependent, but it was approximately dimeric in boiling diethyl ether solution. Wittig's paper was devoted to "ate" complexes, and he wrote the phenyllithium dimer as $Li[Li(C_6H_5)_2]$ and said that it was held together by ion−dipole forces. Phenyl group bridging between the two lithium atoms, he said, was unlikely. Benzyllithium also was found to be dimeric in boiling diethyl ether. Alkyllithium compounds, according to Wittig, were more highly associated: methyllithium a trimer in boiling diethyl ether and *n*-butyllithium a pentamer in boiling benzene. (Ethyllithium was determined cryoscopically in benzene to be a hexamer by Hein and Schramm in 1930.[135])

Geoffrey Coates discussed the alkali-metal alkyls in his 1960 monograph on organometallic compounds.[136] The alkyllithium compounds could not be monomeric, he said, because they are associated in solution and because they have such very low vapor pressures (e.g., C_2H_5Li, $\sim 4.5 \times 10^{-4}$ mm at 60 °C), but, he said, "the constitution of these compounds is obscure." However, Rundle's X-ray crystal structures of dimethylberyllium[137] and trimethylaluminum,[138] which showed methyl bridge bonding between the respective metal atoms, led Coates to conclude that "some kind of covalent bonding" was involved and he suggested that it might be "the same type of half-bonding as that responsible for the association of the alkyls of beryllium and aluminum." In contrast, on considering the properties of the alkyl- and arylsodium compounds, Coates concluded that "these properties are consistent with their formulation as salts, e.g., $CH_3CH_2^-Na^+$."

In only a few more years after the publication of Coates's book, the veil would be lifted. The brilliant X-ray powder diffraction studies of Erwin Weiss would elucidate the solid-state structures of the compounds that once were obscure. ^1H, ^{13}C, and especially ^7Li and ^6Li NMR spectroscopy would help to determine the structures of organolithium compounds in solution and, together with computational studies that became possible, would shed light on the bonding in these compounds. These aspects of the more recent history of the alkyls and aryls of the alkali metals will be covered in Part 2.

Acknowledgments. My thanks to the Archive of the Deutsche Akademie der Naturforscher Leopoldina (Erna Lämmel, Director) and the MIT Museum (Dr. Deborah Douglas, Curator, Science and Technology), for providing photographs, and to Professor Arnold l. Rheingold for providing the cover figures.

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Received November 15, 2005

OM058054A

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