

profoundly from that of the hamster, as the woodchuck is capable of responding to auditory and mechanical stimulation by moving about at body temperatures at which the hamster is completely immobile.

The recorded differences in the electrocorticogram of the hibernating ground squirrel and woodchuck as contrasted with the hamster emphasize that generalizations about physiological processes which occur in hibernating mammals should be guarded and that the species should always be indicated.

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Observations on a Class of Free Radicals Derived from Aromatic Compounds¹

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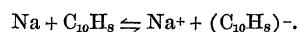
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The reaction of alkali metals with aromatic hydrocarbons has been under investigation for many years. It was not until 1935, however, when it was found that ethers such as methyl ether or 1,2-dimethoxyethane promote the reaction (1, 2), that significant progress was made toward an understanding and utilization of the reaction.

It has been suggested (2-5) that the reaction of an alkali metal with an aromatic hydrocarbon in the presence of one of the above ethers involves the transfer of either one or two electrons from alkali metal atoms to one molecule of hydrocarbon. We have found that the intensely colored substances formed upon reaction of sodium with naphthalene, anthracene, naphthacene, 1,2-benzanthracene, 20-methylcholanthrene, nitrobenzene, *m*-dinitrobenzene, 1,3,5-trinitrobenzene, or 2,3,7-trinitrofluorenone, in 1,2-dimethoxyethane or tetrahydrofuran as solvents, exhibit intense paramagnetic resonance absorptions.^{2, 3} In none of these paramagnetic products does the gyromagnetic ratio deviate from the free electron value by more than a few tenths of 1%. It is difficult to reconcile these observations with the suggestion that the reaction involves the transfer of two electrons from two atoms of sodium to one molecule of aromatic compound. This hypothesis would require that in each case the normal state of these

paramagnetic molecules is a triplet (biradical) electronic configuration. Such a situation is highly unlikely in molecules in which orbital degeneracy does not exist. All the molecules under discussion here belong to the class in which no orbital degeneracy is permitted.

These considerations, in addition to the fact that the over-all reaction involves one aromatic molecule per atom of sodium (1, 2), indicate that we are dealing with free radical ions formed by the transfer of one electron to the aromatic compound. The reaction, using naphthalene as an example, may be represented by the equation:



The analogy between this equation and the equations for the solution of sodium in liquid ammonia and triphenylmethyl in liquid sulfur dioxide is worth noting.

Scott, Walker, and Hansley (2) demonstrated that the reaction is an equilibrium. They also pointed out that methyl ethers, such as dimethyl ether or 1,2-dimethoxyethane, are very effective in shifting the above equilibrium to the right, whereas ethyl ether, for example, is relatively ineffective. It is believed that, in general, it is the magnitude of the energy of solvation of the metal ion (and perhaps also the negative hydrocarbon ion), by the ether which is the principal factor in determining the value of the equilibrium constant for the above reaction. It then follows that ethers which are relatively unhindered sterically (6), or polyethers which can form chelate structures with the metal ion (4), will be most effective in shifting the above equilibrium to the right. This conclusion is in agreement with the qualitative experimental data that are available.

The shape of the paramagnetic resonance absorption curve is dependent on the particular free radical and on its concentration. The hydrocarbon free radicals at concentrations in the neighborhood of 10^{-4} *M* yield a single absorption band about 5 oersteds wide. As the concentration is increased from this value, the band width decreases. Absorption bands narrower than 1 oersted are observed at high concentrations (ca. 0.1 *M*). The only mechanism thus far suggested for such a narrowing involves an exchange of spins between free radical molecules, the exchange proceeding because of orbital interaction (7). The fact that this narrowing is observable at concentrations of the order of 10^{-3} *M* indicates that the orbital interaction in these molecules may be exercised at large distances.⁴

The paramagnetic absorption spectra of the nitro-free radicals, with the exception of the fluorenone derivative, exhibit remarkable structures in dilute solutions. From 1,3,5-trinitrobenzene a free radical is obtained whose absorption shows 8 symmetrically distributed, evenly spaced peaks. Nitrobenzene and *m*-dinitrobenzene each yields a free radical whose absorption has 10 peaks; the relative intensities of the peaks in each pattern are different for the two compounds. The absorption in each case covers about 25 oersteds.

⁴ The average separation between molecules at 10^{-3} *M* is about 100 Å.

¹ Assisted by the joint program of the Office of Naval Research and the Atomic Energy Commission.

² Our observations were made at 9000 megacycles/sec in fields in the neighborhood of 3200 oersteds.

³ We are indebted to the U. S. Industrial Chemicals Co., Division of National Distillers Products Corporation, for the sodium dispersion used in many of our experiments.

It is probable that the observed spectral structures are to be classed as hyperfine—they arise from interactions between the magnetic moments of the nitrogen and hydrogen nuclei in each molecule with the magnetic moment of the odd electron. Despite the complexity and breadth of the spectra of their dilute solutions, the crystals of the nitro-free radicals exhibit a single sharp line.⁵ The trinitrofluorenone derivative yields a rather broad, unresolved resonance peak. It is possible that the fine structure in this case, as in the case of many other free radicals, is unresolved because of its complexity. This complexity arises from the large number of nuclear moments with which the electronic moment interacts.

Although the fact that sodium metal catalyzes the polymerization of unsaturated compounds has been known for a long time, there is no general agreement concerning the mechanism of this catalysis (8). Two sets of experiments have been performed with styrene which indicate that the function of the sodium metal is to bring about the formation of a negative hydrocarbon free radical. This free radical ion then initiates the chain reaction involved in the polymerization, as suggested by Bolland (9) for the sodium-catalyzed polymerization of isoprene. In one experiment a small amount of sodium dispersion was added to a sample of styrene. After some hours the styrene had been converted to a deep-red, rubbery solid which showed a strong paramagnetic resonance absorption. It is believed that the red color and the paramagnetic absorption are due to species such as $(C_6H_5CH=CH_2)^-$ which were trapped in the polymer. The material retained its paramagnetic resonance absorption and its color over a period of several months.⁶ In other experiments, styrene was dissolved in 1,2-dimethoxyethane and a small amount of sodium dispersion was added. A very vigorous reaction set in immediately, accompanied by the formation of a deep-orange color. As the reaction subsided, the reaction mixture became very viscous and the orange color gradually faded away. Since 1,2-dimethoxyethane, as mentioned above, favors the formation of negative hydrocarbon free radicals, it is believed that these observations are further evidence that the actual polymerization catalyst is a species such as $(C_6H_5CH=CH_2)^-$.

Various investigators have suggested (10) that abnormal growth may be explained by a free radical mechanism. Perhaps the carcinogenic activity of 20-methylcholanthrene and 1,2-benzanthracene is due to their ability to form negative hydrocarbon free radicals with mild reducing agents, whereas noncarcinogenic hydrocarbons such as naphthalene and anthra-

cene are able to form such free radicals only with very strong reducing agents.⁷

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⁷ A study of the relative electron affinity of various hydrocarbons is in progress in this laboratory.

Excessive Intake of Vitamin A as a Cause of Congenital Anomalies in the Rat¹

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Congenital anomalies have been produced in animal young when the fetal environment has been influenced by chemical, endocrine, mechanical, and actinic factors (1). Changes in atmospheric pressure (2) (hypoxia) and administration of cortisone (3) have recently been shown to exert teratogenic effects. Similarly, deficiencies in the maternal diet of single nutritional elements such as minerals (copper [4] and iodine [5]) and vitamins (riboflavin [6], pantothenic acid [7], folic acid [8], and vitamin A [9, 10]) have induced defective offspring. Reports (11, 12) of vitamin A excess in the maternal diet have shown a diminished litter rate and a high incidence of fetal resorption *in utero*. In the course of our investigation of the skeletal changes of hypervitaminosis A in mature rats, it was noted that several pregnant animals produced offspring with congenital malformations. An investigation was undertaken to study this phenomenon.

One hundred and fifty female rats of the CF Wistar strain (175-200 g) were mated by exposure for 24 hr, during the pre-oestrous stage, to males of the same strain. Pregnant females were fed the standard Rockland pellet diet and water *ad lib*. From the 2nd, 3rd, or 4th to the 16th day post coitus, 35,000 IU vitamin A in 0.7 ml diluent² were administered daily, via stomach tube, to 100 animals in the experimental group.

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² The vitamin product used was an aqueous preparation containing 50,000 USP u/cc natural vitamin A dispersed in sorbitan monolaurate and water.