renes are not practically obtainable from *trans-β-bromostyrene* at the elevated temperature, when tetrahydrofuran is used as solvent.) However the *cis/trans* ratios of β-d_1-styrene mixtures remain almost unchanged.

Details will be reported in a later paper.

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RECEIVED MAY 25, 1963

Spin–Spin Coupling between Hydrogen and Steroid Angular Methyl Protons

Sir:

Recently[1] it has been demonstrated that in certain fluorosteroids, spin–spin coupling between fluorine and angular methyl protons can occur. To our knowledge, only a single example of a split angular methyl resonance in a steroid nucleus not containing fluorine has been reported; *viz.* the C-18 methyl resonance in the n.m.r. spectrum of the 9,19-cyclo-11-keto steroid I occurred as a three-proton doublet ($J = 0.7$ c.p.s.).[2] It was tentatively suggested that the splitting may be due to long-range coupling. *We have observed a similar*

IIa, R₁ = H
IIb, R₁ = D
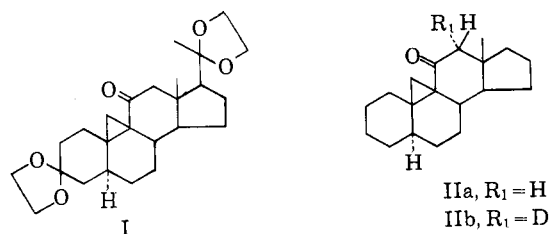
coupling in the closely related ketone IIa and, furthermore, have demonstrated that the methyl protons are coupled to the C-12 axial (12-α) proton. In the 100-Mc. n.m.r. spectrum[3] (Fig. 1a) of IIa, the C-18 methyl resonance
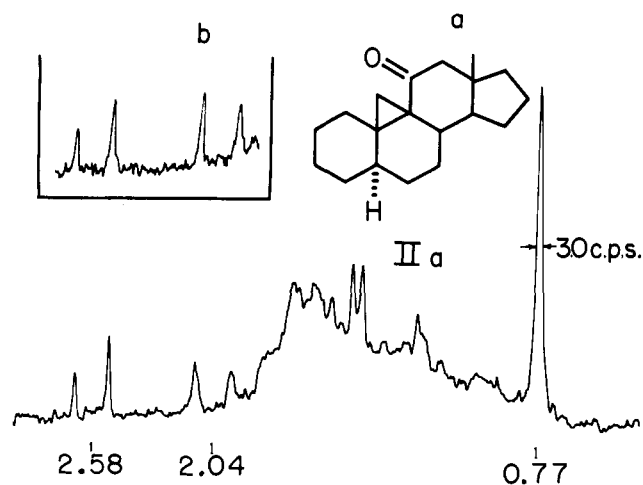

Figure 1.

at $\delta = 0.77$ p.p.m., while not resolvable into a doublet, was broad (half-width $= 3.0$ c.p.s.). The downfield region of the spectrum showed a pair of doublets at $\delta = 2.58$ and 2.04 p.p.m., due to the C-12 equatorial (12-β) and C-12 axial (12-α) protons, respectively; the coupling constant of the two doublets ($J = 15$ c.p.s.) is consistent with geminal coupling. Limited treat-

(1) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736 (1962); *ibid.*, **84**, 3784 (1962).

(2) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1963).

(3) The n.m.r. spectra were obtained on a Varian HR-100 spectrometer. The samples were run as CDCl₃ solutions with a trace of tetramethylsilane added to act as internal reference.

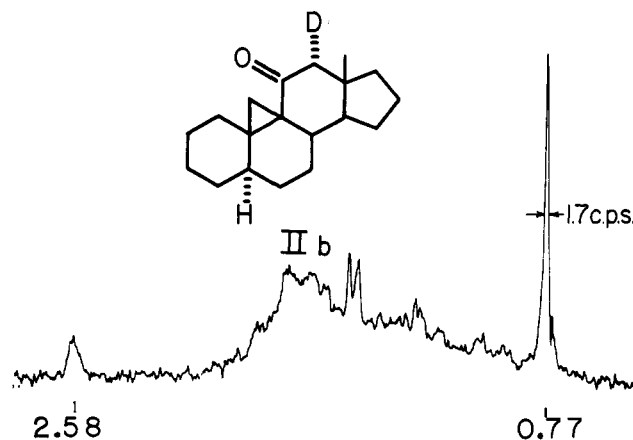Figure 2.

ment[4] (0.5-hr. reflux) of IIa with base in deuterium oxide and deuteriomethanol gave the 12α-d_1-9,19-cyclo-11-one (IIb) (d_0, 4%; d_1, 90%; d_2, 6% from mass spectral determination), the n.m.r. spectrum of which (Fig. 2) showed, as expected, no signals around $\delta = 2.04$ p.p.m. and only a single resonance at $\delta = 2.58$ p.p.m., broadened due to the small coupling of the C-12 equatorial proton with deuterium. *In this spectrum, the half-width of the methyl resonance is now reduced to 1.7 c.p.s.;* this is indicative of spin–spin coupling between the angular methyl protons and the C-12 axial hydrogen in IIa. Such a coupling was established conclusively by performing a double resonance experiment[5] on IIa. On double irradiation at the frequency of the methyl resonance, the doublet at $\delta = 2.04$ p.p.m. was sharpened to give a symmetrical AB system (Fig. 1b), thus clearly demonstrating that the broadening of the C-12 axial proton resonance in the spectrum of IIa (Fig. 1a) is due to coupling with the methyl protons. Alternatively, double irradiation at the frequency of the C-12 axial proton again caused reduction in the half-width of the C-18 methyl resonance, as in the spectrum of the 12α-d_1-ketone IIb (Fig. 2).

These results, and those described by us earlier,[6] along with the reported examples of allylic[7] and homo-allylic[8] coupling, again emphasize the caution which must be exercised in the interpretation of n.m.r. spectra.

Acknowledgment.—The work at Stanford University was supported by Grant No. CRTY-5061 from the National Institutes of Health of the U. S. Public Health Service.

(4) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2091 (1963).

(5) N. S. Bhacca, M. E. Wolff, and R. Kwok, *ibid.*, **84**, 4976 (1962), and references cited therein.

(6) D. H. Williams, N. S. Bhacca, and C. Djerassi, *ibid.*, **85**, 2810 (1963).

(7) D. J. Collins and J. J. Hobbs, *Tetrahedron Letters*, **4**, 197 (1963), and references cited therein; T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963).

(8) J. T. Pinhey, *Tetrahedron Letters*, **4**, 275 (1963).

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RECEIVED JULY 22, 1963

Complexes of Organolithium Compounds with Vacant Orbital Acceptors

Sir:

Organo alkali metal compounds form donor–acceptor complexes with Lewis acids, such as diethylzinc, triethylaluminum, etc. We wish to report that properties, *e.g.*, bond energy, stoichiometry, and association
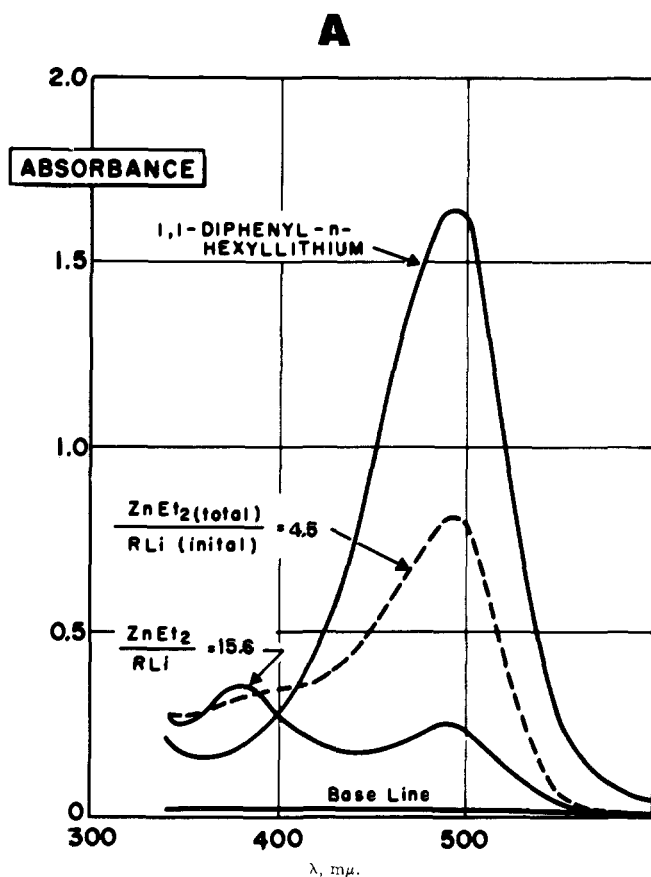
A

Fig. 1A.—The observed spectra for 1,1-diphenyl-n-hexyllithium and its complex at two ratios of diethylzinc to organolithium.

B

C

Fig. 1B and 1C.—The spectra of the complex of 1,1-diphenyl-n-hexyllithium at ratios of $ZnEt_2/RLi_0$ of 4.5 and 15.6, respectively, corrected for the absorption of 1,1-diphenyl-n-hexyllithium.

constants, of these complexes in solution can be evaluated spectroscopically (ultraviolet and visible) by using an organolithium compound having a defined absorption spectrum. Quantitative data for these complexes in solution are not available, nor has any other method to obtain these properties been reported. Addition of a Lewis acid vacant orbital acceptor to an organolithium compound reduces the absorption intensity of the organolithium compound and forms a new absorption maximum at shorter wave length, which we assign to the complex. The shift in the absorption of the organolithium compound caused by complexing with the Lewis acid is a measure of the energy of the dative bond. Data obtained permit determination of the stoichiometry of the complex and calculation of its equilibrium constant.

The chemistry of these "ate" complexes has been investigated principally by Wittig and co-workers.[1-3] Preparative procedures and stability studies of some specific complexes have also been reported by others.[4-7] Wittig found that the isolated complexes usually have a 1:1 stoichiometry. The chemistry of the complexes indicated that in solution they exist in equilibrium with uncomplexed reactants and that their reactivity is due primarily to uncomplexed organo alkali metal compounds.

The deep red colored 1,1-diphenyl-n-hexyllithium (I) has a strong absorption maximum at 496 mμ (log ϵ

(1) G. Wittig, F. J. Meyer, and G. Lange, Ann., 571, 167 (1951), and references therein.

(2) G. Wittig and D. Wittenberg, ibid., 606, 1 (1957).

(3) G. Wittig, Angew. Chem., 70, 65 (1958).

(4) H. I. Schlesinger and H. C. Brown, J. Am. Chem. Soc., 62, 3429 (1940).

(5) E. Wiberg, T. Johannsen, and O. Stecher, Z. anorg. Chem., 251, 114 (1943).

(6) D. T. Hurd, J. Org. Chem., 13, 711 (1948).

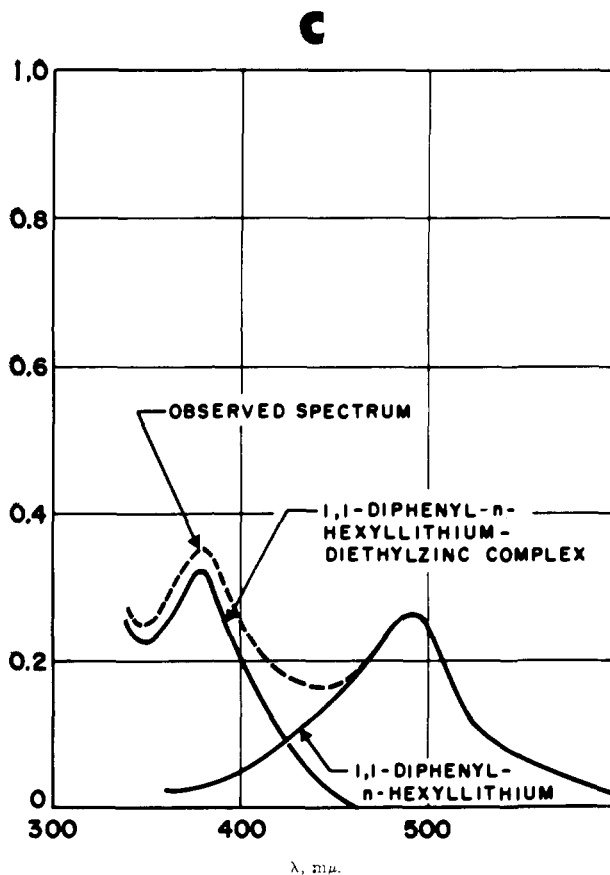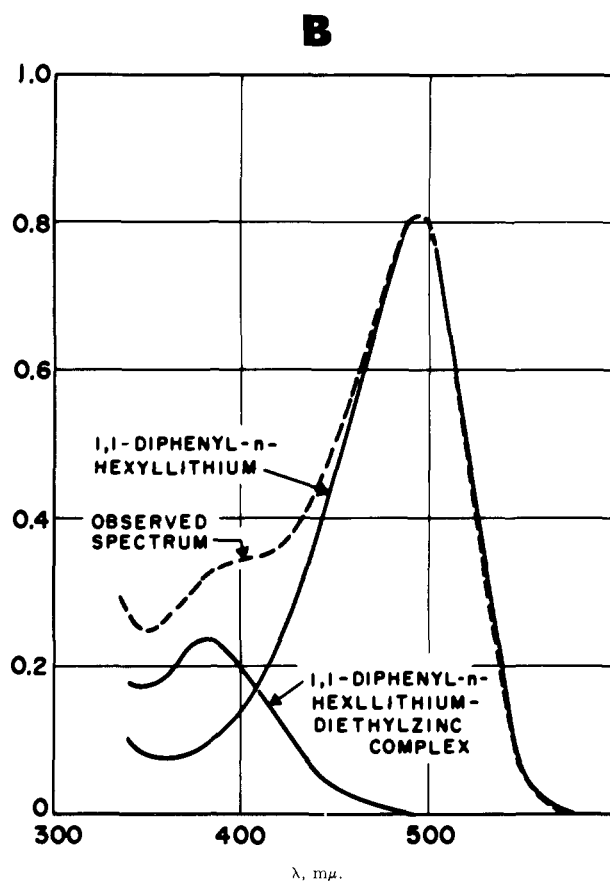(7) E. B. Baker and H. H. Sisler, J. Am. Chem. Soc., 75, 5193 (1953).

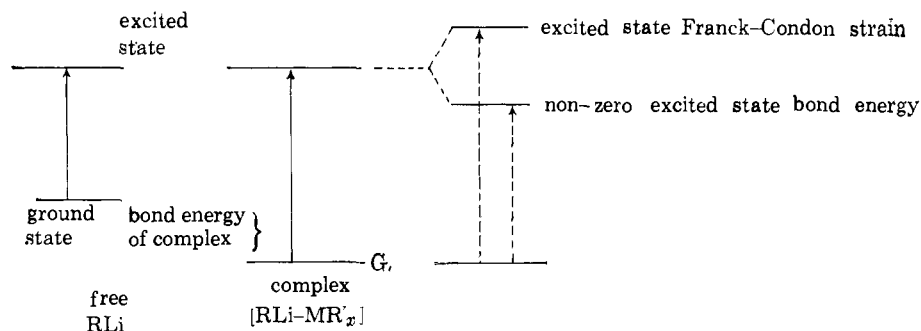SCHEME I: GROUND STATE–EXCITED STATE RELATIONSHIP

4.29) in tetrahydrofuran.[8] Diethylzinc added to I decreases the intensity of the 496 mμ absorption (eventually changing the color to orange) and produces a new absorption band at 375 mμ.[9] This is illustrated in Fig. 1. The molar absorptivity of the complex is 5.4 × 10³. Complete reversibility was demonstrated by first adding sufficient diethylzinc to reduce the absorption of I to ~10% of its original value, and then an excess of nonabsorbing organolithium compound (n-butyllithium[10]) to regenerate ~95% of the original absorption of I. That the recovery was not 100% is due to a slow (~5% in 40 min.) time dependent decrease in the over-all absorptivity of the solution, which is probably due to solvent cleavage by the complex.[2] With aluminum alkyl complexes of I the decrease in absorptivity is much more rapid.

Equilibrium constants are calculated from the known amounts of added Lewis acid (the diethylzinc was used as a 1.5 M solution in hexane) and the accompanying decrease in absorptivity of I at 496 mμ. Consistent values are obtained for the association constant between diethylzinc and I calculated as a 1:1 complex, i.e., $[R^-Li^+] + Et_2Zn \rightleftarrows [RZnEt_2^-Li^+]$. For eight data the average value of K is 103 l./mole with ±1.4 average deviation from the mean. No time effects were observed, thus equilibrium must be established very rapidly.

The bond energy of the complex is obtained by the difference between the transition energy of the complex and that of the free organolithium compound. In 1,1-diphenyl-n-hexyllithium the carbon–lithium bond electrons may be considered to have partial p-character and are able to delocalize over the π-system. Owing to electron delocalization, I is an odd alternate ion in which the mobile electron pair of the C–Li bond occupies (to a first approximation) a nonbonding orbital. In the first electronic excited state, one of these electrons is promoted to the lowest antibonding π-orbital. Participation of the C–Li bond electrons in a dative bond lowers their energy.[11] In the electronic excited state the dative bond of the complex is presumably very weak (it now being a single electron bond), so the energy of the excited state is assumed to be unchanged by complex formation. This relationship is shown in Scheme I. Identifying the difference between the transition energy of the complex and the uncomplexed organolithium compound with the energy of the dative bond is analogous to the procedure used by Brealey and Kasha[12] in evaluating the strength of hydrogen bonds formed between alcohols and carbonyl compounds. In

this manner a bond energy of 18.6 kcal. is obtained for the dative bond between diethylzinc and I. The bond energies so determined may not be exact, owing to two effects.[13] If the bond energy of the excited state of the complex is not zero, the bond energies we obtain will be smaller than the true bond energy by the amount of the excited state bond energy. Secondly, equilibrium solvent orientation and distances in the ground state of the complex may not be the most favorable arrangement in the excited state. Because the solvent cannot reorient during the electronic transition, the observed difference in transition energy may be larger than the bond energy by the amount of the Franck–Condon strain. The transition of the free organolithium compound, however, should also be subject to similar excited state Franck–Condon strain. These effects are presumably small and of similar magnitude for a series of complexes.

We are currently using this spectroscopic technique to study the complexes formed between other Lewis acids and with other organolithium compounds. We have also examined the p.m.r. spectrum of these complexes' which demonstrates conclusively that negative charge migration from the organolithium compound to the Lewis acid occurs on complex formation. This report is in preparation.

(13) G. C. Pimentel, ibid., **79**, 3323 (1957).

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Insulin Peptides. IX. The Synthesis of the A-Chain of Insulin and its Combination with Natural B-Chain to Generate Insulin Activity

Sir:

We wish to report the synthesis of the A-chain of insulin and its combination with natural B-chain to generate insulin activity. This represents the partial synthesis of a protein possessing biological activity.

Degradative studies by Sanger and co-workers led to the elucidation of the amino acid sequence of insulin from various species and the postulation of a complete structure for this protein.[1] The proposed structure for sheep insulin is shown in Chart I.

Studies have been undertaken in our Laboratory directed toward the synthesis of this protein.[2,3] The assumption was made that if chemically synthesized A- and B-chains are available the eventual synthesis of insulin can be achieved by combination of the two chains. This assumption was substantiated by the recent reports of Dixon and Wardlaw,[4] of Wilson, et al.,[5]

(8) R. Waack and M. A. Doran, J. Am. Chem. Soc., **85**, 1651 (1963).

(9) To illustrate this technique, we will detail our results for diethylzinc. A more complete report for other Lewis acids is in preparation.

(10) Diethylzinc in THF or butyllithium and diethylzinc in THF have only end absorption at short wave length.

(11) The positive lithium counter-ion may also be thought of as a vacant orbital acceptor. The transition energy of the completely ionized organolithium should, then, be less than when the carbon–lithium bond has more covalent character: R. Waack and M. A. Doran, J. Phys. Chem., **67**, 148 (1963).

(12) G. J. Brealey and M. Kasha, J. Am. Chem. Soc., **77**, 4462 (1955).

(1) F. Sanger and H. Tuppy, Biochem. J., **49**, 463, 481 (1951); F. Sanger and E. O. L. Thompson, ibid., **53**, 353, 366 (1953); H. Brown, F. Sanger, and R. Kitai, ibid., **60**, 556 (1955); J. I. Harris, F. Sanger, and M. A. Naughton, Arch. Biochem. Biophys., **65**, 427 (1956).

(2) P. G. Katsoyannis, J. Polymer Sci., **49**, 51 (1961).

(3) P. G. Katsoyannis, K. Fukuda, and A. Tometsko, J. Am. Chem. Soc., **85**, 1681 (1963).

(4) G. H. Dixon and A. C. Wardlaw, Nature, **188**, 721 (1960).