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April 1971

AEC Contract No. W-7405-eng-48

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Specific Protonation of the Carcinogen 7,12-Dimethylbenz[a]anthracene and Charge Localization in the σ-Complex

Sir:

In the class of the polycondensed aromatic hydrocarbons, the concept of localized charge in a σ-complex, e.g., the carbonium ion formed by addition of a proton or other electrophile to an aromatic ring, has so far received experimental evidence only in the case of anthracene. The ultraviolet spectrum of this compound in sulfuric acid[1] is similar to that

(1) V. Gold and F. L. Tye, J. Chem. Soc., 2172 (1952).

of the benzhydryl cation, Ph_2C^+Me. This result implies the protonation of anthracene at one meso-carbon atom and the localization of the positive charge at the other. The σ-complex of the potent carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) in acidic medium offers another example of this type of charge localization. The determination of structure was achieved by comparing the NMR spectra of DMBA in neutral and acidic solvents (Figure 1).

The ratio of the integrated intensities of the proton peaks in the spectrum of DMBA (Figure 1A) is, from right to left, 3:3:5:1:1:2:1. The assignment of the 7-CH_3 (δ3.00) and 12-CH_3 (δ3.29) resonances was made by comparison with the spectra of 7-methylbenz[a]anthracene (7-CH_3, δ3.03) and 12-methylbenz[a]anthracene (12-CH_3, δ3.32) under the same conditions. A good general correlation exists between the methyl chemical shifts of the twelve monosubstituted methylbenzanthracenes[2] and the corresponding aryl protons of benzanthracene.[3]

(2) L. K. Keefer, personal communication.

(3) T. J. Batterham, L. Tsai and H. Ziffer, Aust. J. Chem., 18, 1959 (1965).

The spectrum of DMBA in CCl_4-CF_3COOH-H_2SO_4 (Figure 1B) appears generally shifted to lower field with respect to the spectrum in CCl_4 (Figure 1A). This is attributable to the presence of the positive charge as well as to the increased polarity of the solvent system. However, the 12-CH_3 group (details of assignment given below) is shifted toward the aliphatic region (δ1.72) and occurs as a doublet (J=7.6H_z). The appearance of a new quartet at δ5.61 corresponding to the proton added at the basic 12-position (see below) shows the same coupling constant (J=7.6H_z) as the 12-CH_3 doublet. The original compound could be recovered unchanged, by dilution with cold water and extraction into CCl_4.

When DMBA was dissolved in a mixture of CCl_4-CF_3COOD-D_2SO_4 the spectrum of Figure 1C was obtained. In this case, the quartet was absent, the 12-CH_3 appeared as a singlet and the 7-CH_3 was entirely exchanged with deuterium when the spectrum was recorded 1 hr after dissolution.[4] A comparison of Figure 1D with Figure 1A demonstrates

(4) E. Cavalieri and M. Calvin, to be published. The rate of exchange indicates that deuterium substitution is complete in 10 minutes.

unequivocally that the 7-CH_3 has been exchanged and the upfield shifted CH_3-group in Figures 1B and 1C must necessarily be the one substituted in 12-position.

The assignment of the aromatic protons of DMBA (Figure 2) in different solvent systems has been accomplished by comparing its spectra with those of benzanthracene[3] and by applying Martin's empirical rules,[5] which suggest spectral regions for each type of aromatic proton.

(5) a) R. H. Martin, Tetrahedron, 20, 897 (1964); b) R. H. Martin, N. Defay, F. Geerts-Evrard, and S. Delavarenne, Tetrahedron, 20, 1073 (1964).

The chemical shifts of the different protons in benzanthracene[3] and DMBA (Figure 2A') are in the same order with the exception of the sharp doublet, H6, which in DMBA is shifted to lower field than H4. The deshielding effect on H6 is produced by the presence of the interacting 7-CH_3 group (peri-effect). When DMBA is protonated, the peri-effect disappears by virtue of the loss of planarity in the σ-complex and the chemical shifts of H4 and H6 (Figure 2B') revert to the "normal" order, as in benzanthracene. The assignment of H6 is based on its larger coupling constant with respect to the other ortho-couplings ($J=9.4H_z$) and on the partial deuterium exchange of H5, which produces an unsplit center peak in the H6 pattern (see Figures 2C' and 2D'). The characteristic pattern of an ABMX system[4,6] corresponding to the four interacting

(6) E. Cavalieri and M. Calvin (to be published).

nuclei H8, H9, H10 and H11 enables us to designate the protons H9 and H10. In Figure 2B' the complex band-system centered at δ8.25 and corresponding to five protons contains H8 and H11. Since H1 is an angular

proton, it has the largest downfield shift,thus identifying proton H4 as the remaining one.

In short, the results obtained demonstrate the specific protonation on C12 of DMBA in acid medium, producing selective charge localization on C7. Four factors can be outlined as responsible for this effect; i) Of the nine σ-complexes that can be drawn after protonation at the 12-position, the one with positive charge on the 7-carbon atom retains the greatest degree of aromaticity. ii) The reduction of the steric repulsion of the angular 12-CH_3 on the hydrogen H1 in DMBA would contribute to some stabilization of this protonated form. The presence of the methyl group in the 7-position induces a hyperconjugative stabilization of the carbonium ion.[7] Conversely, the positive charge should

(7) The methyl group also induces larger stabilization of trialkylcyclopropenyl cations, J. Ciabattoni and E. C. Nathan, Tetrahedron Letters, 4997 (1969).

stabilize an adjacent carbanionic center.

Such chemical reactivity of the aromatic hydrocarbons, which is presumably related to their carcinogenic activity, may be induced by the active "positive" oxygen of the hydroxylating enzymes.[8]

(8) E. Cavalieri and M. Calvin, Proc. Nat. Acad. Sci., June 1971.

Acknowledgment. The financial support, in part, of the Cancer Research Funds of the University of California, Berkeley, and, in part, of the U. S. Atomic Energy Commission, is gratefully acknowledged.

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Figure 1. The 220 MH_z NMR spectra of DMBA in different solvent systems at 17°. The scale is referred to TMS as internal standard. Accuracy of the coupling constant measurements is $\pm$ 0.1 H_z.

A DMBA (2.5% $\frac{wt}{v}$) in CCl_4

B DMBA (4.0% $\frac{wt}{v}$) in CCl_4-CF_3COOH-H_2SO_4 (volume ratios 50: 46.6: 3.3)

C DMBA (4.0% $\frac{wt}{v}$) in CCl_4-CF_3COOD-D_2SO_4 (" " ")

D DMBA (2.5% $\frac{wt}{v}$) in CCl_4. The solution of DMBA in Figure C was quenched in D_2O after 1.75 hr, and extracted with CCl_4 in which solvent the spectrum was recorded.

Figure 2. 220 MH_z NMR spectra of the aromatic proton regions of DMBA--conditions correspond to Figure 1.

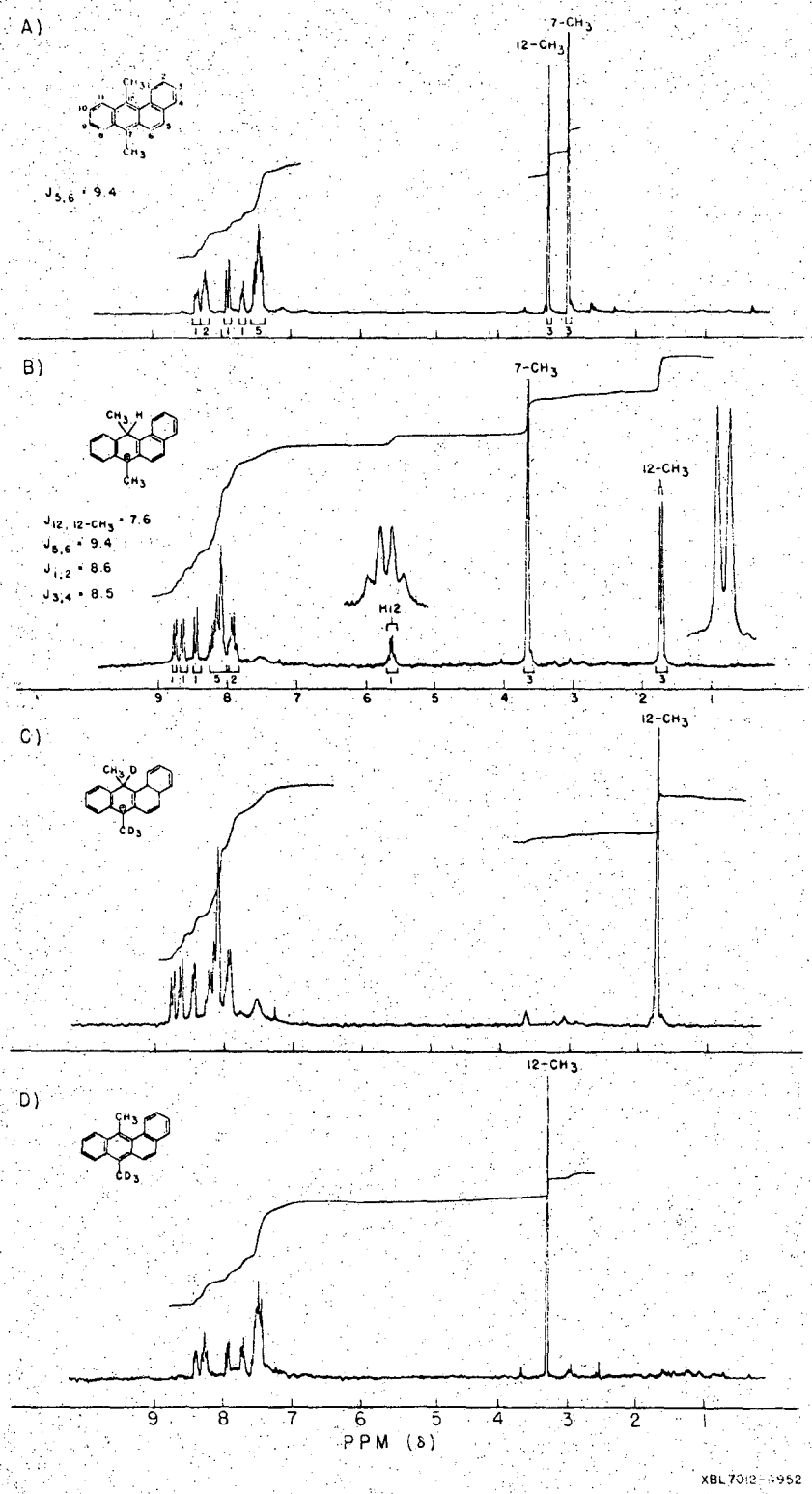
A)
7-CH3
12-CH3
J5,6 = 9.4
B)
7-CH3
12-CH3
H12
J12, 12-CH3 = 7.6
J5,6 = 9.4
J1,2 = 8.6
J3,4 = 8.5
C)
12-CH3
D)
12-CH3
PPM (δ)
XBL 7012-4952

Fig. 1

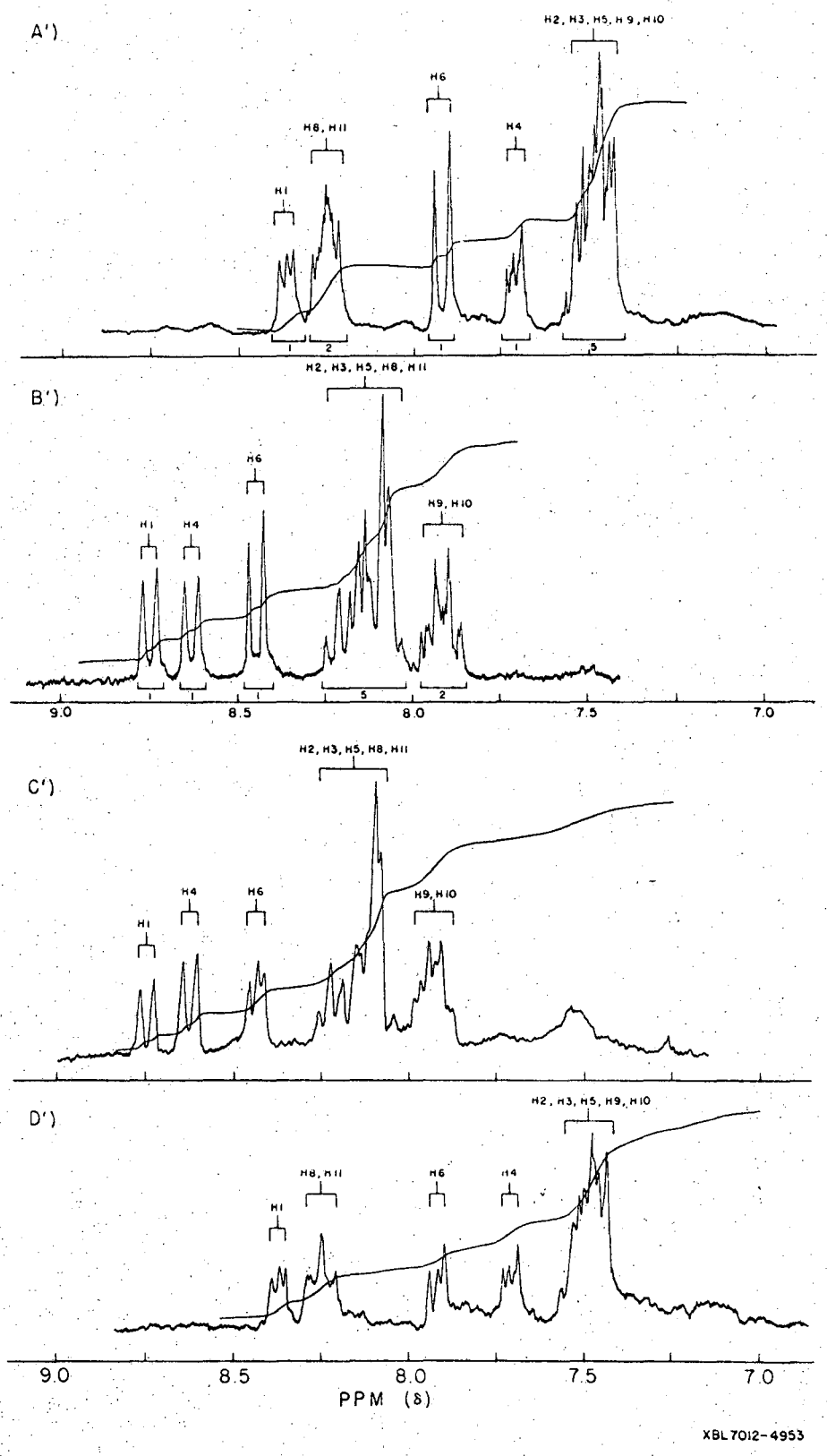
A')
H2, H3, H5, H9, H10
H6
H8, H11
H4
H1
B')
H2, H3, H5, H8, H11
H6
H9, H10
H1
H4
C')
H2, H3, H5, H8, H11
H4
H6
H9, H10
H1
D')
H2, H3, H5, H9, H10
H8, H11
H6
H4
H1
9.0
8.5
8.0
7.5
7.0
PPM (δ)
XBL 7012-4953

Fig. 2

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