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Directive Effects of Fluorine on Deuteriodeprotonation of Dibenzo[*a*,*i*]pyrene[1,2]

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The effects of fluorine substitution on the rate of deuteriodeprotonation of the carcinogen dibenzo[*a*,*i*]pyrene (DBP) at its reactive meso anthracenic (5 and 8) sites were studied by 270-MHz proton NMR as part of a program to investigate its mode of action. In addition to 2-F-DBP-5-^{13}C described in our previous paper, we have now synthesized 3-F-DBP-8-^{13}C, enabling us to assign the H-5 and H-8 resonances of the 2-fluoro, 3-fluoro, and 2,10-difluoro DBP's unambiguously. Our studies of the deuteriodeprotonation of the three fluoro compounds in comparison to DBP itself indicate that at large distances, resonance and π-inductive effects cancel at carbons conjugated to fluorine, so that the rate of exchange is unaffected. By contrast, exchange at nonconjugated carbons proceeds more slowly due to operation of the π-inductive effect alone. Thus fluorine can transmit deactivating electronic effects across large molecular distances, suggesting at least a partial explanation for the observed drastic reduction in carcinogenic potency of dibenzo[*a*,*i*]pyrene upon monosubstitution.

It has long been appreciated that replacement of hydrogen by the nearby isosteric fluorine atom can have a profound effect on the physiological properties of molecules.[3,4] The presumption is that the strength of the carbon–fluorine bond (ca. 100–120 kcal/mol) and its resistance to metabolism prevent metabolic transformation at the substituted carbon atom, so that a loss of biological activity upon fluorination implies that the position blocked by fluorine is involved in the activity of the unfluorinated parent. The fluorine substitution methodology has been developed into an important tool for probing metabolic pathways. As part of a program aimed at a detailed characterization of the effects of fluorine substitution on the electronic structures, chemical reactivities, and biological activities of polycyclic aromatic hydrocarbon (PAH) carcinogens, we have been applying the methodology to the hexacyclic carcinogen dibenzo[*a*,*i*]pyrene[2] (DBP), the most powerful and fast-acting sarcomatic agent among the PAH carcinogens.[5]

Little is known about its metabolism, although our observation that attachment of fluorine atoms at the 2- and 10-positions of DBP totally abolishes carcinogenicity provided the first direct evidence of the involvement of the angular (or "bay region") benzo rings, consistent with the inferential results of a metabolic activation study.[6]

The point of departure of this study was our observation that fluorine substitution profoundly influences the carcinogenic potency of dibenzo[*a*,*i*]pyrene.[2,7] Substitution of one fluorine in each bay-region benzo ring, as in 2,10-difluorodibenzo[*a*,*i*]pyrene, completely abolishes carcinogenicity. Blockage of one benzo ring, as in 3-F-DBP, attenuates but does not eliminate carcinogenicity, consistent with the presence of one unblocked benzo ring. However, substitution of a single fluorine in the 2-position (2-F-DBP) totally eliminates carcinogenicity, in spite of the fact that one site still remains unblocked. The possibility of transmission of substituent electronic effects over such large molecular distances, hitherto uninvestigated, intrigued us, and, in the hope of finding a chemical precedent for such a differential and long-range effect of fluorine, we began a study of the deuteriodeprotonation of DBP and its 2-fluoro, 3-fluoro, and 2,10-difluoro derivatives, the results of which are reported in this paper.

Results

We studied the effects of fluorine substitution on the rates and sites of deuteriodeprotonation of DBP and its fluoro derivatives by high-field (270 MHz) proton NMR spectroscopy, paying particular attention to both the overall activating or deactivating effect of fluorine substituents and to the differential electronic effect in the reactivities of molecular sites which are symmetry equivalent in DBP itself.

Assignment of NMR Spectra. The very narrow range of the proton chemical shifts in dibenzo[*a*,*i*]pyrene and its fluoro derivatives (less than 1.5 ppm) leads to extensive peak overlap, making spectral analysis very difficult at low-field strengths.[8] However, at 270 MHz, spectral definition is excellent, resonances are well-separated, and the spectra are easily assignable.[9,10]

Dibenzo[*a*,*i*]pyrene itself shows absorptions in three distinct NMR spectral regions. "Bay-region" protons (H-1,12,13,14) occur at lowest field (δ 9.0–9.2), presumably due to steric deshielding.[8] Protons 1 and 12 (δ 9.04) are approximately doublets due to coupling with H-2 and H-11, respectively, while H-13 and H-14 (δ 9.21) give rise to a singlet. At mid range (δ 8.2–8.3) are the proton pairs H-5,8 (δ 8.29, s) and H-4,9 (δ 8.24, d). Finally, at the high-field end of the range (δ 7.7–7.9) are the pair H-6,7 (δ 7.80, s) and a complex multiplet due to the equivalent pairs H-2, H-3 and H-11, H-10 (δ 7.8).

(1) Presented in part at the 69th annual meeting of the American Association for Cancer Research, Washington, DC, Apr, 1978, paper no. 184 (*Proc. Am. Assoc. Cancer Res.* 1978, *16*, 46).

(2) Dibenzopyrenes and Their Fluoro Derivatives. 3. (a) Part 1: Boger, E.; O'Malley, R. F.; Sardella, D. J. *J. Fluorine Chem.* 1976, *8*, 513. (b) Part 2: Sardella, D. J.; Mariani, H. A.; Mahathalang, P.; Boger, E. *J. Labelled Comp. Radiopharm.* 1979, *16*, 633.

(3) Miller, J. A.; Miller, E. C.; Finger, G. C. *Cancer Res.* 1953, *13*, 93.

(4) Newman, M. S. In "Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism and Carcinogenesis"; Freudenthal, R. I.; Jones, P. W., Eds.; Raven Press: New York, 1976; Vol. I, p 203.

(5) (a) Buu-Hoi, N. P. *Cancer Res.* 1964, *24*, 1511. (b) Sellakumar, A.; Shubik, P. *J. Natl. Cancer Inst.* 1974, *53*, 1713. (c) Hoffman, D.; Schmeltz, I.; Hecht, S. S.; Wynder, E. L. In "Polycyclic Hydrocarbons and Cancer"; Gelboin, H. V., T'so, P. O. P., Eds.; Academic Press: New York, 1978; Vol. I, p 97.

(6) Boger, E.; Treger, A. *Proc. Am. Assoc. Cancer Res.* 1972, *13*, abstract No. 37.

(7) Mahathalang, P. Ph.D. Thesis, Boston College, 1977.

(8) (a) Haigh, C. W.; Mallion, R. B.; Armour, E. A. G. *Mol. Phys.* 1970, *18*, 751. (b) Haigh, C. W.; Mallion, R. B. *Ibid.* 1970, *18*, 767.

(9) Cavalieri, E.; Calvin, M. *Proc. Natl. Acad. Sci. U.S.A.* 1971, *68*, 1251.

(10) The protocol used for the deuteriodeprotonation experiments is given in: Cavalieri, E.; Calvin, M. *J. Chem. Soc., Perkin Trans. 1* 1972, 1253.

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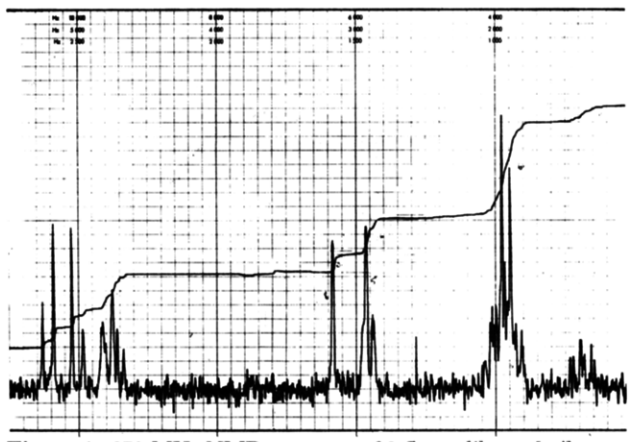


Figure 1. 270-MHz NMR spectrum of 3-fluorodibenzo[a,i]pyrene in $CDCl_3$.

Fluorine substitution destroys the symmetry plane normal to the C-6, C-7 and C-13, C-14 bonds, making all protons nonequivalent. Moreover, protons ortho to fluorine shift upfield 0.3–0.4 ppm. In general, however, resonances remain within the three characteristic regions. The case of 3-fluorodibenzo[a,i]pyrene is typical (Figure 1). At extreme low field is an AB quartet due to the proton pair H-13,14. Protons 1 and 12, likewise nonequivalent, appear as partially overlapping doublets. At mid range are two singlets due to the meso anthracenic protons H-5 and H-8, with the higher field singlet partially overlapped by a doublet assigned to H-9. The absorption of H-4, ortho to fluorine, has shifted upfield 0.45 ppm under the complex multiplet arising from the nonequivalent protons H-10 and H-11. Rising above the rather uniformative multiplet due to H-4, H-10, and H-11 are two intense singlets (δ 7.79 and 7.82) representing the inner lines of a severely skewed AB quartet corresponding to the "K-region" protons H-6 and H-7. Finally, at δ 7.56 a one-proton absorption (grossly a "triplet", actually the M portion of an ABMX spectrum) is assigned to H-2, shifted upfield 0.27 ppm by the ortho fluorine. The spectra of the 2-fluoro and 2,10-difluoro compounds are analogous and unexceptional.

Deuteriodeprotonation Studies. To assess the effects of fluorine substitution on the chemical reactivity of DBP, we investigated its rate of deuteriodeprotonation.[10] Solutions of DBP in concentrated D_2SO_4 were allowed to stand at 0 °C for periods of several minutes and then were diluted into an excess of D_2O, and the DBP was extracted into chloroform. NMR analysis showed facile incorporation of deuterium only at positions 5 and 8—the meso anthracenic positions (peri to the site of initial epoxidation) postulated variously to be involved either directly (as sites of metabolism)[11] or indirectly (as sensitizing sites[9] or in some other unspecified fashion)[12] in carcinogenesis. All three fluoro derivatives likewise undergo deuteriodeprotonation at H-5 and H-8, although the perturbing influence of fluorine exerts a differential effect on their reactivities. Analysis of the results required definite assignment of H-5 and H-8 in each molecule, leading us to synthesize two ^{13}C-labeled compounds: 2-fluorodibenzo[a,i]pyrene-5-^{13}C[2] and 3-fluorodibenzo[a,i]pyrene-8-^{13}C.

The synthesis and spectral characteristics of 2-fluorodibenzo[a,i]pyrene-5-^{13}C and its precursors are described in detail elsewhere.[2b] 3-Fluorodibenzo[a,i]pyrene-8-^{13}C was synthesized as shown in Scheme I, all compounds being characterized by melting or boiling points, mass spectroscopy and NMR spectroscopy. The principal difference in the proton NMR spectra is the appearance of widely spaced doublets due to directly bonded ^{13}CH couplings, the magnitudes of which are revealed in Table I. As expected, couplings involving sp^3-hybridized carbons are in the range 130–150 Hz, while 3-F-DBP-8-^{13}C with its sp^2-hybridized carbon exhibits a coupling of 160 Hz.

Scheme I

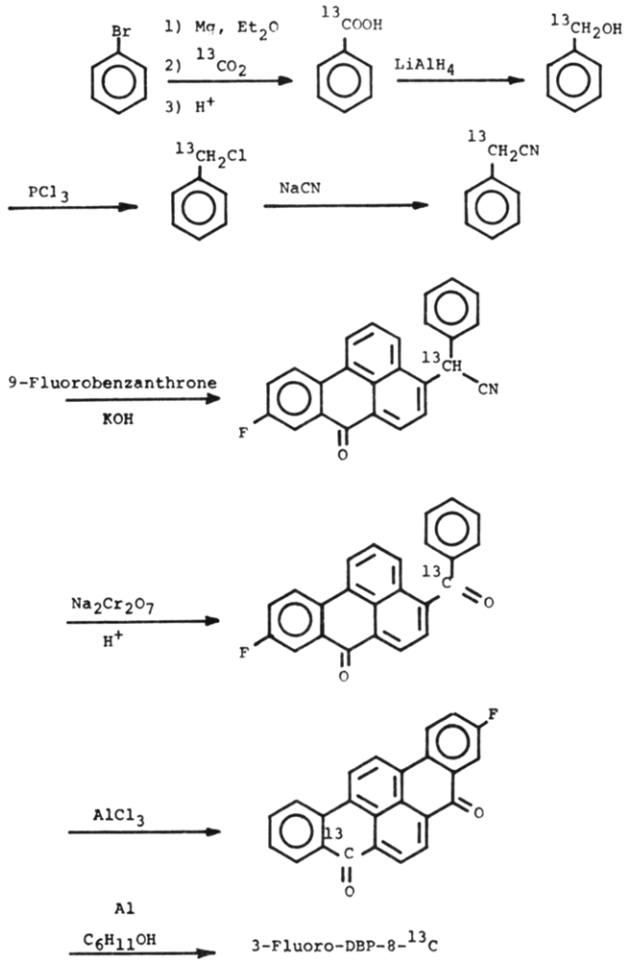


Table I. Directly Bonded ^{13}C-H Couplings in 3-Fluorodibenzo[a,i]pyrene-8-^{13}C and Its Precursors

compd	$^1J_{CH}$, Hz
benzyl-α-^{13}C alcohol	144
benzyl-α-^{13}C chloride	144
benzonitrile-α-^{13}C	136
α-phenyl-9-fluoro-7-oxo-7*H*-benz[*de*]anthracene-4-acetonitrile-α-^{13}C	132
3-fluorodibenzo[a,i]pyrene-8-^{13}C	160

Table II. Proton Chemical Shifts of Meso Anthracenic Protons in Dibenzo[a,i]pyrenes

compd	δ(5)	$\Delta\delta$	δ(8)	$\Delta\delta$
DBP	8.29		8.29	
2-F-DBP	8.25	−0.04	8.29	0.00
3-F-DBP	8.22	−0.07	8.32	0.03
2,10-F_2-DBP	predicted 8.28		8.22	
	obsd 8.31		8.22	

Assignment of H-5 and H-8 Resonances. Carbon-13 enrichment at a protonated carbon leads to loss of the proton resonance at the center band and the appearance of a new doublet due to the directly bonded ^{13}C–H coupling

(11) Cavalieri, E.; Roth, R.; Rogan, E. G. In "Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism and Carcinogenesis"; Freudenthal, R. I., Jones, P. W., Eds.; Raven Press: New York, 1976; Vol. I, p 181.

(12) Jerina, D. M.; Daly, J. W. "Drug Metabolism"; Parke, D. V., Smith, R. L., Eds.; Taylor and Francis: London, 1976; p 15ff.

Table III. Times Required for 50% Deuteriodeprotonation in DBP Derivatives

compd	$t_{1/2}$, min		k_{rel}	
	H-5[a]	H-8[a]	H-5	H-8
DBP	7	7	1.0	1.0
2-F-DBP	10	7	0.70	1.0
3-F-DBP	8	16	0.87	0.44
2,10-F_2-DBP	(26)[b]	12	0.30	0.58

[a] Estimated uncertainty, less than ±1 min. [b] Not observed directly, estimated from linear extrapolation with incubation times ranging from 0 to 16 min.

(for an sp^2-hybridized carbon, $J \approx 165$ Hz). In the case of 2-F-DBP, the δ 8.25 resonance was replaced by a doublet (J = 160 Hz), and the higher field δ 8.29 singlet was unaffected, indicating the resonances to correspond to H-5 and H-8, respectively. Similarly, ^{13}C enrichment of C-8 in 3-F-DBP also led to disappearance of the lower field singlet (δ 8.32) and appearance of a doublet (J = 159 Hz), indicating the same order of the relative shifts: H-5, δ 8.19; H-8, δ 8.32.

Knowledge of these shifts allowed assignment of the 5- and 8-position resonances in 2,10-F_2-DBP, assuming additivity of the individual fluorine effects. Relevant data are summarized in Table II. From the observed substituent-induced chemical shifts, the shifts of the 5- and 8-protons in 2,10-F_2-DBP are calculated to be $\delta(5) = 8.29 - 0.04 + 0.03 = 8.28$ and $\delta(8) = 8.29 + 0.00 - 0.07 = 8.22$, as compared to observed shifts of δ 8.31 and δ 8.22, respectively. The very good agreement between calculated and observed shifts indicates here a reversal of the shielding pattern seen in the monofluoro compounds, with H-5 less shielded than H-8. This ordering is also consistent with the kinetic data given below.

Deuteriodeprotonation: Differential Effects. The four DBP derivatives were incubated with concentrated D_2SO_4 for various times, quenched with D_2O, immediately extracted into chloroform, and then analyzed by 270-MHz proton NMR spectroscopy. The amplitudes of the meso anthracenic proton resonances decreased with increasing incubation time. From plots of peak area vs. time, we derived $t_{1/2}$, the time required for 50% deuterium incorporation at each position. These "half-times" are given in Table III. Clearly the effects, while small, are real, with the differential electronic effect of fluorine substitution being evident. Moreover, the substituent effect is transmitted in some cases over quite large molecular distances.

Fluorine in position 2 deactivates the proximate meso anthracenic position (C-5) but has no detectable effect on C-8. In contrast, the reverse holds true for substitution in position 3, where the proximate position is unaffected while the remote one is deactivated. Interestingly, the positions of unaltered reactivity are conjugated to the fluorine substituent while the deactivated sites are not conjugated.[13]

As mentioned above, the exchange data for 2,10-difluorodibenzo[a,i]pyrene are consistent with the data for the monofluorinated compounds given the assignments of H-5 and H-8 made on the basis of chemical shift additivity arguments. To test the assumption that individual fluorine substituent effects are independent and cumulative, we calculated the half-times for deuteriodeprotonation of the peri positions from the data in Table III as follows: $t_{1/2}(5) = 7/(0.70 \times 0.44) = 23$ min, $t_{1/2}(8) = 7/(0.87 \times 1.0) = 8$ min. These compare favorably with the experimentally observed values of 26 and 12 min, respectively.

Discussion

As indicated above, our observation that the carcinogenic activity of DBP is markedly reduced or even eliminated upon substitution of a single fluorine atom in one of its two otherwise equivalent bay-region benzo rings suggested that fluorine is capable of altering or inhibiting metabolic activation in an unsubstituted benzo ring at a great distance from the point of substitution. Since to our knowledge the feasibility of propagation of electronic effects across such large π systems had not hitherto been established, the goal of this study was to evaluate this possibility.

Deuteriodeprotonation studies afforded a convenient and attractive probe, particularly in view of the fact that the sites of attack, the meso anthracenic positions, had been proposed to undergo electrophilic attack either irreversibly, as the site of metabolic activation,[11] or reversibly, as a "sensitizing" site which gave rise to electron-deficient sites elsewhere in the π system which in turn were targets for nucleophilic attack.[9]

Our results, by confirming that fluorine exerts a deactivating effect across large molecular distances, support at least the possibility of its influencing the remote bay-region benzo ring by an electronic effect, for example, by destabilizing electron-deficient species formed during metabolic activation.

A second aspect of this study which leads to intriguing conclusions is the manner in which fluorine influences the electronic distribution in large π systems. The classic, simplistic picture of electronic effects is one in which field and/or inductive effects are assumed to attenuate rapidly with increasing distance, while resonance effects are efficiently transmitted, virtually without diminution, to remote sites in the molecule. The implication is that remote, unconjugated sites will be essentially unaffected, while conjugated sites will be activated. In fact, this is the opposite of what we see. Both our chemical shift data and our deuteriodeprotonation data indicate no effect on conjugated meso anthracenic sites and deactivation of unconjugated ones.

Shift Data. It is generally agreed that chemical shifts are related to electron density (nuclear shielding increasing with increasing electron density), although, particularly in the case of protons, other factors such as steric crowding, neighboring-group anisotropy, ring currents, and solvent effects play a significant and ofter dominant role.[14] However, in a series of molecules such as DBP and its three fluoro derivatives, the rigidity of the framework and the remoteness of the substitution site from the meso anthracenic positions make it likely that all factors except electron density will remain relatively constant, so that the proton shifts at these positions can yield qualitative information about electron-density variations.

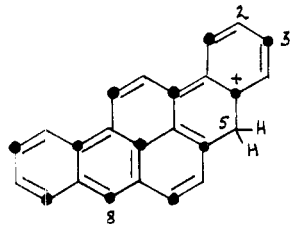
Inspection of the proton shift data in Table II reveals that attachment of fluorine in the 2-position results in increased shielding of H-5 and no change in H-8. By contrast, in the 3-F-DBP H-5 is shielded, while H-8 is deshielded. These data are consistent with the hypothesis that fluorine exerts two effects: a resonance effect in which

(13) A reviewer has pointed out that, owing to the steepness of the acidity function near 100% H_2SO_4, small amounts of protic water contamination could cause large variations in rate. In the case of intramolecular competition between the sterically equivalent meso anthracenic positions, a differential rate effect seems very unlikely. Such errors are, indeed, possible where intermolecular comparisons are involved. However, the internal consistency of both the kinetic and chemical shift data argue against such a possibility.

(14) Farnum, D. G. *Adv. Phys. Org. Chem.* **1975**, *11*, 123.

electron density accumulates on carbons conjugated with fluorine, resulting in shielding of the attached protons, and a field effect in which the π system is polarized, approximately about the DBP symmetry plane, with the half near fluorine uniformly acquiring electron density and the remote half being depleted.[15] Furthermore, the fact that at H-8 in 2-F-DBP (which is depleted of electrons by the field effect and enriched by the resonance effect) the net shift is zero suggests both effects to be of about equal importance. While this may seem at odds with intuition, it is interesting, and corroboratory, that our CNDO calculations on transmission of electronic effects in a series of 1-phenyl-*trans,trans*-1,3,5-hexatrienes indicate that resonance and field/inductive effects are nearly equally important even at moderate molecular distances.[16]

Deuteriodeprotonation Rates. Analysis of the relative rates of deuteriodeprotonation leads to a similar conclusion regarding the apparent relative importance of resonance and field/inductive effects. The transition state for deuteriodeprotonation will likely resemble strongly the protonated intermediate (in which the positive charge is located on the dotted carbon atoms, structure I). If ex-



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change occurs at C-5, fluorine substituted at C-2 will exert only an inductive effect, leading to deactivation, while fluorine attached to C-3 will exert offsetting resonance and inductive effects, consistent with the only modest deactivation observed (k_{rel} = 0.87). For exchange at C-8, on the other hand, fluorine at position 2 exerts both resonance and inductive effects, and no change is observed in rate (k_{rel} = 1.0). Fluorine bound to C-3 exerts only an inductive effect, resulting in deactivation, as observed. Thus, both chemical shift data and rates of deuteriodeprotonation concur in indicating that the assumed dominance of resonance effects at large distances may not be correct and that, in fact, both effects are comparable in importance. Sites not conjugated to the substituent will be most strongly affected, while conjugated ones will exhibit relatively little variation in reactivity.

The answer to the question of why this effect has not been noted previously in studies of substituent effects in other aromatic systems depends, we think, on two factors: (1) the stability of the cation intermediate and (2) the number of reactive sites and their disposition relative to the substituent. Release of electrons into a neutral π system creates charge separation and should consequently be less important than release of electrons into a cationic π system, where it serves to disperse charge. With very stable cations (such as the conjugate acid of DBP) the balance of resonance and field/inductive effects will be more even than, for example, that in benzene.

More significant, we feel, is the second factor. In most polycyclic aromatic systems of modest size and with several sites of equal or comparable reactivity, substitution places the substituent ortho or para to at least one site, influencing its reactivity far more than any of the others. For halogens this means activation of a single site. For an ortho position, the resonance effect dominates. In DBP, the meso anthracenic positions are by far the most reactive sites toward electrophilic attack,[17,18] and substitution in the angular benzo ring is incapable of redirecting attack to another site (such as ortho to fluorine). At the same time, the site of substitution is also well away from both positions, at distances large enough for the cancellation of resonance and field/inductive effects to be observed. Indications of this type of behavior can also be found in literature analyses of ^{13}C chemical shift data by the dual substituent parameter approach, where infelicitous disposition of reactive sites is not an issue.[19]

Experimental Section

Routine proton NMR spectra were recorded on one or more of several instruments: Varian Associates Models FT-80A (79.5 MHz), A-60A, and T-60 (60 MHz).

High-field proton NMR spectra (270 MHz) were obtained on a Bruker WH-270 Fourier transform spectrometer located at the Massachusetts Institute of Technology.

NMR samples were run in 5-mm tubes, with deuteriochloroform serving as both solvent and lock signal for the Fourier transform spectrometer. Chemical shifts were measured relative to chloroform (δ 7.25) and are accurate to better than 0.01 ppm.

Mass spectra were run on a Hitachi Perkin-Elmer Model RMS-4 medium-resolution spectrometer.

Infrared spectra were obtained by using a Perkin-Elmer Model 421-C spectrometer.

Melting and boiling points are uncorrected.

Deuteriodeprotonation experiments were performed as in the following description of a typical experiment. Dibenzo[a,i]pyrene (6 mg) was dissolved completely in concentrated sulfuric acid-d_2 (1.5 mL) at 0 °C, and the temperature was kept below 17 °C. The mixture was immediately shaken and the chloroform layer separated. The aqueous layer was extracted again with chloroform (5 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. The residue (ca. 5 mg) was dissolved in chloroform-*d* (1 mL) and filtered through cotton directly into a 5-mm NMR tube, and its spectrum was recorded.

Benzoic acid-^{13}C was obtained from the reaction between phenylmagnesium bromide (0.13 mol) and carbon dioxide (90% ^{13}C enriched) by using a procedure described elsewhere. The overall yield was 86%; mp 120.5–121.5 °C.

Benzyl-α-^{13}C alcohol was synthesized by the reduction of benzoic acid-^{13}C with lithium aluminum hydride in ether using the procedure we described for *p*-fluorobenzyl-α-^{13}C alcohol,[2b] affording an 87% yield of purified material. Its proton NMR spectrum was identical with that of unlabeled material, except for the disappearance of the benzyl singlet and the appearance of a doublet (J = 144 Hz) due to ^{13}C–^{1}H coupling.

Benzyl-α-^{13}C Chloride. Treatment of benzyl alcohol with phosphorus trichloride in dichloromethane in 20 min at 0 °C according to our previously described procedure yielded, after distillation, benzyl-α-^{13}C chloride (75% yield). Its NMR spectrum, identical with that of unlabeled material except for the doublet (J = 144 Hz) benzyl resonance, confirmed its structure.

Benzyl-α-^{13}C cyanide was obtained from the reaction of benzyl-α-^{13}C chloride with sodium cyanide, as described in ref 2b. It was distilled in vacuo [bp 120–125 °C (20 mmHg)] and characterized by its mass spectrum and proton NMR spectrum ($^{1}J_{CH}$ = 140 Hz).

α-Phenyl-9-fluoro-7-oxo-7*H*-benz[*de*]anthracene-4-acetonitrile-α-^{13}C [4-(Cyanobenzyl)-9-fluoro-7*H*-benz[*de*]anthracen-7-one-α-^{13}C]. To a cooled solution of 2.4 g of po-

(15) These are the R and π_F effects: (a) Katritzky, A. R.; Topsom, R. D. *J. Chem. Educ.* **1971**, *48*, 427. (b) Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1.

(16) Carter, F. R. M.S. Thesis, Boston College, 1979.

(17) Buu-Hoi, N. P.; Lavit, D. *Recl. Trav. Chim. Pays-Bas* **1956**, 75, 1194.

(18) Unseren, E.; Fieser, L. F. *J. Org. Chem.* **1962**, *27*, 1386.

(19) Kitching, W.; Bullpitt, M.; Gartshorne, D.; Adcock, W.; Khor, T. C.; Doddrell, D.; Rae, I. D. *J. Org. Chem.* **1977**, *42*, 2411.

tassium hydroxide in 7.5 mL of 2-propanol in a side-arm test tube were added 0.76 g of 9-fluorobenzanthrone[2a] and 3 mL of benzyl-α-^{13}C cyanide. The mixture was heated to 40–45 °C for 4 h while air was bubbled through it, during which time the color changed to blue and then indigo. The reaction mixture was cooled to room temperature, 2.2 mL of glacial acetic acid was added, and the mixture was allowed to stand overnight. The solid was filtered off, washed with hot methanol, and dried at 90 °C for 1 h, yielding 0.90 g (82%) of crude product, mp 202–205 °C (lit.[2a] mp 224 °C).

4-Benzoyl-9-fluoro-7*H*-benz[*de*]anthracen-7-one-α-^{13}C. A mixture of 1.5 g of anhydrous sodium acetate, 1.35 g of sodium dichromate, 1.0 g of 4-(cyanobenzyl)-9-fluoro-7*H*-benz[*de*]-anthracen-7-one-α-^{13}C and 7 mL of glacial acetic acid was heated on a boiling water bath for approximately 3 h and then allowed to cool to room temperature. Upon slow addition of water (7 mL) a yellow solid precipitated which was filtered and washed repeatedly with hot water until the filtrate was colorless. The material was dried in a vacuum oven (55 °C), affording 0.79 g (80%) of product, mp 220 °C (from benzene–petroleum ether).

3-Fluorobenzo[*rst*]pentaphene-5,8-dione-8-^{13}C. A mixture of 0.45 g of potassium chloride, 0.45 g of sodium chloride, 5.1 g of *technical*[2b] grade aluminum chloride, and 0.3 g of *m*-nitrobenzoic acid was heated to 125 °C in an Erlenmeyer flask. To the melt was added 0.79 g of 4-benzoyl-9-fluoro-7*H*-benz[*de*]-anthracen-7-one-α-^{13}C, and the mixture was maintained at 125 °C for 5 h. The reaction mixture was cooled, and 25 mL of dilute HCl (1:10 v/v) was added dropwise and with stirring. A red solid precipitated which was filtered and dissolved in 35 mL of a boiling mixture of water, hydrochloric acid, and ethanol (5:1:1 v/v/v). After the mixture was filtered and cooled 0.98 g of the red product was collected and air-dried.

3-Fluorodibenzo[*a,i*]pyrene-8-^{13}C (3-Fluorobenzo[*rst*]-pentaphene-8-^{13}C). Aluminum turnings (1.4 g) were dissolved in refluxing cyclohexanol (30 mL) in the presence of a trace of mercury(II) chloride. To the green-black solution was added 0.5 g of 3-fluorobenzo[*rst*]pentaphene-5,8-dione-8-^{13}C, and the mixture was heated under reflux for 48 h.

The reaction mixture was worked up as described previously,[20] and the product was purified by chromatography on silica gel: yellow crystals; mp 265 °C (from xylene); yield 40%.

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Registry No. Benzoic acid-^{13}C, 3880-99-7; benzyl-α-^{13}C alcohol, 54522-91-7; benzyl-α-^{13}C chloride, 57742-41-3; benzyl-α-^{13}C cyanide, 73368-35-1; α-phenyl-9-fluoro-7-oxo-7*H*-benz[*de*]anthracene-4-acetonitrile-α-^{13}C, 73368-36-2; 9-fluorobenzanthrone, 61735-79-3; 4-benzyl-9-fluoro-7*H*-benz[*de*]anthracen-7-one-α-^{13}C, 73368-37-3; 3-fluorobenzo[*rst*]pentaphene-5,8-dione-8-^{13}C, 73384-25-5; 3-fluorodibenzo[*a,i*]pyrene-8-^{13}C, 73384-26-6; 2-*F*-DBP, 73368-38-4; 2,10-F_2-DBP, 61735-78-2; DBP, 189-55-9; 3-*F*-DBP, 61735-77-1; phenyl bromide, 108-86-1.

(20) Tilak, F. B. D.; Unni, M. K.; Venkataraman, K. *Tetrahedron* **1958**, *3*, 62.

New Extended Hammett Equation with Donor and Acceptor Resonance Contributions

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It is shown that the equation $Q = \rho_I\sigma_I + \sigma_{R+}\sigma_R^+ + \rho_{R-}\sigma_R^- + h$ effectively copes with wide variations of electronic effects as precisely as the formulation of Ehrenson et al. It is also shown that the Tsuno–Yukawa equation is a mathematical artifact of this equation.

Different substituent constants and different modifications of the original Hammett equation have been derived in order to cope with experimental data involving wide variations in resonance contributions. Mathematical formulations based on a dual-parameter model such as by Ehrenson, Brownlee, and Taft,[2] Yukawa and Tsuno,[3] Swain and Lupton,[4] Hine,[5] and Wepster[6] enjoy high recognition. None of these equations, however, is generally applicable. Recently, Happer and Wright[7] have advanced a complex exponential model to account for these variations. The underlying theme of the most recent work is that no single set of σ_R constants is sufficient to correlate all experimental data. This was demonstrated by Ehrenson et al. using eq 1 (where "σ_R" is different for different

$$\Delta Q = \rho_I\sigma_I + \rho_R\text{“}\sigma_R\text{”} \quad (1)$$

reaction sites). Usually, for the best fit in a specific practical application, the substituent constants and, eventually, the LFER equation are selected by the method of trial and error. This uncertainty and ambiguity, however, would be eliminated if an equation of universal applicability to electronic effects would be derived with certain fixed sets of substituent constants. Equation 2,

$$Q = \rho_I\sigma_I + \rho_{R+}\sigma_R^+ + \rho_{R-}\sigma_R^- + h \quad (2)$$

which was introduced by us and tested on various exam-

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(2) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1–80.

(3) Tsuno, Y.; Ibata, T.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 960–5. Yukawa, Y.; Tsuno, Y. *Ibid.* **1959**, *32*, 965–71, 971–81. Yukawa, Y.; Tsuno, Y.; Sawada, M. *Ibid.* **1966**, *39*, 2274–86.

(4) Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328–37.

(5) Hine, J. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1962, pp 81, 381–2.

(6) Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 102–4. Hoefnagel, A. J.; Monshouwer, J. C.; Snorn, E. C. G.; Wepster, B. M. *Ibid.* **1973**, *95*, 5350–6. Hoefnagel, A. J.; Wepster, B. M. *Ibid.* **1973**, *95*, 5357–66. Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *Ibid.* **1976**, *98*, 6194–7.

(7) Happer, D. A. R.; Wright, G. J. *J. Chem. Soc., Perkin Trans. 2* **1979**, 694–8.

0022-3263/80/1945-2068$01.00/0