^{13}C Nuclear Magnetic Resonance Study on the Nature of Resonance Interactions in 4-Substituted Benzonitriles, Acetophenones, and Methyl Benzoates

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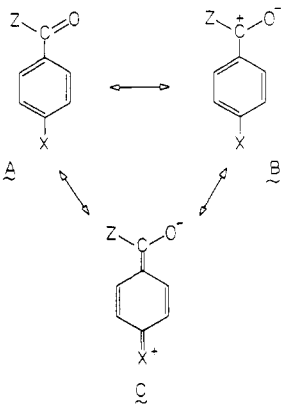
The effect of X substituents on the C(α) chemical shift of the CN, COMe, and COOMe groups in 2,6-dimethyl-4-substituted-benzonitriles DM-1, 2,6-dimethyl-4-substituted-acetophenones DM-2, and methyl 2,6-dimethyl-4-substituted-benzoates DM-3 has been studied. The data as such and after a dual substituent parameter (DSP) treatment have been compared with those obtained from the corresponding 2,6-unsubstituted compounds 1, 2, and 3. While the comparison between 1 and DM-1 allowed exclusion of any appreciable nonsteric effect of the two methyl groups, on going from acetophenones 2 to DM-2 remarkable differences have been observed as a consequence of steric inhibition of the conjugation between the acetyl group and the ring in DM-2. By contrast, the response in benzoates 3 and DM-3 is quite similar, in spite of a marked deviation from coplanarity between the aromatic ring and the COOMe group in DM-3. In addition, a notable similarity was found between benzoates 3 or DM-3 and acetophenones DM-2. These results constitute evidence that also in the unhindered methyl benzoates 3 the carbonyl-carbon chemical shift is not appreciably affected by through-conjugation with the para substituent, π-polarization appearing to be the dominant resonance effect.

The possible use of ^{13}C NMR spectroscopy as a tool for investigating the electron-density distribution in organic molecules keeps on attracting the attention of numerous authors.[1,2] In particular, the study of the chemical shift of the α-carbon of functional groups bonded to a benzene ring, pioneered by Stothers,[1a] has been recently and extensively developed by Brownlee et al.[1b-d] The latter authors reported inter alia that the ^{13}C chemical shifts of the cyano carbon in para-substituted benzonitriles or of the carbonyl carbon in para-substituted benzoyl fluorides are linearly related to their ab initio calculated π-electron densities. Moreover, they dissected the effect of 4-X substituents on the α-carbon chemical shift [substituent chemical shift (SCS) = $\delta_{4\text{-X}} - \delta_{4\text{-H}}$] of, e.g., a cyano, acetyl, or ethoxycarbonyl group in disubstituted benzenes into its polar ($\rho_I\sigma_I$) and resonance ($\rho_R\sigma_R$) components [dual substituent parameter (DSP) model],[3] according to the equation SCS = $\rho_I\sigma_I + \rho_R\sigma_R$. The negative ρ_I value ("reverse" polar effect, by which, e.g., electron-withdrawing substituents shield the probe carbon), shared by all the series examined, was interpreted on the basis of a polarization of the π-system of the functional group, induced by the substituent dipole. With regard to the resonance contribution, ρ_R was found to be positive for acetophenones, but negative ("reverse" resonance effect) for benzonitriles and ethyl benzoates; thus, in the latter two series of compounds, electron-donating substituents deshield the cyano or the carbonyl carbon. The dichotomic behavior of ketones and esters was explained[1b,d] by admitting that on going from the former to the latter the relative importance of structure A vs structure B increases. It was therefore argued that the main resonance interaction of an electron-donating para substituent produces, in acetophenones (B $\leftrightarrow$ C), a "normal" effect at C(α), as it is really a conjugating site, while it causes in ethyl benzoates (A $\leftrightarrow$ C) a "reverse" effect, as C(α) is now a nonconjugating site.

However, the observed different effects could alternatively hinge upon the occurrence of, besides through-conjugation, a second well-recognized[4] resonance effect: the polarization of the π-system of the probe group induced by the charge-density variation that the conjugative interaction between the aromatic ring and the 4-X substituent determines on C(1). The importance of this π-polarization component of the resonance effect which by itself



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(1) (a) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; Chapter 8. (b) Craik, D. J.; Brownlee, R. T. C. *Prog. Phys. Org. Chem.* **1983**, *14*, 1. (c) Bromilow, J.; Brownlee, R. T. C.; Craik, D. J. *Aust. J. Chem.* **1977**, *30*, 351. (d) Bromilow, J.; Brownlee, R. T. C.; Craik, D. J.; Fiske, P. R.; Rowe, J. E.; Sadek, M. *J. Chem. Soc., Perkin Trans. 2* **1981**, 753. (e) Goethals, G.; Uzan, R.; Nadjo, L.; Doucet, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1982**, 885. (f) Bromilow, J.; Brownlee, R. T. C.; Craik, D. J.; Sadek, M.; Taft, R. W. *J. Org. Chem.* **1980**, *45*, 2429. (g) Bromilow, J.; Brownlee, R. T. C.; Lopez, V. O.; Taft, R. W. *J. Org. Chem.* **1979**, *44*, 4766. (h) Sardella, D. J.; Keane, C. M.; Lemonias, P. *J. Am. Chem. Soc.* **1984**, *106*, 4962.

(2) De Benedetti, P. G.; Folli, U.; Iarossi, D.; Frassineti, C. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1527. Mullen, G. P.; Narender, P. L.; Dunlap, R. B.; Odom, J. D. *J. Org. Chem.* **1985**, *50*, 811. Adcock, W.; Butt, G.; Kok, G. B.; Marriott, S.; Topsom, R. D. *J. Org. Chem.* **1985**, *50*, 2551. Iyer, P. S.; Krishnamurthy, V. V.; Olah, G. A. *J. Org. Chem.* **1985**, *50*, 3059. Jason, M. E.; Kurzweil, P. R.; Leonard, K. E. *J. Org. Chem.* **1986**, *51*, 2550. Pomerantz, M.; Chou, W.-N.; Witczak, M. K.; Smith, C. G. *J. Org. Chem.* **1987**, *52*, 159. Bank, S.; Dorr, R. *J. Org. Chem.* **1987**, *52*, 501. Robinson, C. N.; Slater, C. D. *J. Org. Chem.* **1987**, *52*, 2011. Barchiesi, E.; Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1091.

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

(4) Dewar, M. J. S.; Golden, R.; Harris, J. M. *J. Am. Chem. Soc.* **1971**, *93*, 4187 and references therein. Craik, D. J.; Levi, G. C.; Brownlee, R. T. C. *J. Org. Chem.* **1983**, *48*, 1601 and references therein.

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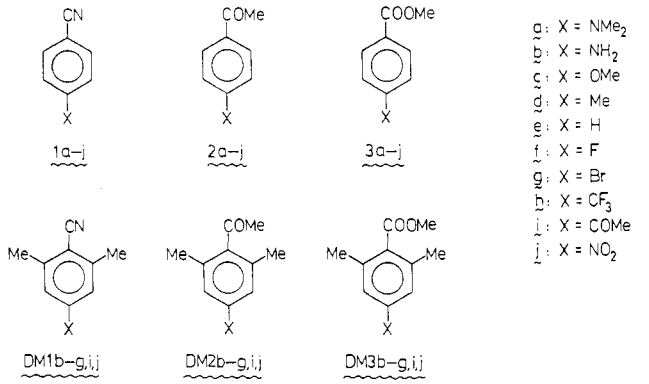
would obviously lead to a reverse substituent resonance effect on the C(α) chemical shift has been recently stressed by us[5a] and others,[5b] even in cases where through-conjugation is not precluded. A different balance between the through-conjugation and π-polarization effects could thus offer a rationale for the different behavior of, e.g., the carbonyl-carbon chemical shifts of acetophenones and ethyl benzoates.

In order to contribute to the definition of this interesting matter, we have undertaken a comparative ^{13}C NMR study between benzonitriles **1**, acetophenones **2**, and methyl benzoates **3** vs their corresponding 2,6-dimethyl derivatives DM-1–DM-3, at low concentration in $CDCl_3$.[6] Pertinent



literature data for compounds **1** and **2** have been utilized.[1c,d,f] The main objective was to compare the effects of the X substituents on the chemical shifts of the carbonyl carbon in **2** and **3** with those in the corresponding sterically hindered DM-**2**[7] and DM-**3**, where, at variance with the previous systems, the acetyl[1a,8] or the methoxycarbonyl group[9] is expected to exhibit a marked rotation angle with respect to the plane of the aromatic ring. The comparison between nitriles **1** and DM-**1** has been run in order to test whether the two methyl groups in DM-**1** electronically interfere with the transmission of the para-substituent effect to the α-carbon of the probe, whose linear structure is expected to minimize steric interactions with the methyl groups themselves.

Experimental Section

A. Syntheses. Commercial methyl benzoate **3e** was purified by distillation; DM-**1d**,[10] DM-**1e**,[11] DM-**1g**,[12] DM-**1j**,[13] DM-**2b**,[14] DM-**2c**,[15] DM-**2d**,[16] DM-**2e**,[14] DM-**3d**,[17] DM-**3j**,[18] **3a**,[19] **3b**,[20] **3c**,[21] **3d**,[22] **3f**,[23] **3g**,[24] **3h**,[25] **3i**,[26] and **3j**[27] were prepared as reported; DM-**3c**,[28] DM-**3e**,[18] and DM-**3g**[28] were synthesized as described for DM-**3d**.[17]

4-Amino-2,6-dimethylbenzonitrile (DM-1b) and methyl 4-amino-2,6-dimethylbenzoate (DM-3b) were quantitatively prepared by hydrogenation of the corresponding nitro derivatives DM-**1j** and DM-**3j** over 10% Pd/C in CH_2Cl_2. DM-**1b**: mp 196–197 °C (EtOH–H_2O); ^1H NMR ($CDCl_3$) δ 6.35 (s, 2 H), 3.95 (br s, 2 H), and 2.40 (s, 6 H). Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.06; H, 6.92; N, 19.20. DM-**3b**: mp 91–92 °C (EtOH–H_2O); ^1H NMR ($CDCl_3$) δ 6.33 (s, 2 H), 3.85 (s, 3 H), 3.69 (br s, 2 H), and 2.26 (s, 6 H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.00; H, 7.34; N, 7.86.

2,6-Dimethyl-4-methoxybenzonitrile (DM-1c) was obtained by dehydration of the corresponding amide with $SOCl_2$ (3-h reflux):[29] 79% yield; mp 71–72 °C (petroleum ether, bp 30–50 °C) (lit.[30] mp 85–88 °C); ^1H NMR ($CDCl_3$) δ 6.62 (s, 2 H), 3.81 (s, 3 H), and 2.48 (s, 6 H). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.57; H, 6.95; N, 8.80.

2,6-Dimethyl-4-fluorobenzonitrile (DM-1f). 2,6-Dimethyl-4-fluoroaniline[31] was diazotized and subjected to Sandmeyer reaction:[12] 40% yield; mp 97–98 °C (EtOH); ^1H NMR (Me_2SO-d_6) δ 7.17 (d, J_{HF} = 9.5 Hz, 2 H) and 2.47 (s, 6 H). Anal. Calcd for C_9H_8FN: C, 72.47; H, 5.41; N, 9.39. Found: C, 72.26; H, 5.35; N, 9.39.

2,6-Dimethyl-4-fluoroacetophenone (DM-2f) and methyl 2,6-dimethyl-4-fluorobenzoate (DM-3f) were prepared from the corresponding amines DM-**2b** and DM-**3b** via the Schiemann reaction.[32] DM-**2f** was purified by chromatography [silica gel, CH_2Cl_2–petroleum ether (bp 30–50 °C) (1:1)]. The colorless–pale yellow fractions with higher R_f were collected together, and a careful fractionation (Vigreux) gave a yellow residue, which was distilled under reduced pressure. DM-**2f** was collected as an oil: 1.1 g; bp 115 °C (20 mmHg); ^1H NMR ($CDCl_3$) δ 6.70 (d, J_{HF} = 9.5 Hz, 2 H), 2.43 (s, 3 H), and 2.20 (s, 6 H). Anal. Calcd for $C_{10}H_{11}FO$: C, 72.27; H, 6.67. Found: C, 72.09; H, 6.70. DM-**3f** was separated from the reaction mixture by distillation under reduced pressure: bp 78 °C (3 mmHg); mp 33–34 °C; ^1H NMR (Me_2SO-d_6) δ 6.97 (d, J_{HF} = 9.8 Hz, 2 H), 3.84 (s, 3 H), and 2.24 (s, 6 H). Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.92; H, 6.09. Found: C, 66.06; H, 6.17.

4-Bromo-2,6-dimethylacetophenone (DM-2g) was synthesized from DM-**2b** via Sandmeyer reaction:[33] 51% yield; bp 88–89

(5) (a) Consiglio, G.; Spinelli, D.; Arnone, C.; Sancassan, F.; Dell'Erba, C.; Noto, R.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2* **1984**, 317. (b) Hiberty, P. C.; Ohanessian, G. *J. Am. Chem. Soc.* **1984**, *106*, 6963.

(6) The set of substituents was chosen, according to earlier suggestions, to avoid alignment or clustering of points when plotting the resonance parameters of the X substituents vs the corresponding polar ones. See ref 1b and Johnels et al.: Johnels, D.; Edlund, U.; Grahn, H.; Hellberg, S.; Sjostrom, M.; Svante, W.; Clementi, S.; Dunn, W. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 863.

(7) A comparison between the effects of the X substituents on the chemical shifts of the carbonyl carbon in **2** and DM-**2** was already reported (ref 1e), but it was restricted to the cases where X = NMe_2, NH_2, OMe, Me, H.

(8) (a) Abraham, R. J.; Bergen, H. A.; Chadwick, D. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1161. (b) Oakley, M. G.; Boykin, D. W. *J. Chem. Soc., Chem. Commun.* **1986**, 439.

(9) (a) Baumstark, A. L.; Balakrishnan, P.; Dotrong, M.; McCloskey, C. J.; Oakley, M. G.; Boykin, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 1059. (b) Mugnoli, A.; Sancassan, F.; Novi, M.; Petrillo, G., manuscript in preparation.

(10) Fuson, R. C.; Denton, J. J. *J. Am. Chem. Soc.* **1941**, *63*, 654.

(11) Fuson, R. C.; Scott, S. L.; Horning, E. C., Mc Keever, C. H. *J. Am. Chem. Soc.* **1940**, *62*, 2091.

(12) Fuson, R. C.; Scott, S. L.; Lindsey, R. V. *J. Am. Chem. Soc.* **1941**, *63*, 1679.

(13) Leaketehdas Orion Oy. Br. Patent 896 720, 1962; *Chem. Abstr.* **1962**, *57*, 11113*h*.

(14) Fuson, R. C.; House, H. O. *J. Org. Chem.* **1953**, *18*, 496.

(15) Laarhoven, W. H.; Wivard, R. J. F.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 775.

(16) Noller, C. R.; Adams, R. *J. Am. Chem. Soc.* **1924**, *46*, 1889.

(17) Newman, M. S. *J. Am. Chem. Soc.* **1941**, *63*, 2431.

(18) Goering, H. L.; Rubin, T.; Newman, M. S. *J. Am. Chem. Soc.* **1954**, *76*, 787.

(19) Johnston, J. *Z. Phys. Chem., Stoechiom. Verwandtschaftsl.* **1906**, *57*, 557; *Chem. Abstr.* **1907**, *1*, 812.

(20) Klotz, I. M.; Gruen, D. M. *J. Am. Chem. Soc.* **1945**, *67*, 843.

(21) Kuhn, L. P.; Corwin, A. H. *J. Am. Chem. Soc.* **1948**, *70*, 3370.

(22) Tommila, E.; Brehmer, L.; Elo, H. *Ann. Acad. Sci. Fenn., Ser. A2* **1945**, *16*, 14; *Chem. Abstr.* **1947**, *41*, 903*d*.

(23) Bacon, F.; Gardner, J. H. *J. Org. Chem.* **1938**, *3*, 281.

(24) Vorlander, D. *Chem. Ber.* **1938**, *71*, 1688.

(25) Okamoto, Y.; Inukai, T.; Brown, H. C. *J. Am. Chem. Soc.* **1958**, *80*, 4969.

(26) Emerson, W. S.; Deebel, G. F. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 579.

(27) Weisler, L.; Helmkamp, R. W. *J. Am. Chem. Soc.* **1945**, *67*, 1167.

(28) Bender, M. L.; Chen, M. C. *J. Am. Chem. Soc.* **1963**, *85*, 37.

(29) Krynitsky, J. A.; Carhart, H. W. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 436.

(30) Houben, J.; Fischer, W. *Chem. Ber.* **1933**, *66*, 339.

(31) Valkanas, G. *J. Chem. Soc.* **1963**, 5554.

(32) Roe, A. *Org. React. (N.Y.)* **1949**, *5*, 193.

(33) Elson, L. A.; Gibson, C. S.; Johnson, J. D. A. *J. Chem. Soc.* **1930**, 1128.

Table I. SCS ($\Delta\delta$) Values[a] on the α-Carbon of the CN, COMe, and COOMe Groups in Compounds 1-3 and DM-1-DM-3 (0.2 M in $CDCl_3$)

X	1[b]	DM-1	2[b]	DM-2	3	DM-3
NMe_2	1.90		-1.70		0.35	
NH_2	1.40	1.33	-1.60	-0.36	0.02	-0.12
OMe	0.47	0.55	-1.22	-0.38	-0.27	-0.23
Me	0.35	0.36	-0.34	0.12	0.10	0.12
H	0.00	0.00	0.00	0.00	0.00	0.00
F	-0.78	-0.62	-1.70	-0.96	-0.98	-0.73
Br	-0.74	-0.64	-1.07	-1.21	-0.77	-0.84
CF_3	-1.34		-1.22		-1.27	
COMe	-0.88	-0.76	-0.58	-0.96	-0.90	-0.79
NO_2	-1.94	-1.75	-1.75	-2.23	-1.95	-1.75
δ-H[c]	118.71	117.26	198.01	208.42	166.96	170.34

[a] Negative figures correspond to shielding effects. [b] Data from ref 1c,d. [c] Chemical shifts (ppm from Me_4Si) for the parent systems (X = H).

°C (8 mmHg) [lit.[34] bp 60–61 °C (0.5 mmHg)].

4-Acetyl-2,6-dimethylbenzonitrile (DM-1i), 1,4-Diacetyl-2,6-dimethylbenzene (DM-2i), and Methyl 4-Acetyl-2,6-dimethylbenzoate (DM-3i). The diazonium tetrafluoroborates obtained[32] from the corresponding amines DM-**1b**, DM-**2b**, and DM-**3b** were reacted in Me_2SO solution with $FeSO_4$ in the presence of excess biacetyl.[35] DM-**1i** was obtained in 15% overall yield by chromatography [silica gel, CH_2Cl_2–hexane (8:1)]: mp 130–131 °C (EtOH); ^1H NMR (Me_2SO-d_6) δ 7.79 (s, 2 H), 2.60 (s, 3 H), and 2.52 (s, 6 H). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.15; H, 6.32; N, 8.07. DM-**2i** was obtained in 16% overall yield by preparative HPLC [silica gel, CH_2Cl_2–ether (15:1)]: mp 61–62 °C (pentane); ^1H NMR (Me_2SO-d_6) δ 7.66 (s, 2 H), 2.56 (s, 3 H), 2.48 (s, 3 H), and 2.24 (s, 6 H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.66; H, 7.50. DM-**3i** was obtained in 14% overall yield by preparative HPLC [silica gel, CH_2Cl_2]: mp 64–65 °C (petroleum ether, bp 30–50 °C); ^1H NMR (Me_2SO-d_6) δ 7.68 (s, 2 H), 3.89 (s, 3 H), 2.57 (s, 3 H), and 2.29 (s, 6 H). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.02; H, 6.77.

2,6-Dimethyl-4-nitroacetophenone (DM-2j) was prepared from DM-**2b** as reported[36] for **2j**: 35% yield; mp 104–105 °C (EtOH); ^1H NMR ($CDCl_3$) δ 7.90 (s, 2 H), 2.50 (s, 3 H), and 2.34 (s, 6 H). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.10; H, 5.83; N, 7.31.

B. ^{13}C NMR Measurements. The low concentration NMR data of **3**, DM-1, DM-2, and DM-3 were obtained from 0.2 M solutions in $CDCl_3$, as those reported in literature for 1 and **2**.[1c,d,f] The spectra of DM-1 and DM-2 were recorded on a Varian FT-80 spectrometer at 20 MHz, 8K data points being collected over a spectral width of 4 kHz for DM-1 and 4.5 kHz for DM-2, giving digital resolutions of 0.05 and 0.06 ppm respectively. The spectra of **3** and DM-3 were run on a Varian XL-200 spectrometer at 50 MHz; 32K data points were collected over a spectral width of 11 kHz, giving a digital resolution of 0.014 ppm. All chemical shifts were measured relative to Me_4Si in proton noise decoupled spectra. Assignments were assisted by the proton coupled spectra.

Results and Discussion

The chemical shifts observed for the α-carbon of the CN, COMe, and COOMe groups in the parent compounds (X = H), reported in Table I, are similar to those quoted by Stothers[1a] for the same compounds in more concentrated solutions. While the substantial (10 ppm) deshielding observed on going from **2e** to DM-**2e** was attributed[1a] to steric inhibition of conjugation in the latter compound, the smaller (3 ppm) deshielding on going from **3e** to DM-**3e** was related[1a] to a lower extent of steric inhibition to conjugation in the case of the hindered ester. However, this interpretation should be questioned on the basis of recent molecular mechanics results[8b,9a] indicating for **2d** and **3d** quasi-planar structures, and for DM-**2d** and DM-**3d** similar rotation angles (57° and 54° respectively) between the planes of the carbonyl group and the aromatic ring. In addition, an X-ray diffraction study[9b] of the crystal structure of DM-**3c** brought to evidence a 64° rotation angle between COOMe and the aryl group, together with a residual hindering between the two moieties: it is therefore conceivable that also in the isolated molecule, and in the weakly interacting $CDCl_3$ solvent, the lack of coplanarity be substantial throughout the DM-3 series.

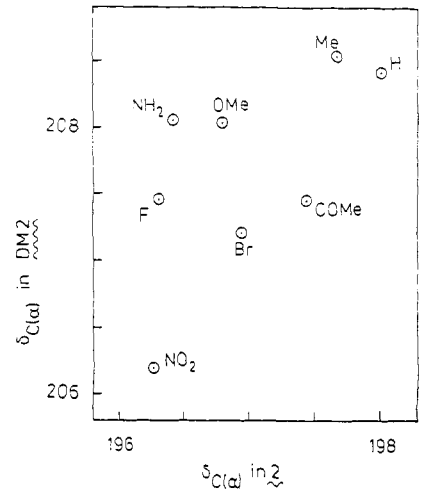


Figure 1. Carbonyl-carbon chemical shifts in hindered acetophenones DM-**2** vs those in the corresponding acetophenones **2**.

A more proper definition of the effect of 2,6-dimethyl substitution in the examined compounds can be reached by considering its influence on the response of the chemical shift of the various probe carbons to a convenient set of 4-substituents. As a first step, this aim can be simply pursued by plotting, for each probe group, the chemical shifts of the α-carbon in the 2,6-dimethyl derivatives vs those in the corresponding 2,6-unsubstituted compounds. In the case of nitriles, such a plot yielded a straight line (r = 0.999; slope = 0.92 ± 0.01), showing that the two methyl groups in DM-1 exert, if any, only a slight attenuation (and by a constant factor) of the effects of the 4-X substituents on the cyano carbon; it is therefore conceivable that the same methyl groups exert a similarly low and constant electronic effect on the C(α) chemical shift values also in DM-2 and DM-3, where any major effect played by such groups should therefore be steric in nature. In the case of acetophenones **2** and DM-2, the analogous plot presents a remarkable scattering of points (r = 0.623, Figure 1), showing that the different rotation angle between the carbonyl group and the aromatic ring in the two

(34) Yates, K.; Mandrapilias, G. *J. Org. Chem.* **1980**, *45*, 3892.
(35) Citterio, A.; Serravalle, M.; Vismara, E. *Tetrahedron Lett.* **1982**, *23*, 1831.
(36) Klosa, J. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1953**, *286*, 417.

Table II. Results of the DSP Analysis of SCS Values on the α-Carbon of the CN, COMe, and COOMe Groups in Compounds 1–3, 3′, and DM-1–DM-3 in $CDCl_3$

	1[a]	DM-1	2[a]	DM-2		3′[a]	3	DM-3
ρ_I	−2.69	−2.34	−2.58	−2.92	−2.98	−2.58	−2.61	−2.32
ρ_R	−1.13	−1.04	+0.78	−0.19	−0.70	−1.04	−0.95	−0.77
resonance scale	σ_R^+	σ_R^+	σ_R^+	σ_R^+	σ_R^0	σ_R^0	σ_R^0	σ_R^0
ρ_R/ρ_I	0.42	0.44	−0.30	0.06	0.23	0.40	0.36	0.33
n	13	8	13	8	8	13	10	8
SD	0.10	0.07	0.18	0.23	0.18	0.09	0.09	0.11
f	0.09	0.07	0.14	0.22	0.17	0.09	0.10	0.14

[a] Data from ref 1c,d.

Table III. SCS (Δδ) Values[a] on C(1) in Compounds 1–3 and DM-1–DM-3 (0.2 M in $CDCl_3$)

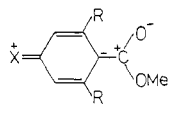
X	1[b]	DM-1	2[b]	DM-2	3	DM-3
NMe_2	−15.11		−11.79		−13.22	
NH_2	−12.54	−11.40	−9.32	−9.22	−10.50	−10.42
OMe	−8.48	−8.05	−6.80	−7.03	−7.56	−7.66
Me	−3.14	−3.02	−2.43	−2.68	−2.71	−2.97
H	0.00	0.00	0.00	0.00	0.00	0.00
F	−3.81	−3.81	−3.54	−3.89	−3.78	−3.96
Br	−1.13	−0.95	−1.26	−1.20	−1.08	−1.13
CF_3	3.69		2.62		3.15	
COMe	3.93	4.08	3.11	4.10	3.71	4.21
NO_2	5.94	5.91	4.37	5.52	5.31	5.80
δ-H[c]	112.35	113.41	137.00	142.57	130.07	133.73

[a] Negative figures correspond to shielding effects. [b] Data from ref 1f. [c] Chemical shifts (ppm from Me_4Si) for the parent systems (X = H).

series of compounds has a marked influence on the C(α) chemical shift values; this outcome can be straightforwardly rationalized by admitting that the conjugation between the aryl and the acetyl groups is effective in **2** and strongly inhibited in DM-2 for sterical reasons. By contrast, the relevant plot for methyl benzoates **3** and DM-3 gives a straight line (r = 0.988) with a slope (0.87 ± 0.05) that is not statistically different from that obtained for nitriles **1** and DM-1. This result is surprising, as it suggests that the effect of a 4-substituent on the carbonyl carbon be similar in nature in the two series of esters, irrespective of the quasi-planar structure of **3**[9a] and the large deviation from coplanarity between the methoxycarbonyl and the aromatic moieties in DM-3.[9] Thus the behavior of the carbonyl-carbon chemical shift fails to monitor any substantial conjugative interaction between the 4-substituent and the COOMe group also in the unhindered **3**.

In an attempt to gain a more detailed picture of the nature of the substituent effects involved, we have carried out a DSP analysis[1b,3] of the C(α) SCS values. The results of such treatment for compounds **3** and DM-1–DM-3 are collected in Table II, together with literature data[1c,d] referring to compounds **1** and **2**; data[1c,d] for ethyl benzoates **3′** are also reported, which show a strict similarity with the present methyl benzoates **3**. For each series of compounds, the results obtained with the resonance scale (chosen from among σ_R^0, σ_R^{BA}, and σ_R^+) that gives the best fit to the experimental data are reported. The goodness of fit, judged[1b,3] on the basis of both SD (standard deviation) and f (the ratio between SD and the root-mean-square size of the experimental data), is similar to that observed for analogous DSP analyses,[1b-d] indicating that the SCS figures herein are mainly determined by electronic effects of 4-X substituents. It is noteworthy that, while the best fit requires the use of the same resonance scale for benzonitriles **1** and DM-1 (σ_R^+) as well as for benzoates **3** and DM-3 (σ_R^0), two different scales provide best results for acetophenones **2** and DM-2 (σ_R^+ and σ_R^0 respectively). However, for a more meaningful comparison with acetophenones **2**, the results obtained for DM-2 with the σ_R^+ parameters are also reported. Inspection of Table II reveals that on going from **1** to DM-1, as well as from **3** to DM-3, no change in the sign of both ρ_I and ρ_R occurs and their ratio remains practically constant. This is clear evidence that the above-reported linear correlations between the C(α) chemical shifts of nitriles as well as of benzoates are not the consequence of a fortuitous compensation of changes in the polar and resonance components of the SCS values. The results obtained for DM-2, although to be considered with some caution because of the somewhat less satisfactory values of the agreement factors, show at least a significant change in the ρ_R/ρ_I value with respect to **2**, in keeping with the lack of a linear correlation between the C(α) chemical shifts of the two series.

With regard to the analysis of the single components of the SCS values, the reverse character of the polar contribution in all the examined series can be properly interpreted as previously reported.[1b,d] Conversely, the resonance effect appears to be either normal or reverse according to the particular series of compounds. This finding has to be considered together with the SCS values obtained for C(1) (Table III), which in every case appear to be mainly governed by normal resonance effects. Thus in methyl benzoates **3** and DM-3, for which the unimportance of through-conjugation with the 4-X substituent on the C(α) chemical shift has been well assessed above, the reverse resonance effect observed on C(α) can be straightforwardly rationalized on the grounds of π-polarization. The present interpretation (which is similar to that given[1b,d] for the behavior of the carbonyl-carbon chemical shift in para-substituted phenylacetyl fluorides, where through-conjugation is obviously precluded) corresponds to an enhanced contribution of structure D in the case of



D

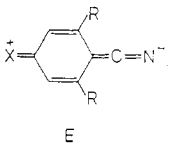
R = H, Me

electron-donating substituents. It seems noteworthy that such a structure is characterized by the occurrence, in the C(1)—C=O moiety, of a charge alternation pattern, whose

importance in unsaturated systems has been repeatedly stressed.[37]

For acetophenones **2**, the normal resonance effect observed at both C(α) and C(1) can be explained[1b-d] on the basis of the prevalence of conjugative interactions between the aromatic moiety and the acetyl group, which are enhanced by +R and reduced by -R substituents. On the other hand, in DM-**2** the change of the resonance scale and the shift of ρ_R toward negative values suggest (i) remarkable analogies with methyl benzoates **3** and DM-**3** and (ii) a prevalence of π-polarization over through-conjugation in determining the C(α) chemical shift also in DM-**2**. The analogies between the DM-**2** and **3** series find strong substantiation in the comparison of the plots of the C(α) chemical shifts of **3** vs those of **2** or DM-**2**: while scattering of points is observed in the former case (r = 0.550), a satisfactory linear correlation (r = 0.972, slope = 0.89 ± 0.08) is obtained between the C(α) chemical shifts of **3** and DM-**2**.[38]

Finally, the behavior of benzonitriles **1** and DM-**1**, characterized by a reverse resonance effect of 4-substituents on the cyano carbon, can suggest tight analogies between the CN and the COOR groups. These analogies could hinge upon a large polarizability of the CN group and/or a scarce importance of canonical structures such as E, because of their cumulene character.[39]



E

R = H, Me

Further studies are in progress in order to confirm the picture herein and to shed some light onto the reasons for the different behavior of unhindered acetophenones and alkyl benzoates, with particular regard to the reasonable possibility that the conjugation within the COOR group play a role in limiting the conjugation of the same group with the aromatic ring.

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Registry No. DM-**1b**, 114820-10-9; DM-**16**·HBF_4, 114820-19-8; DM-**1c**, 19111-77-4; DM-**1c**(amide), 114820-17-6; DM-**1d**, 2571-52-0; DM-**1e**, 6575-13-9; DM-**1f**, 14659-61-1; DM-**1g**, 5757-66-4; DM-**1i**, 114820-11-0; DM-**1j**, 31664-87-6; DM-**2b**, 83759-88-0; DM-**2b**·HBF_4, 114820-21-2; DM-**2c**, 60999-76-0; DM-**2d**, 1667-01-2; DM-**2e**, 2142-76-9; DM-**2f**, 114820-12-1; DM-**2g**, 53379-63-8; DM-**2i**, 114820-13-2; DM-**2j**, 114820-14-3; **3a**, 1202-25-1; **3b**, 619-45-4; **3c**, 121-98-2; **3d**, 99-75-2; **3e**, 93-58-5; **3f**, 403-33-8; **3g**, 619-42-1; **3h**, 2967-66-0; **3i**, 3609-53-8; **3j**, 619-50-1; DM-**3b**, 79909-92-5; DM-**3b**·HBF_4, 114820-23-4; DM-**3c**, 37934-88-6; DM-**3d**, 2282-84-0; DM-**3c**, 14920-81-1; DM-**3f**, 14659-60-0; DM-**3g**, 90841-46-6; DM-**3i**, 114820-15-4; DM-**3j**, 114820-16-5; biacetyl, 431-03-8.

(37) Pople, J. A.; Gordon, M. *J. Am. Chem. Soc.* **1967**, *89*, 4253. Fliszar, S. *J. Am. Chem. Soc.* **1972**, *94*, 7386.

(38) As expected, a very good linear correlation (r = 0.995; slope = 0.80 ± 0.03) was obtained by plotting the C(α) chemical shifts of DM-**3** vs those of the corresponding DM-**2**.

(39) The minor importance of the cumulene-type structure in the VB description of the acetonitrile anion was evidenced by the SCF + CI computations. See: Delbecq, F. *J. Org. Chem.* **1984**, *49*, 4838.

Diels-Alder Reactions of 7-Azalumazines. Synthesis of Condensed Lumazines and 8-Deazalumazines

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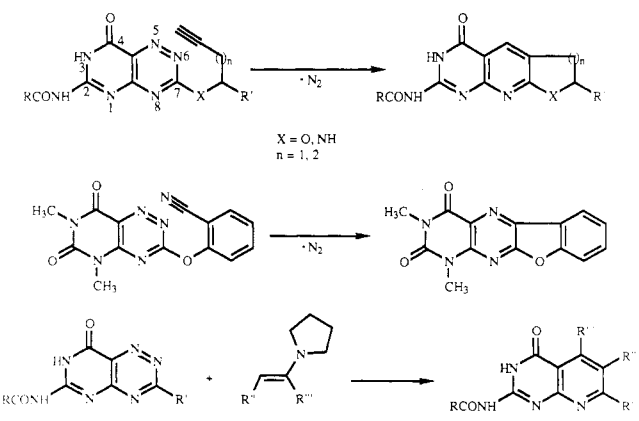
7-Azalumazines tethered at the C6 position with a series of dienophilic side chains undergo intramolecular Diels-Alder reactions to provide 6,7-annulated lumazines and 8-deazalumazines. The rates of these cycloaddition reactions are markedly faster than for previously reported cycloadditions of isomeric C7-tethered 6-azalumazines. On the other hand, 7-azalumazines do not undergo intermolecular Diels-Alder reactions with enamine dienophiles, whereas under identical conditions, 6-azalumazines react readily. Reasons for this striking reversal in reactivity observed for inter- and intramolecular Diels-Alder reactions of 6- vs 7-azalumazines are discussed.

We have previously reported a number of facile intramolecular Diels-Alder reactions of 6-azapterins and 6-azalumazines (pyrimido[4,5-*e*]-1,2,4-triazines) with dienophilic side chains tethered to C7 of the azapteridine skeleton that give access to an array of 6,7-annulated 5-deazapteridines and lumazines.[1,2] Analogous intermolecular inverse electron demand Diels-Alder reactions of 6-azapteridines with enamines have also been described that similarly provide a wide selection of 5-deazapteridines (Scheme I).[3] Derivatives of this latter ring system are of intense current interest as antimetabolites of the folate family of enzyme cofactors,[4] and some (e.g., DDATHF[5]) exhibit extraordinary antimitotic activity against a broad range of solid tumors.[6-11] We report herein our studies

Scheme I



(1) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159.
(2) Taylor, E. C.; Pont, J. L.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 800.
(3) Taylor, E. C.; McDaniel, K. F.; Warner, J. C. *Tetrahedron Lett.* **1987**, *28*, 1977.
(4) Palmer, D. C.; Skotnicki, J. S.; Taylor, E. C. In *Progress in Medicinal Chemistry*; Ellis, G. P., ed.; Elsevier: New York, in press.