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Communications

Substituent Effects on One-Bond $^{13}C-^{13}C$ NMR Coupling Constants between the Carbonyl Carbon and C_1 in Methyl Benzoates. Is There a Dependence on π-Bond-Order Changes?

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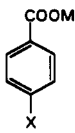
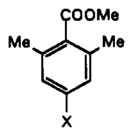
Summary: Substituent effects on $^1J_{CO,C1}$ in methyl 4-X-benzoates **1** and 2,6-dimethyl-4-X-benzoates **2** appear to be related with chemical-shift variations at the two involved carbon nuclei rather than with π-bond-order changes.

We have recently reported[1a,b] that in both $CDCl_3$ and $(CD_3)_2SO$ the response of the carbonyl carbon chemical shift to the effect of 4-substituents is much the same in methyl 4-X-benzoates and in the corresponding sterically hindered[2] 2,6-dimethyl derivatives. This and other[1c-g] results suggest a minor role for conjugative interactions between the methoxycarbonyl group and the aryl moiety even in 2,6-unsubstituted derivatives.



1a-k



2a-g,j,k

a: X = NMe_2
b: X = NH_2
c: X = OMe
d: X = F
e: X = Br
f: X = Me
g: X = H
h: X = CF_3
i: X = CN
j: X = NO_2
k: X = COMe

On the other hand, previous work[4a] on one-bond $^{13}C-^{13}C$ coupling constants in some 4-substituted methyl benzoates in $CDCl_3$ mainly attributed the observed substituent effects on $^1J_{CO,C1}$ to changes in the π-bond order between the two carbon atoms. This conclusion was based essentially on the finding that $^1J_{CO,C1}$ increases with electron-donating (OMe, Me, F, Cl, and Br) substituents, while a little effect in the opposite direction is exhibited by the only electron-withdrawing group considered (CF_3).

For a better insight into the matter, we have undertaken an investigation aimed at comparing $^1J_{CO,C1}$ values for a more representative set of methyl 4-X-benzoates **1** with those for the corresponding sterically hindered[2] 2,6-dimethyl derivatives **2**. Literature on ^1J coupling constants[5]

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(2) An X-ray diffraction study of the crystal structure of **2c** has evidenced a 64° rotation angle between the COOMe and the aryl moieties, together with a residual hindering between the former and the *o*-methyl groups.[3] These results, together with the possibility of an even larger torsion angle in solution, allow the conclusion that a marked steric hindrance to conjugation is effective in compounds **2**.

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Table I. One-Bond ^{13}C–^{13}C Coupling Constants[a,b] between the Carbonyl Carbon and C_1 and Substituent Effects on the C_1 and Carbonyl-Carbon Chemical Shifts[c] for Compounds 1 and 2[d]

		1		2		1		2	
	X	$^1J_{CO,C1}$	$\Delta^1J_{CO,C1}$	$^1J_{CO,C1}$	$\Delta^1J_{CO,C1}$	$\Delta\delta_{C1}$	$\Delta\delta_{CO}$	$\Delta\delta_{C1}$	$\Delta\delta_{CO}$
a	NMe_2	78.5	3.8	76.7	3.0	−13.84	0.14	−13.35[e]	0.08[e]
b	NH_2	78.1	3.4	76.4	2.7	−13.86	0.12	−13.74	0.02
c	OMe	77.2	2.5	75.8	2.1	−7.75	−0.32	−7.73	−0.16
d	F	76.4	1.7	74.7	1.0	−3.38	−0.90	−3.61	−0.70
e	Br	75.7	1.0	74.6	0.9	−0.83	−0.67	−0.81	−0.79
f	Me	75.6	0.9	74.3	0.6	−2.68	−0.02	−2.90	0.10
g	H	74.7	0.0	73.7	0.0	0.00	0.00	0.00	0.00
h	CF_3	74.7	0.0			3.77	−1.01		
i	CN	74.8	0.1			3.74[e]	−1.40[e]		
j	NO_2	75.0	0.3	74.1	0.4	5.36	−1.45	5.82	−1.40
k	COMe	74.5	−0.2	73.4	−0.3	3.59	−0.61	4.00	−0.53

[a] Values in Hz, measured at natural abundance at 50 MHz by the INADEQUATE[6] pulse sequence, with an accuracy of ±0.1 Hz. [b] 4 M solutions in CD_3CN at 40 °C. [c] From ref 1b, unless otherwise specified (0.3 M solutions in DMSO-d_6). [d] Compounds **1g**,**i** were commercial samples, purified before use. Compounds **1a–f**, **h**, **j**, **k** and **2b–g**,**j**,**k** were synthesized as reported in ref 1a. Methyl 4-(dimethylamino)-2,6-dimethylbenzoate (**2a**)[7] was prepared by methylation of **2b** according to a known[8] procedure. [e] This work.

is indeed lacking in comparative studies of this kind.

The $^1J_{CO,C1}$ values obtained for compounds **1** and **2** in CD_3CN are reported in Table I, together with the relevant substituent effects ($\Delta J = J_{4\text{-}X} - J_{4\text{-}H}$) and main experimental details. For compounds **1c–g** the values are very close to those previously reported[4a] in $CDCl_3$, confirming that in benzoates **1** electron-donating substituents significantly increase $^1J_{CO,C1}$. On the other hand, the electron-withdrawing groups considered exhibit at most very small effects,[9] with no definite trend, which could hardly be related to the expected decrease in the π-bond order between the carbonyl carbon and C_1.

The comparison of the $^1J_{CO,C1}$ values obtained for the parent compounds **1g** and **2g** shows that the 2,6-dimethyl substitution causes only a 1.0 Hz decrease,[10] possibly related[5] to the slightly longer CO–C_1 bond[3] in compounds **2**. More interestingly, the 4-substituent effect on $^1J_{CO,C1}$ proves to be qualitatively similar in the two series of compounds. Accordingly, by plotting the $^1J_{CO,C1}$ values of **2** vs those of the corresponding **1**, a good linear correlation is obtained ($r = 0.991$, $n = 9$, CL > 99.9%, slope = 0.80 ± 0.04, intercept = 14.1 ± 2.9), evidencing just a moderate and constant attenuation in the substituent effect on the $^1J_{CO,C1}$ values when going from **1** to the corresponding **2**. All these results suggest that the observed coupling constants are governed by similar factors in the two series of benzoates. Therefore, it appears that conjugative interactions between the methoxycarbonyl group and the aryl moiety do not play a major role in affecting $^1J_{CO,C1}$ even in the unhindered benzoates **1**. Surprisingly enough, however, in a search for possible linear correlations between $\Delta^1J_{CO,C1}$ values and known substituent parameters,[11] either series of benzoates gives the best fit with σ_R^+ constants[12] (**1**: $r = 0.991$, $n = 11$, CL > 99.9%, slope = −2.01 ± 0.09, intercept = 0.32 ± 0.07; **2**: $r = 0.981$, $n = 9$, CL > 99.9%, slope = −1.59 ± 0.12, intercept = 0.24 ± 0.10). As far as compounds **1** are concerned, this outcome could appear to hinge upon a strong dependence of $\Delta^1J_{CO,C1}$ on CO–C_1 π-bond-order variations; however, such rationale does not hold in the light of (a) the not-definite trend displayed by strong electron-withdrawing substituents and (b) the analogous good correlation obtained for the sterically hindered **2**.

A proper explanation of the observed substituent effects could be based on a relationship between the $\Delta^1J_{CO,C1}$ values and the changes in the electronic environment of the two involved carbon nuclei.[4b] In this light we have attempted, for each series of benzoates, a biparameter correlation of $\Delta^1J_{CO,C1}$ vs the substituent effects on C_1 and CO chemical shifts ($\Delta\delta_{C1}$ and $\Delta\delta_{CO}$, respectively, previously measured in DMSO-d_6,[1b] see Table I). For benzoates **1** and **2**, the following equations have been obtained, respectively:

$$\Delta^1J_{CO,C1} = -0.26\ (\pm 0.01)\Delta\delta_{C1} - 0.87\ (\pm 0.16)\Delta\delta_{CO} + 0.14\ (\pm 0.13)$$

$$(n = 11;\ r = 0.993;\ f = 0.09,\ \text{CL} > 99.95\%)$$

$$\Delta^1J_{CO,C1} = -0.21\ (\pm 0.02)\Delta\delta_{C1} - 0.91\ (\pm 0.26)\Delta\delta_{CO} + 0.07\ (\pm 0.18)$$

$$(n = 9;\ r = 0.979;\ f = 0.14,\ \text{CL} > 99.95\%)$$

The reasonably low f-values[12] support the reliability of such correlations and hence the hypothesis of a link between the various factors governing substituent effects on coupling constants and on chemical shifts.[13,14] For electron-donating groups, a full analysis of either equation reveals that the very high $\Delta\delta_{C1}$ values make the relevant contributions to the ΔJ the dominant ones; as $\Delta\delta_{C1}$ values are in turn mainly governed by the +R effect of the same substituents,[15] this result explains the above-mentioned

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(7) Compound **2a** was an oil: ^1H NMR (DMSO-d_6, 200 MHz) δ 6.39 (s, 2 H, Ar-H), 3.76 (s, 3 H, $COOCH_3$), 2.91 (s, 6 H, 2 $ArCH_3$), 2.23 (s, 6 H, 2 NCH_3); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.56 (CO), 150.69 (C_4), 136.80 (C_2), 120.41 (C_1), 111.07 (C_3), 51.09 ($COOCH_3$), 39.62 (2 NCH_3), 20.67 ($ArCH_3$). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.57, H, 8.25, N, 6.80.

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(10) The corresponding effect (−0.2 ± 0.5 Hz) of a single *o*-methyl group could hardly be appreciated. See: Hansen, P. E.; Poulsen, O. K.; Berg, A. *Org. Magn. Res.* **1977**, *9*, 649.

(11) Previous work[4a] on 4-X-benzoates did not report any such correlations.

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

(13) Similar correlations, with only slightly less favorable f-values are obtained when using the $\Delta\delta_{C1}$ and $\Delta\delta_{CO}$ values previously measured[1a] in $CDCl_3$. Therefore, the results of such correlations do not seem to be appreciably solvent-dependent.

(14) Better trends of one-bond ^{13}C–^{13}C coupling constants with ^{13}C chemical shifts rather than with π-bond orders have recently been reported for ring carbons of dithienopyridines. See: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.; Edlund, U.; Eliasson, B.; Johnels, D. *Magn. Res. Chem.* **1990**, *28*, 33.

correlations between $\Delta^1J_{\mathrm{CO,C1}}$ values and σ_R^+. On the other hand, for electron-withdrawing groups, the similar and opposite contributions of the $\Delta\delta_{\mathrm{C1}}$ and $\Delta\delta_{\mathrm{CO}}$ terms could explain the very small, if any, ΔJ values.

Further studies are in progress to better understand the nature of substituent effects on $^1J_{\mathrm{CO,C1}}$ in benzoates, also through their theoretical simulation, at the INDO level, according to Ramsey's theory.[16] Moreover, in order to test if the results obtained herein for benzoates are just a consequence of minor conjugative interactions between the COOMe group and the aryl moiety, we have also undertaken an analogous study of $^1J_{\mathrm{CO,C1}}$ in acetophenones, where vice versa effective conjugative interactions between the acetyl group and the ring have to be expected.[1a]

Acknowledgment. Financial support from MURST is gratefully acknowledged.

Registry No. **1a**, 1202-25-1; **1b**, 619-45-4; **1c**, 121-98-2; **1d**, 403-33-8; **1e**, 619-42-1; **1f**, 99-75-2; **1g**, 93-58-3; **1h**, 2967-66-0; **1i**, 1129-35-7; **1j**, 619-50-1; **1k**, 3609-53-8; **2a**, 141753-67-5; **2b**, 79909-92-5; **2c**, 37934-88-6; **2d**, 14659-60-0; **2e**, 90841-46-6; **2f**, 2282-84-0; **2g**, 14920-81-1; **2j**, 114820-16-5; **2k**, 114820-15-4.

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(15) The dual-substituent-parameter treatment[12] of $\Delta\delta_{\mathrm{C1}}$ for methyl 4-X-benzoates, attempted to dissect the polar and resonance effects of substituents, gives the best fit with the σ_R^+ resonance scale [$\Delta\delta_{\mathrm{C1}} = 4.89\ (\pm1.10)\sigma_I + 8.82\ (\pm0.37)\sigma_R^+ + 0.18\ (\pm0.49)$ ($n = 11$, $r = 0.995$, $f = 0.09$)]. The analogous treatment for **2** gives $\Delta\delta_{\mathrm{C1}} = 5.13\ (\pm1.72)\sigma_I + 8.71\ (\pm0.57)\sigma_R^+ + 0.13\ (\pm0.73)$ ($n = 9$, $r = 0.991$, $f = 0.12$). These results show that in either case the resonance contribution to $\Delta\delta_{\mathrm{C1}}$ values is the dominant one for electron-donating substituents.

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Sequential Diastereoselective Addition and Allylic Azide Isomerization of *syn*- and *anti*-α-Azido-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoates with Acetals: Asymmetric Synthesis of γ-Hydroxy-α-amino Acid Synthons

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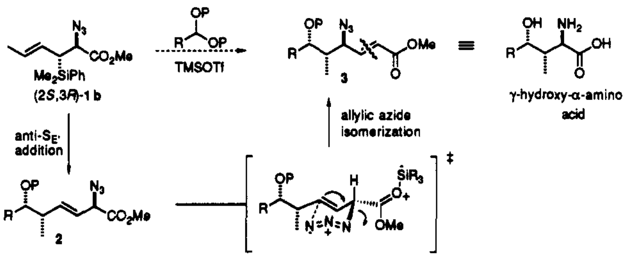
Summary: *syn*- and *anti*-methyl α-azido-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoates (2*R*,3*R*)-**1a** and (2*S*,3*R*)-**1b** undergo highly diastereo- and enantioselective addition reactions with oxonium ions catalyzed by the action of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to generate α-azido-β,γ-unsaturated esters **2**, with well-defined 1,4- and 1,5-stereochemical relationships, and a subsequent stereospecific allylic azide isomerization generated 1,3-azido ethers **3**, synthetic equivalents of γ-hydroxy-α-amino acids.

Scheme I



Natural products that contain unusual γ-hydroxy-α-amino acid residues are being found in increasing numbers in a wide variety of structural types.[1] As a consequence of the growing importance of molecules containing these structural units, the development of new reaction methodology that provides a stereoselective approach to this class of compounds is becoming an active area of research.[2] In earlier reports we have described the results of investigations concerning the development of functionalized (*E*)-crotylsilanes as carbon nucleophiles in diastereoselective addition reactions to acetals and aldehydes. Those studies resulted in the development of a useful strategy for the asymmetric construction of homoallylic ethers[3] and tetrahydrofurans.[4] Herein we disclose our results of experiments intended to further explore the utility of related α-azido (*E*)-crotylsilanes, (2*R*,3*R*)-**1a**[5] and (2*S*,3*R*)-**1b**,[6] in a sequential Lewis acid catalyzed condensation–allylic azide isomerization reaction with acetals.

In 1960, Winstein had reported that allylic azides existed as an equilibrating mixture of two isomers, interconverting by a rapid isomerization at room temperature and that the rate of equilibration was insensitive toward solvent type.[7] Lacking a well-defined regio- and stereochemistry, the reaction has remained highly underdeveloped and no general approach to effecting a controllable, stereoselective isomerization has been reported. Recent examples of

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(7) Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956–5957.