Reactivity Parameters. Part 2.† The Usefulness of ^{13}C-^{1}H One-bond Coupling Constants as Selectivity Parameters in the Synthesis of Organolithium Compounds

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^{13}C–H One-bond coupling constants have been used as selectivity parameters for identifying the reactive positons of aromatic systems in lithiation reactions. For differencies of coupling constants >5 Hz correct predictions are always made. For differencies of 2—5 Hz correct predictions are also made, if no hetero-substituents are present. The possibility of using incorrect predictions for assignment of true *ortho*-directing effects of hetero-substituents due to complexing of lithium with the substituent in the transition state is discussed.

The reaction of organolithium reagents with the C–H bonds of aromatic compounds is a convenient route to their substituted analogues. In contrast to a variety of organic reactions,[1] for example electrophilic aromatic substitution, no selectivity parameters have yet been found for the lithiation of aromatic compounds.[2-4]

There are various theories regarding orientation in the metallation of aromatic systems. Bryce-Smith[5] felt that the position of metallation by organosodium compounds is influenced primarily by the thermodynamic stability of the carbon–hydrogen bond undergoing scission, while Benkeser,[6] using both organosodium and -potassium compounds, proposed that initial attack is kinetically controlled, but that the final position of metallation is a result of thermodynamic stabilities. In directed metallations it has been found that the lithium atom is directed to a proton site adjacent to the directing substituent. Jones *et al.*[7] found *ortho*-metallation of *NN*-dimethylbenzylamine although the methylene group essentially insulates the ring from any inductive influence of the nitrogen atom. An interesting situation arises for metallation of thiophens containing an *ortho*-directing substituent. Not unexpectedly, compounds such as 3-methoxy-[8] or 3-methylthio-thiophen[9] are metallated largely or exclusively in the 2-position. However, the corresponding 2-substituted thiophens[10,11] are metallated in the 5- rather than the 3-position.

DISCUSSION

The stability of carbanions with localized charge is known to depend qualitatively on the amount of *s*-character in the lone pair.[12] It is also known that a linear relationship exists between the *s* character of the corresponding protonated carbon and the one-bond $J_{^{13}C-H}$ value.[13] In accordance with the above findings a correlation of kinetic acidities of small-ring cycloalkanes with the appropriate $J_{^{13}C-H}$ value has been found[14,15] (the coupling constants become greater with increasing acidity). From the one-bond $J_{^{13}C-H}$ values of furan[16] and thiophen,[17] it should then be expected that furan is more readily metallated in the α-position than thiophen. However, competitive reactions between thiophen and furan for an insufficient quantity of butyl-lithium show that thiophen is metallated almost

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exclusively.[18] This observation clearly demonstrates that great care should be taken in estimating kinetic acidities of different aromatic molecules from small differences in one-bond ^{13}C–H coupling constants.

One-bond $J_{^{13}C-H}$ values for furan and thiophen

For the reactivity of the different positions in an aromatic molecule itself, with an organolithium reagent, secondary effects like solvation and *d* orbital participation are considerably reduced. The greater one-bond ^{13}C–H coupling constants at the α-positions of furan and thiophen correctly predicts the greater reactivity at that position with butyl-lithium. The question then arises how small can the difference between coupling constants be and still give correct predictions of the reactivity order. This problem can be solved by examining more closely Tables 1 and 2.

For the heteroaromatic compounds (4)—(9), (11), (12), and (14)—(17) given in Table 1 there is a difference of 13.5—27 Hz between the two greatest one-bond ^{13}C–H coupling constants of a particular molecule. For all these molecules it is possible using an organolithium reagent to exchange hydrogen, which has the greater coupling constant, with lithium. In 3-methylthiophen (10) the difference between the two greatest coupling constants in the 2- and 5-positions is reduced to 1 or maybe 3.1 Hz, as reported by another group. As seen from Table 1 the coupling constants correctly predict that 3-methylthiophen is mainly metallated in the 5-position. For this compound, also, metallation at the 2-position occurs. However, the ratio 1 : 3 for metallation of the 2- and 5-positions is rather close to random lithiation and it may be foreseen that for even smaller differences of coupling constants, secondary effects such as the geometry and solvation of the transition state would determine the position of lithiation.

TABLE 1

One-bond coupling constants and lithiation yields of compounds (1)—(17)

	Position									
	$J_{^{13}C-H}$/Hz					Yield (%)				
Compound	1	2	3	4	5	1	2	3	4	5
Naphthalene (1) [a]	157.5	157.5[19]				9	9[20]			
Toluene (2) [b]		155.89	157.58	158.83[21]			2	5—6	2[22]	
Pyrene (3) [c]	158.91	158.75		158.2[23]		15	5		30[24]	
N-Methylpyrrole (4) [d]		182.0	168.5[25]				70[26]			
Furan (5) [c]		201	175[16]				98[27]			
2-Methylfuran (6) [c]			174	173	199[16]					77[28]
Benzo[*b*]furan (7) [c]		201.8	176.6[25]				47[29]			
Thiophen (8) [c]		185	168[17]				87[30]			
2-Methylthiophen (9) [c]			164	165	186[17]					75[10]
3-Methylthiophen (10) [c]		184		165	185[17]					
		182.8		166.8	185.9[31]		19			61[32]
Selenophen (11) [c]		189	166[33]				57[34]			
Tellurophen (12) [c]		183	159[35]				45[36]			
N-Phenylpyrazole (13) [c,e]			186	177	185[37]					60[38]
N-Methylimidazole (14) [c]		207		188	189 [f]		86[39]			
N-Phenylimidazole (15) [c,g]		208		190	188[37]		76[39]			
Thiazole (16) [h]		211.1		186.5	189.1[40]		40[41]			
4-Methylthiazole (17) [c]		212.0			185.0[42]		93[43]			

[a] Lithiating agent (solvent) BuLi(THF). [b] BuLi(TMEDA). [c] BuLi(Et_2O). [d] EtLi(Et_2O–TMEDA). [e] One-bond $J_{^{13}C-H}$: 2′, 164; 3′, 161; 4′, 162; 20% yield at 2′ for lithiation. [f] This investigation. [g] One-bond $J_{^{13}C-H}$: 2′, 160; 3′, 162; 4′, 160. [h] PhLi (Et_2O).

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Toluene, naphthalene, pyrene, and *N*-phenylpyrazole are also examples indicating that 2 Hz is the smallest difference in coupling constants from which correct predictions of reactivity may be obtained.

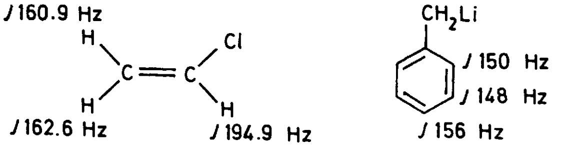
TABLE 2

One-bond coupling constants and lithiating yields for compounds (18)—(31)

	Position						
	$J_{^{13}C-H}$				Yield (%)		
	2	3	4	5	2	3	5
NN-Dimethylaniline (18) [a]	157.2	157.2	161.1 [b]		$31^{44,45}$		
Anisole (19) [c]	159	159	162^{46}		65^{47}		
2-Methoxythiophen (20) [c]		167	168	189^{17}			67^{10}
3-Methoxythiophen (21) [c]	184		168	187^{17}	86^{8}		
	183.5		167.2	187.3^{31}			
2-(Methylthio)thiophen (22) [c]		169	168	188^{17}			87^{11}
3-(Methylthio)thiophen (23) [c]	187		169	189^{17}	79^{9}		
Thioanisole (24) [c]	160	161	162 [b]		37 [d,48]		
Fluorobenzene (25) [e]	163.14	162.00	162.16^{49}		60^{50}		
1,2-Difluorobenzene (26) [e]		164.6	165.3^{51}			74^{52}	
1,3-Difluorobenzene (27) [e]	165.5		165.20	165.60^{49}	81^{52}		
3-Bromothiophen (28) [c]	191		174	189^{17}	? [f, 53]		
	188		175.8	187.5^{31}			
2,4-Dibromothiophen (29) [c]		179.5		194.5^{54}			36^{53}
2-Cyanothiophen (30) [c]		174	173	192^{17}			4^{55}
3-Cyanothiophen (31) [g]	192		174	191^{17}	80^{55}		

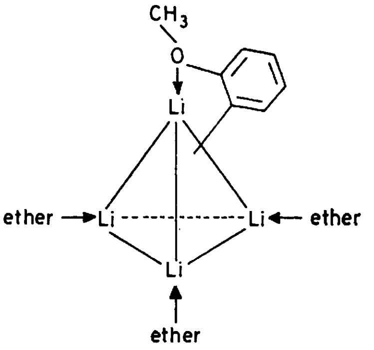
[a] BuLi(hexane). [b] This investigation. [c] BuLi(Et_2O). [d] *ortho* + *meta*. [e] BuLi(THF). [f] A complicated mechanism was suggested for lithiation at the 2-position, but no yield was given. [g] 3-Thienyl-lithium(Et_2O).

The usefulness of $J_{^{13}C-H}$ as a selectivity parameter can be extended to an alkene such as vinyl chloride, which can be lithiated in the α-position (in accord with the coupling constants [56]). Subsequent reaction with CO_2 produces α-chloroacrylic acid in 99—100% yield.[57,58] Even more interesting is benzyl-lithium.[59] For metallation of benzyl-lithium with butyl-lithium the order of reactivity has been found [44] to be *para* > *ortho* > *meta*, which is in accordance with the predictions that can be made from the one-bond coupling constants.



One-bond $J_{^{13}C-H}$ values for vinyl chloride and benzyl-lithium

Directed Metallation.—In directed metallation of an aromatic system, a lithium atom replaces a hydrogen atom on the carbon adjacent to the site of the directing substituent. For the substituents such as OMe, NMe_2, and F, a pseudo-five-membered co-ordinated ring can be invoked for the transition states, if a suitable oligomer structure (tetramer) for butyl-lithium is assumed.[3] However, inductive stabilization of the anion can also be invoked. No quantitative method seems to be available to decide which of the two effects is operating in a given aromatic system. As can be seen from Table 1 a very good prediction can be made for the position of lithiation of an aromatic molecule, without a hetero-substituent, by observing the one-bond ^{13}C–H coupling constants. Substituents, which promote 2-metallation of aromatic substrates, generally include heteroatoms. But stabilities of transition states like the one shown cannot of course be predicted from ^{13}C–H coupling constants. If 2-metallation for those substituents would not have been expected by comparison with the one-bond ^{13}C–H coupling constants, as outlined above, a direct measure of the *ortho*-directing power of that substituent which can be regarded as



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being due to complexing of the lithium atom with the hetero-atom in the transition state, is obtained.

As seen from Table 2 anisole (19) is an example of this. Although $J_{^{13}C-H}$ for the *para*-position is 3 Hz greater than for the two other positions, lithiation is only found to occur in the *ortho*-position. From that it may be concluded that methoxy is a true *ortho*-directing group. A similar example is 3-methoxythiophen (21), where two groups report the coupling constant at the 5-position to be 3 or 3.8 Hz greater than at the 2-position. 86% Metallation at the 2-position in this case also demonstrates the *ortho*-directing power of the methoxy-group. For 2-methoxythiophen (20) it might have been predicted that the *ortho*-directing methoxy-group should promote lithiation at the 3-position, but only metallation at the 5-position has been observed. At the 5-position $J_{^{13}C-H}$ is 21—22 Hz greater than at the 3- and 4-positions. This corresponds to such great differences in reactivities that the *ortho*-directing power of the methoxy-group due to complexing with the lithium atom cannot reverse the predicted reactivities. Similar trends are observed for the methylthio-group in thioanisole, 2-(methylthio)thiophen, and 3-(methylthio)thiophen, which verify its *ortho*-directing power. A third, well established, example of an *ortho*-directing group is dimethylamino. *NN*-Dimethylaniline has a one-bond coupling constant at the *ortho*-position which is 3.9 Hz less than that at the *para*-position, but lithiation occurs at the *ortho*-position clearly indicating the *ortho*-directing power of the dimethylamino-group.

The fluorobenzenes (25)—(27) with differences between all one-bond coupling constants in a given molecule <1.2 Hz are only lithiated *ortho* to fluorine. This may be due to a true *ortho*-directing effect of the fluorine atom. For the bromothiophens (28) and (29) the one-bond $^{13}C-H$ coupling constants correctly predict lithiation *ortho* to bromine, and no conclusions can therefore be made about the *ortho*-directing effect of the bromine atom. Similar conclusions may be drawn for 3-cyanothiophen (31) where the coupling constants correctly predict lithiation at the 2-position. 2-Cyanothiophen (30), like 2-methoxy- and 2-(methylthio)thiophen, is an example where the one-bond coupling constants indicate such great differences in reactivities that potential *ortho*-directing substituents cannot change the order of reactivity.

Conclusions.—For aromatic and heteroaromatic systems the most reactive carbon with sp^2 hybridization in lithiation reactions can be predicted as that with the greatest one-bond $^{13}C-H$ coupling constant. This observation holds for differences in $J_{^{13}C-H}$ as small as 2 Hz. However, if hetero-substituents are present, they may change the order of reactivities for differences of coupling constants of 2—5 Hz. Such discrepancies in reactivities can be used as a tool for identifying the true *ortho*-directing effect of certain substituents such as NMe_2, OMe, SMe, and F.

EXPERIMENTAL

^{13}C N.m.r. spectra were recorded on a JEOL JNM-FX60 spectrometer using the Fourier transform pulse technique applying the gated decoupling technique. Ether–chloroform (1 : 1) was used as solvent and the coupling constants were obtained by first-order analysis.

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