Novel Regioselectivity under Conformational Control in the Methylation of 2,3-Dihydroxy-1-naphthaldehyde

Francis M. Dean, Gassan El-Kass, and Lalit Prakash

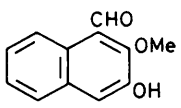
The Robert Robinson Laboratories, The University of Liverpool, Liverpool L69 3BX, U.K.

Methylation of 2,3-dihydroxy-1-naphthaldehyde with iodomethane and potassium carbonate in acetone selectively etherifies the *chelated* 2-hydroxy group because ionisation of this destroys the stabilising hydrogen bond and allows the formyl group to take up a preferred conformation away from the reaction centre.

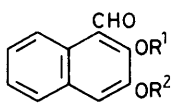
We were astonished to obtain 3-hydroxy-2-methoxy-1-naphthaldehyde† (**1**) by restricted methylation of 2,3-dihydroxy-1-naphthaldehyde (**2**) with potassium carbonate and iodomethane in hot acetone. A little of the dimethyl ether (**3**) was produced but the expected ether (**4**) was not. Since its introduction in 1913 this method (along with various modifications) has been used for what must be hundreds of such methylations, but no previous record seems to exist of a case where a strongly hydrogen-bonded (and somewhat hindered) hydroxy group reacted in preference to a free group.[1] We have confirmed that methylation of 2,3-dihydroxybenzaldehyde affords 2-hydroxy-3-methoxybenzaldehyde (with some 2,3-dimethoxybenzaldehyde) in the normal way.

The new ether (**1**) is certainly an aldehyde, δ 10.79s (^{1}H);

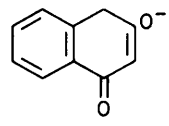
†M.p. 166—167 °C (subl.). Satisfactory elemental analyses were obtained.



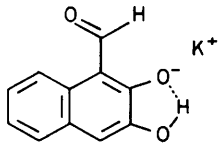
(1)



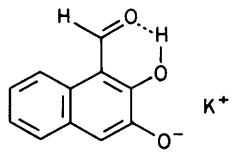
(2) $R^1 = R^2 = H$
(3) $R^1 = R^2 = Me$
(4) $R^1 = H, R^2 = Me$



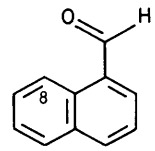
(5)



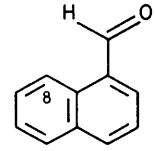
(6)



(7)



(A)



(B)

192.0d (^{13}C), and not a methoxymethylene quinone derivative. Further methylation affords 2,3-dimethoxy-1-naphthaldehyde which gives the (known[2]) 2-hydroxy-3-methoxy-1-naphthaldehyde (**4**) upon selective dealkylation by boron chloride.[3]

The mild base in these alkylations is thought to ionise a phenolic hydroxy group so enabling a nucleophilic displacement with iodomethane.[4] However, the naphthalene nucleus is less 'aromatic' than the benzene nucleus and the mono-salt from naphthalene-1,3-diol is known to tautomerise into the carbonyl form[5] (**5**) which is stabilised by charge delocalisation in the vinylogous carboxylate system and could protect one hydroxy group from alkylation. Such tautomerism is improbable in the 2,3-dihydroxynaphthalene nucleus and we found that one equivalent of base merely complicates the aromatic resonances of the initially symmetrical diol without producing a methylene band.

It is known that 1-naphthaldehyde strongly prefers conformation (A) as opposed to the other planar conformation (B) (Table 1); no comparable preference has yet been announced for a benzaldehyde derivative.[6] However, the hydrogen-bonding in 2-hydroxy-1-naphthaldehyde is enough to change the conformation to (B), such bonding being impossible in (A). Instead of the substituent chemical shift methods used by other workers, we have employed the aromatic-solvent induced shift technique[7] (ASIS) with 8-H as the probe; in conformation (A) this proton signal appears to move downfield when the solvent is changed from $CDCl_3$ to C_6D_6, whereas in conformation (B) it appears to move upfield. The results (Table 1) confirm the earlier work and show that our 2-methoxy compounds have conformation (A), whereas our (hydrogen-bonded) 2-hydroxy compounds have conformation (B).

The structure and conformation of the starting phenol is therefore normal, but loss of the proton from the 2-hydroxy group would remove the hydrogen bonding and permit a conformational change from (B) to (A). We find that this does occur. When simple phenols change into their salts, all the nuclear proton signals move *upfield* because of the increased electron density around the ring.[8] When one equivalent of base (Bu^tOK) is added to a solution of 2-hydroxy-1-naphthaldehyde in $[^2H_6]Me_2SO$, however, all the nuclear proton signals move upfield by about 0.8 p.p.m. except one, the 8-proton signal, which moves *downfield* by 0.15 p.p.m. In 2,3-dihydroxy-1-naphthaldehyde the base-induced upfield shift is 0.4 p.p.m.; while the shift in the 8-H resonance is also 0.4 p.p.m., it is again downfield. This can only mean that the formyl group swings around so that its magnetic deshielding cone can affect 8-H more than the anion formation does.

We surmise, therefore, that the salt (**6**) is rather more stable than the isomer (**7**), the gain in conformational energy plus the inter-oxide hydrogen bond outweighing the loss of hydrogen bonding to the formyl group; and attribute the abnormal methylation to this factor. No reason for the conformational preferences in 1-naphthaldehydes has become known to us, and since the vast majority of selective alkylations have been confined to the benzene series it is possible that the abnormal methylation reported here is also to be found in other areas.

Table 1. Chemical shifts[a] and ASIS values for the 8-proton in 1-naphthaldehyde derivatives.

Substituent in 1-naphthaldehyde	δ ($CDCl_3$)	δ (C_6D_6)	ASIS[b]	Conformation
None	9.20	9.48	−0.28	(A)
2-OH	8.24	7.60	0.64	(B)
2-OMe	9.26	9.72	−0.46	(A)
2,3-$(OH)_2$	8.28	7.59	0.69	(B)
2-OH, 3-OMe	8.24	7.66	0.58	(B)
2-OMe, 3-OH	9.07	9.49	−0.42	(A)

[a]At 220 or 250 MHz, ambient temperature with Me_4Si as internal standard. [b]$\delta(CDCl_3) - (C_6D_6)$.

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