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JANUS-TYPE ISOPROPYL GROUPS REVEALED BY ^{1}H-NMR SPECTRA OF ALKYLPYRIDINES WITH LANTHANIDE SHIFT REAGENTS (LSR)

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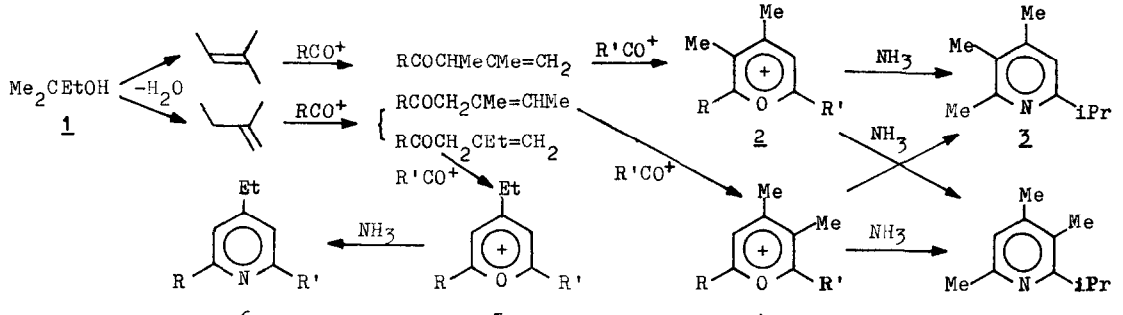
Abstract. Two isomeric pyridines were designed and prepared : 2-isopropyl-4,5,6-trimethyl- (3) and 2-isopropyl-3,4,6-trimethyl-pyridine (7) ; the latter, with a buttressed isopropyl, leads to much lower induced shifts by $Eu(dpm)_3$ and $Pr(dpm)_3$ than the former, owing to the conformation in which the Janus-type iPr group shows to the LSR a t-butyl-like face.

The fact that according to their rotating orientation isopropyl groups may present an ethyl-like or a tert-butyl-like face caused them to be named [1] Janus-type groups. In this paper we present additional evidence for this behaviour based on ^{1}H-NMR spectra of alkyl-substituted pyridines in the presence of lanthanide shift reagents (LSR). The gearing of alkyl groups linked to pyridines or pyrylium cations has been demonstrated by the "negative buttressing effect" presented by such compounds.[2]

In continuation of earlier studies on the LSR-induced shifts in alkylpyridines,[3] we prepared via pyrylium salts [4] two isomeric isopropyl-trimethylpyridines 3 and 7, by starting from tert-pentyl alcohol (1) via acetylation and isobutyrylation (either in this order, or in the reverse one). In the former case 1 was dehydrated with 33 % H_2SO_4 to a mixture of 2-methylbutenes, which was treated [5] with AcCl + $SnCl_4$; the ketonic fraction was isolated, and was treated with iPrCOCl + $AlCl_3$ then with $HClO_4$; the major product was



Scheme 1.

the crystalline pyrylium perchlorate 2, R = Me, R' = iPr, m.p. = 103-105°C, which was converted with ammonia into the corresponding pyridine 3, b.p. = 73°C/1 Torr. In the latter case (treatment of the same alkene mixture with iPrCOCl + $SnCl_4$), isolation of the ketonic fraction and its treatment with AcCl + $AlCl_3$ then with $HClO_4$ afforded a complex oily mixture of pyrylium salts which was converted into pyridines. GLC showed the presence of about 40 % of pyridine 7, 30% of pyridine 3 together with 10 % 2,6-diisopropyl-4-methylpyridine (alkene monoacylation is reversible [6]) and other pyridines such as 6 in lower amounts. From this reaction mixture pure pyridines 3 and 7 were isolated by preparative GLC on column filled with 20 % silicone oil SE-30 and 6 % polyethyleneglycol on Chromosorb W 30 - 60 mesh. In Scheme 1 only the β,γ -unsaturated ketones are shown, although the α,β -tautomers prevail, because only the former ones afford pyrylium cations on the second acylation step.

Chemical shifts [7] are in agreement with those of related alkylpyridines ;[8] all assignments are straightforward.

Electron-impact mass spectra of 3 and 7 present the base peak at m/z = 148 ($M - CH_3$), the molecular peak (m/z = 163 with 30 % relative intensity I), the M-1 peak with I = 38 %, and they differ in the intensity of peaks m/z = 135 ($M-C_2H_4$: I = 60 % for 7 and 28 % for 3) and m/z = 121 ($M-C_3H_6$: I = 25 % for 7 and 15 % for 3). Thus the buttressed isopropyl group in 7 is fragmented more readily than the freely rotating isopropyl group of 3.

The Table presents the lanthanide-induced shifts using $Ln(fod)_3$ and $Ln(dpm)_3$ as LSR with Ln = Eu or Pr under comparable conditions of concentration range and solvent, pairwise for the two isomeric pyridines 3 and 7. Whereas $Ln(fod)_3$ does not lead to marked differences in molar induced shifts (MIS), a dramatic difference is apparent in the MIS values obtained in the presence of $Ln(dpm)_3$: in the latter case 7 hardly gives evidence for complex formation, but 3 presents strong complexation. This was confirmed in an experiment using a 1 : 1 mixture of 3 and 7 with increasing amounts of $Eu(dpm)_3$ in carbon disulphide ; 3 gave significant MIS values while the ^{1}H-NMR peaks of 7 were almost unshifted.[9] The MIS values with $Eu(dpm)_3$ for 7 are comparable to those of the same LSR with 2-t-butyl-4,6-dimethylpyridine, while for 3 they are similar to those obtained with 2-ethyl-4,6-dimethylpyridine.[8] This finding indicates that the bulky $Ln(dpm)_3$ chelate experiences a strong steric interaction with 7, as if the 2-iPr group were a t-butyl group, whereas with 3 the 2-iPr group behaves as if were sterically equivalent to an ethyl group (Scheme 2).

Secondly, the ratios of MIS values for the isopropyl CH and methyl groups, both with $Eu(fod)_3$ and $Eu(dpm)_3$ are 4.0 ± 0.4 for 3 and 1.0 ± 0.2 for 7. For $Pr(dpm)_3$ and $Pr(fod)_3$ this ratio is larger : 6.0 ± 0.7 for 3 and 2.6 ± 0.1 for 7.

A third observation concerns the chemical shift of the isopropyl proton which in 7 is deshielded by 0.3 ppm relative to 3.[7]

These three facts are rationalized by admitting that in 7 the buttressing and gearing between the 2,3,4-alkyl groups cause the isopropyl group to adopt a preferred least congested conformation with both methyls facing the nitrogen heteroatom just as with a t-butyl group ; since the 2-isopropyl group in 3 has no buttressing adjacent methyl group, it is free to adopt all possible conformations so that in the most probable conformation one hydrogen and one methyl group face the nitrogen heteroatom. Thus the approaching chelates

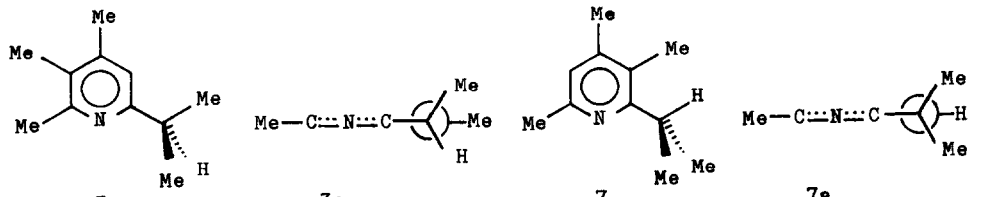
Table. Molar induced shifts (MIS, ppm [a]) of 2-isopropyl-4,5,6-trimethylpyridine 3 and 2-isopropyl-3,4,6-trimethylpyridine 7.

LSR (solvent)	Position : Compd.	2	3	4-Me	5	6-Me	Ratio CH/Me_2
Eu(dpm)$_3$ (in CS_2)	3	17.0 (CH) 3.7 (Me)	4.8 (H)	2.8	3.0 (Me)	10.5	4.5
	7	0.5 (CH) 0.6 (Me)	0.3 (Me)	0.3	0.2 (H)	0.8	0.8
Eu(fod)$_3$ (in $CDCl_3$)	3	8.3 (CH) 2.3 (Me)	1.8 (H)	0.9	0.9 (Me)	3.5	3.6
	7	3.7 (CH) 3.0 (Me)	0.9 (Me)	0.9	1.6 (H)	3.2	1.2
Pr(dpm)$_3$ (in CS_2)	3	-42.3 (CH) -8.0 (Me)	-8.1 (H)	-3.8	-5.2 (Me)	-24.4	5.3
	7	-1.9 (CH) -0.7 (Me)	-0.4 (Me)	-0.4	-0.2 (H)	-1.6	2.7
Pr(fod)$_3$ (in $CDCl_3$)	3	-6.7 (CH) -1.0 (Me)	-1.8 (H)	-0.8	-1.0 (Me)	-8.0	6.7
	7	-3.1 (CH) -1.2 (Me)	-0.8 (Me)	-0.8	-1.8 (H)	-6.0	2.6

[a] MIS values are reproducible within 0.15 ppm ; for 7 with Ln(dpm)$_3$ the low absolute MIS values lead to larger relative errors than in all other cases.

Ln(dpm)$_3$ or Ln(fod)$_3$ "see" the edge-on pyridines as 3a and 7a, respectively ; for 3 the isopropyl-CH proton is much closer to the LSR leading to the much higher MIS ratio CH/Me_2 than for 7, in agreement with the second experimental observation. The fact that MIS values for Ln(fod)$_3$ with 3 are only slightly higher than with 7 indicates that the less bulky Ln(fod)$_3$ is less sensitive to steric hindrance than Ln(dpm)$_3$. Indeed, the MIS values of 2-ethyl-4,6-dimethylpyridine with Eu(fod)$_3$ are only slightly higher than those of 2-t-butyl-4,6-dimethylpyridine with the same LSR, as indicated in the preceding paper.

In the least crowded conformation of 7, the isopropyl-CH proton is in the pyridine plane and experiences the deshielding caused by the ring current ; in 3 the isopropyl-CH proton is out of this plane in the most probable conformation. The corresponding chemical shifts reflect these (de)shielding effects,[7] accounting for the third observation.



Scheme 2. 3 3a 7 7a

The intermolecular comparison between 3 and 7 reveals thus that isopropyl groups adopt different conformations ; in the preceding paper [8] similar conformational differences were observed by intramolecular comparison in 2,6-diisopropyl-3,4-dimethylpyridine or in 2,3,6-triisopropyl-4-methylpyridine.

The relative MIS values for one and the same pyridine (3 or 7) on changing Eu by Pr are not constant for the α-substituents, indicating either a small contribution of Fermi contact mechanism, or non-axial symmetry of the magnetic susceptibility tensors in the complex.

In conclusion, if one adds a β-standing methyl group to 2-isopropyl-4,6-dimethylpyridine (either in the 3- or in the 5- position) one can force the Janus-like 2-isopropyl to turn either of its two faces behaving in the former case like a t-butyl group, and in the latter case like an ethyl group. Also 7 provides an intriguing example of a substrate that coordinates effectively with $Ln(fod)_3$ but very poorly with $Ln(dpm)_3$. This example rings a warning bell regarding the importance of the matching between steric requirements of the substrate and of the LSR ligands.

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References and notes

1. C.Roussel, A.Liden, M.Chanon, J.Metzger and I.Sandström, J.Amer.Chem.Soc., 98, 3847 (1976) ; U.Berg and C.Roussel, ibid., 102, 7848 (1980) ; U.Berg, T.Liljefors, C.Roussel and J.Sandström, Acc.Chem.Res., 18, 80 (1985).
2. C.Roussel, A.T.Balaban, U.Berg, M.Chanon, R.Gallo, G.Klatte, J.A.Memiaghe, J.Metzger, D.Oniciu and J.Pierrot-Sanders, Tetrahedron, 39, 4209 (1983).
3. A.T.Balaban, A.Bota, F.Chiraleu, E.Sliam, A.Hanes and C.Drăghici, Rev.Roum.Chim., 22, 1003 (1977).
4. A.T.Balaban, W.Schroth and G.Fischer, Adv.Heterocyclic Chem., 10, 241 (1967) ; A.T.Balaban, A.Dinculescu, G.N.Dorofeenko, G.W.Fischer, A.V.Koblik, V.V.Mezheritskii and W.Schroth, "Pyrylium Salts", Adv.Heterocyclic Chem., Suppl., vol.2, Academic Press, New York, 1982 ; A.T.Balaban, in "New Trends in Heterocyclic Chemistry" (Ed. R.B.Mitra et al.), Elsevier, Amsterdam 1979, p.79.
5. J.Colonge and K.Mostafavi, Bull.Soc.Chim.Fr., 342 (1939).
6. A.T.Balaban, in "Omagiu pentru Prof. Raluca Ripan", Editura Acad. R.S.Romania, Bucharest 1966, p.103 ; M.Frangopol, A.Genunche, N.Negoiță, P.T.Frangopol and A.T.Balaban, Tetrahedron, 23, 841 (1967).
7. ^{1}H-NMR (δ in CS_2) : for 3, 1.16 (Me_2CH, 6H, d, J=7.5 Hz), 2.10 (5-Me, 3H, s), 2.17 (4-Me, 3H, s), 2.34 (6-Me, 3H, s), 2.80 (Me_2CH, 1H, septet), 6.60 (2-H, 1H, s) ; for 7, 1.12 (Me_2CH, 6H, d, J=6.5 Hz), 2.13 (2 and 3-Me, 6H, s), 2.27 (6-Me, 3H, s), 3.13 (Me_2CH, 1H, septet), 6.57 (5-H, 1H, s).
8. See preceding paper in this issue.
9. In a similar experiment with a mixture of 3 and 7 in $CDCl_3$, $Eu(fod)_3$ gives rise to considerable induced shifts for both pyridines.

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