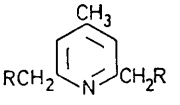
Steric Origin of Isotope Effects in Nuclear Magnetic Resonance Shifts Induced by Lanthanide Shift Reagents; Effect of Deuteriation of Methyl Substituted Pyridines

By ALEXANDRU T. BALABAN,[a,b]* ILEANA I. STANOIU,[a] and FILIP CHIRALEU[c]

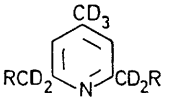
([a] *Institute of Atomic Physics, P.O.B. 5206, Bucharest;* [b] *Organic Chemistry Department, The Polytechnic, Bucharest; and* [c] *Organic Chemistry Research Centre, Bucharest, Rumania*)

Summary Deuteriation of all the methyl groups, or the 2- and 6-methyl groups, in 2,4,6-trimethylpyridine causes a large (*ca.* 6%) isotope effect on the lanthanide-induced shift for the 3- and 5-hydrogen atoms, whereas the effect of deuteriation of the 4-methyl group is not detectable ($< 0{\cdot}2\%$); a steric origin is proposed for the secondary isotope effect in lanthanide-induced shifts.

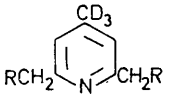
2,4,6-TRI[$^2H_3$]METHYLPYRIDINE (**3**)[1] (prepared from ammonia and the corresponding pyrylium perchlorate[1] which is readily obtained by deuteriation of 2,4,6-trimethylpyrylium perchlorate[2] in refluxing D_2O for 2 h) with Eu(dpm)$_3$ in CS_2 shows a lanthanide-induced shift (L.I.S.) for the 3- and 5-hydrogen atoms which is 5·8% greater than the corresponding shift for the non-deuteriated compound (**1**), *i.e.* when a mixture of (**1**) and (**3**) is treated with Eu(dpm)$_3$, the ^1H n.m.r. peak is split (*cf.* Table). This is the highest effect yet reported for any deuteriated substrate,[3] although it is only *ca.* 1% per deuterium atom.



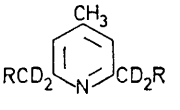
(1) R = H
(2) R = Me



(3) R = D
(4) R = Me



(5) R = H
(6) R = Me



(7) R = D
(8) R = Me

TABLE. Molar induced shifts by $Eu(dpm)_3$ in CS_2 (p.p.m. *vs.* Me_4Si)

Protons	τ[a]	(1)	(3)	(5)	(7)	τ[a]	(2)	(4)	(6)	(8)
2- and 6-CH_3 (-CH_2)	7·63s	15·0	—	15·0	—	7·34q	6·50	—	6·50	—
3- and 5-H	3·33s	6·00	6·35	6·00	6·34	3·33s	2·52	2·80	2·52	2·80
4-CH_3	7·78s	3·82	—	—	4·05	7·75s	1·62	—	—	1·65
Me of α-Et	—	—	—	—	—	8·78t	1·80	1·89	1·80	1·89

[a] Chemical shift and multiplicity without deuteriation and addition of $Eu(dpm)_3$.

Since 2,4,6-trimethylpyrylium perchlorate is deuteriated about 12 times faster† at the 4- than at the 2- and 6-methyl groups,[4] heating it at 80 °C in D_2O for 10 min affords mostly 2,6-dimethyl-4-[$^2H_3$]methylpyrylium perchlorate, which can be converted into (**5**), which shows no isotopic effect; a 0·2% effect would have been detectable and so the isotopic effect depends strongly on the position of the label.

De-deuteriation of the 4-methyl group of 2,4,6-tri[$^2H_3$]-methylpyrylium perchlorate by heating at 80 °C for 20 min and reaction of the product with ammonia gave (**7**) which shows a similar effect for the 3- and 5-hydrogen atoms as that for (**3**), and also a similar isotope effect for the 4-methyl peak.

2,6-Diethyl-4-methylpyridine (**2**)[5] on deuteriation of the α-methylene groups shows analogous behaviour to that of (**1**) with slightly smaller isotopic shifts for (**4**) and (**8**) (Table; *ca.* 5% for the 3- and 5-hydrogen atoms and 4% for the methyl part of the α-ethyl groups, *i.e.* again *ca.* 1% per deuterium atom). Compound (**6**), however, like (**5**), shows no detectable isotopic effect. Absolute molar induced shift values for (**2**) are much smaller than for (**1**) because of the steric requirements of $Eu(dpm)_3$. Accordingly, 2,6-di-isopropyl-4-methylpyridine, which was also prepared with selective deuteriation from a study of kinetic isotope effects of the corresponding pyrylium salt,[5] shows practically no L.I.S. with $Eu(dpm)_3$ or $Eu(fod)_3$ because the α-substituents are too bulky.

The pK_a values of compounds (**1**), (**3**), (**5**), and (**7**) increase additively by *ca.* 0·025 per CD_3 group,[6] in agreement with the electron-releasing effect of CD_3 *vs.* CH_3 groups.[7] Therefore a difference in basicity is not the origin of the isotope effect for the L.I.S. results. Our findings are best interpreted in terms of a steric origin, in agreement with Brown's arguments,[8] with the known smaller steric requirements of deuterium than of hydrogen.[9]

Contact shifts[10] may also be involved. It should also be mentioned that the isotopic effects are actually *on*, rather than due *to* the deuterium.[11]

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† The isotopic purities of (**1**), (**2**), (**5**), and (**6**) are thus 98—100%, while those of (**3**), (**4**), (**7**), and (**8**) are only 80—85%.

[1] A. T. Balaban, E. Gârd, A. Vasilescu, and A. Barabas, *J. Labelled Compounds*, 1965, **1**, 266.
[2] A. T. Balaban and C. D. Nenitzescu, *Org. Synth.*, 1974, Coll. Vol. 5, 1106.
[3] G. V. Smith, W. A. Boyd, and C. C. Hinckley, *J. Amer. Chem. Soc.*, 1971, **93**, 6319; C. H. De Puy, P. C. Fünfschilling, and J. M. Olson, *ibid.*, 1976, **98**, 276; C. C. Hinckley, W. A. Boyd, and G. V. Smith, *Tetrahedron Letters*, 1972, 879; C. C. Hinckley, W. A. Boyd, G. V. Smith, and F. Behbahany, in 'Nuclear Magnetic Resonance Shift Reagents,' ed. R. E. Sievers, Academic Press, New York, 1973, p. 1; D. S. Dyer, J. A. Cunningham, J. J. Brooks, R. E. Sievers, and R. E. Rondeau, *ibid.*, p. 21; J. J. Brooks and R. E. Sievers, *J. Chromatog. Sci.*, 1973, **11**, 303.
[4] E. Gârd, A. Vasilescu, G. D. Mateescu, and A. T. Balaban, *J. Labelled Compounds*, 1967, **3**, 196; E. Gârd, I. I. Stănoiu, F. Chiraleu, and A. T. Balaban, *Rev. Roumaine Chim.*, 1973, **18**, 257.
[5] I. I. Stănoiu, F. Chiraleu, E. Gârd, and A. T. Balaban, *Rev. Roumaine Chim.*, in the press.
[6] A. T. Balaban, I. I. Stănoiu, and E. Gârd, *Rev. Roumaine Chem.*, in the press.
[7] E. A. Halevi, M. Nussim, and A. Ron, *J. Chem. Soc.*, 1963, 866.
[8] H. C. Brown, 'Boranes in Organic Chemistry,' Cornell University Press, Ithaca, 1972, pp. 66 and 71 and references therein.
[9] K. Clusius and K. Weigand, *Z. phys. Chem.*, 1940, B **46**, 1.
[10] G. Beech and R. J. Morgan, *Tetrahedron Letters*, 1974, 973.
[11] E. K. Thornton and E. R. Thornton, in 'Isotope Effects in Chemical Reactions,' ed. C. J. Collins and N. P. Bowman, Van Nostrand, New York, 1970, pp. 213 and 217 and references therein.