CATALYTIC LABELLING AND ^3H NMR ANALYSES OF SOME AROMATIC AND HETEROCYCLIC COMPOUNDS

Zhang Liming (张丽明)

(Institute of Nuclear Research Academia Sinica, Shanghai 201800, China)

John R.Jones

(Chemistry department, University of Surrey, Surrey, U.K.)

(Received January 1989)

ABSTRACT

This paper described the ^3H NMR determination of the positions and content of 24 tritium labeled aromatic and heterocyclic compounds prepared by catalytic tritiation derivatives, pyrrole, 1,2,4- triazole, thiazole, benzothiazole, purine and derivatives, indole, indanol, piperidine and derivative, diphenylamine, N- phenylanthranilic acid, 8- OH- quinoline, naphthol, diphenylether have been tritiated by catalytic exchange method using tritiated water and platinum catalyst (from the dioxide and sodium borohydride), and the pattern of labelling has been assigned by ^3H NMR spectroscopy. The results show that this exchange process can give general labelling compounds at various time and temperatures. For 4- Br- diphenylether, Raney nickel was used instead of Pt as a catalyst.

Keywords: ^3H NMR ^3H labeled heterocyclic compounds ^3H labeled aromatic compounds Catalytic labelling

Ⅰ. INTRODUCTION

For searching a rapid, simple method to prepare labeled compounds, people pay more attention to tritium exchange method because of its law cost and high activity. In past decade, J.A.Elvidge et al have made great contributions in ^3H NMR to determine the positions and contents of labeled compounds[1-5]. In this work, we used platinum, freshly prepared by reduction of PtO_2 to introduce tritium from tritiated water into 24 aromatic and heterocyclic compounds at different temperatures and reaction time. Raney Ni was used as a catalyst for 4- bromo- diphenylether. The tritiated compounds included 24 heteroatomic nitrogen, heteroatomic nitrogen with heteroatomic sulphur, heteroatomic oxygen compounds, and other aromatic compounds connecting with nitrogen or oxygen. All of the results are listed in Table 1 and 2. The typical spectra of ^1H and ^3H are shown in Figs.22, 23 and 24.

Ⅱ. EXPERIMENTAL

The reaction conditions for the tritiation of a range of 24 compounds are listed in Table 1. After reaction, labile tritium was removed by treatment with methanol, the methanol was evaporated under the dried nitrogen. For NMR analysis the tritiated

compounds were dissolved in deuterated solvent, a trace of TMS was added, and the ^3H and ^1H spectra were recorded (at 25°C) at 96 MHz, respectively (the former with ^1H decoupling), running the spectra on Bruker WH90 Fourier transform spectrometer and with quadrature detection, pulse widths were 1.5—3μ s and the repetition interval 1.6—3.4 s as appropriate. A display spectral width of ca. 13 ppm, usually at 21.31 Hz cm^{-1} for ^3H spectra and 20.00 Hz cm^{-1} for ^1H spectra which was used to provide indentical ppm scales. Referencing was to a ghost reference generated from the ^1H resonance frequency of the internal standard (measured at 90MHz) by multiplying by the Larmor ratio 1.06663974[6].

Table 1

Tritiated aromatic and heterocyclic compounds by catalysed exchange in solution

No.	of compound	HTO (μ l)	Sample weight (mg)	PtO_2 (mg)	Exchange time (h)	Temp. (°C)
1	Imidazole	5	10	20	180	85
2	1,3- Dibenzolum 2- Me imidazolium bromide	5	20	20	24	140
3	1- Dodecyl 2- Me 3- benzyl imidazolium chloride	5	20	40	20	140
4	1- Me imidazole	5	20	20	27	165
5	1,2, Dimethyl imidazole	5	20	20	27	165
6	2- Et 4- Me imidazole	5	20	20	20	135
7	Benzimidazole	5	20	15	8	200
8	Benzothiazole	5	20	20	60	85
9	Thiazole	5	500	20	96	85
10	Purine	5	20	20	27	85
11	Caffeine	5	10	30	60	175
12	Theophylline	5	10	30	66 (22)	85 (130)
13	Indole	5	20	20	27	85
14	5- Indanol	5	10	20	140	85
15	Piperidine	5	500	45	140	85
16	4- Hydroxy piperidine	5	10	20	20 (30)	85 (110)
17	1,2,4- Triazole	5	20	20	60	85
18	Pyrrole	5	100	20	110	85
19	Diphenyl ether	5	20	10	30	145
20	4- Bromo diphenyl ether	5	20	" R" 20	30	185
21	Diphenylamine	5	10	20	18	65
22	N- Phenylanthranilic acid	5	10	20	18	195
23	8- Hydroxy quinoline	5	10	30	30	115
24	Naphthcl	5	10	30	12	115

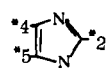
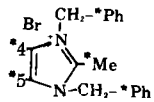
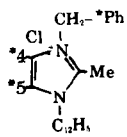
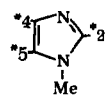
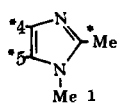
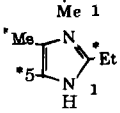
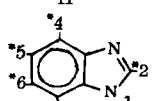
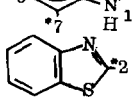
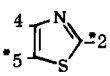
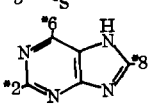
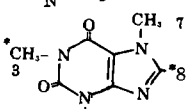
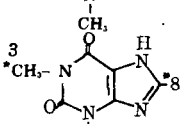
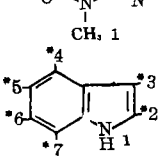
" R" = Raney Ni

III. RESULTS AND DISCUSSION

All ^3H NMR results are summarized in Table 2, assignment was carried out by the correspounding ^1H chemical shifts, the most ^1H chemical shifts of the aromatic and heterocyclic compounds were available either from standard spectra[7] (for compounds 1,5,9,11,12,17,18,20,24, etc.), from the information in Ref.[8], (for compounds 4,7,8,10, etc.), from the information in Ref.[9] (for compound 13), from the information in

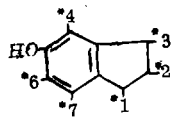
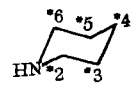
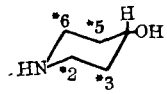
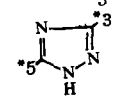
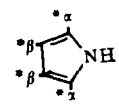
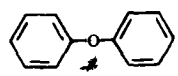
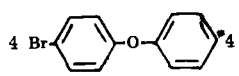
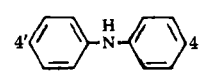
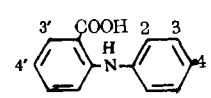
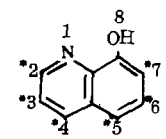
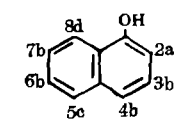
Table 2

^{3}H NMR results for tritiated heterocyclic compounds listed in Table 1

No. of compound	Solvent	Total activity (×37 MBq)shift	Chemical δ (ppm)	Assignment	T(%)
1 	d_6- DMSO	2.7	7.81	2	33
			7.16	4, 5	67
2 	d_6- DMSO	3.3	7.46	Ph	72
			7.92	4, 5	18
			2.64	Me	10
3 	d_6- DMSO	1.9	7.43	Ph	55
			7.90	4, 5	5
			2.65	Me	22
			7.75	Im.	18
			7.68	Im.	
4 	d_6- DMSO	6.5	3.63	Me	45
			7.60	2	21
			6.93	4	16
			7.16	5	17
5 	d_6- DMSO	11.1	3.51	1- Me	10
			2.24	2- Me	49
			6.68	4	23
			6.97	5	18
6 	d_6- DMSO	8.4	1.16	2- Me	32
			2.52	2- CH_2	24
			2.06	4- Me	35
			6.50	5	4
7 	d_6- DMSO	9	8.33	2	20
			7.71	4, 7	51
			7.28	5, 6	29
8 	d_6- DMSO	3	9.1	2	100
9 	d_6- DMSO	2.2	9.19	2	20
			7.83	5	10
10 	d_6- DMSO	4	8.74	8	70
			9.02	2	11
			9.23	6	19
11 	20%DCl/D_2O	2.6	3.61	1- Me	29
			4.21	3- Me	37
			9.01	8	34
12 	20%DCl/D_2O	1.5	3.64	3- Me	65
			8.95	8	35
13 	d_6- DMSO	9	7.35	2	18
			6.49	3	15
			7.05	5	17
			7.47	7	18
			7.14	6	18
			7.60	4	13

(to be continued on the next page)

Table 2 *(continued)*

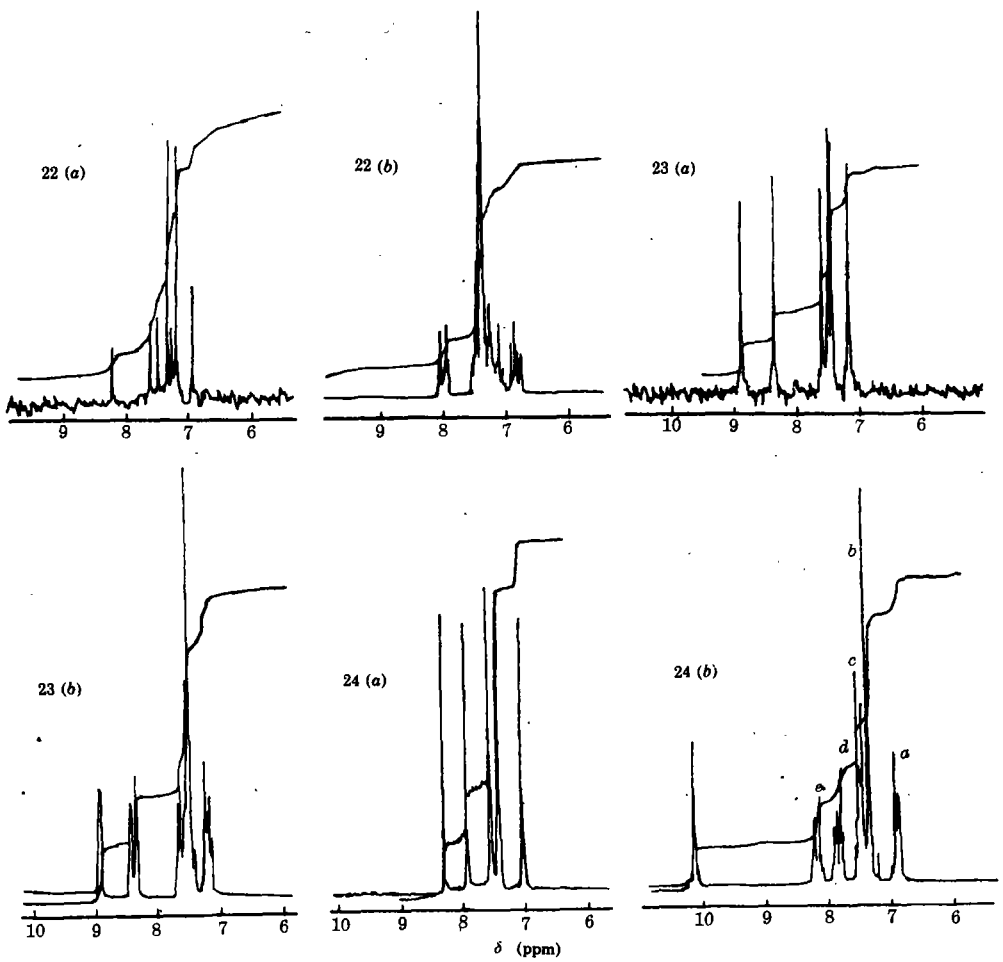
No. of compound	Solvent	Total activity (×37 MBq)shift	Chemical δ (ppm)	Assignment	T(%)
14 	d_6- DMSO	2.2	2.74	1	33
			1.95	2	25
			2.71	3	23
			6.68 (6.56)	4 (6)	10 (10)
			7.02	7	9
15 	$CDCl_3$	2.2	2.75	2, 6	66
			1.49	3, 4, 5	34
16 	$CDCl_3$	1.5	3.07	2,6e	22
			2.60	2,6a	31
			1.89	3,5e	32
			1.40	3,5a	9
			2.78	Im.	6
17 	d_6- DMSO	1.1	8.34	3,5	100
18 	d_6- DMSO	3.7	6.73	α	40
			6.21	β	44
			4.50	Im.	16
19 	d_6- DMSO	3	7.04	2	21
			7.43	3	53
			7.17	4	26
20 	d_6- DMSO	1	7.19	4	87
			2.29	Im.	13
21 	d_6- DMSO	2.4	7.12	2, 2′, 6, 6′	40
			7.27	3, 3′, 5, 5′	42
			6.86	4,4′	18
22 	d_6- DMSO	2.1	7.14	2,6	25
			7.29	3,5	25
			6.88	4	10
			8.17	3′	6
			7.24	4′	9
			7.55 (7.44)	5′ (6′)	11 (14)
23 	d_6- DMSO	7.5	8.92	2	16
			7.62	5	17
			8.39	4	16
			7.53	7	17
			7.20	3	19
			7.47	6	16
24 	d_6- DMSO	17	7.0	2*a*	12
			7.37 (7.40)	3,4*b*	28
			7.51 (7.53)	6,7*b*	28
			7.87	5*c*	16
			8.25	8*d*	16

Notice: Im. = Impurity a = axial e = equatorial

Ref.[10](for compounds 15,16, etc.), from the information in Ref.[11] (for compound 23), or from our own measurements of the ^1H NMR spectrum of unlabelled material (for compounds 2,3,6,14,19,21,22, etc.). Quantitative information was obtained directly from signal intensities. Nuclear Overhauser Effect was considered to be negligible in

quantitative analysis[12].

Figs. (22—24)*a* stand for the ^{3}H NMR spectra of the labeled compounds, Figs. (22—24)*b* represent the ^{1}H NMR spectra of corresponding labeled material, which was the same as ^{1}H NMR of unlabeled material. The same number are used for each compound in Table 1,2 and Figs.22—24. From the results of table 1 and 2, it is obvious that PrO_2 catalyst is a very useful catalyst to label the chosen compounds. All labeled



Figs. 22—24 ^{3}H and ^{1}H NMR spectra of compounds 22,23 and 24

compounds obtained by catalytic exchange in solution with tritiated water were of generally labelling. PrO_2 catalyst was suitable not only for aromatic compounds but also for heterocyclic compounds of N, O and S. Thiazole and benzothiazole are two typical examples, their ^{3}H NMR signal are obtained on 2,5- positions for thiazole,

2- position for benzothiazole. The labelling pattern of other heterocyclic compounds has been investigated by ^{3}H NMR spectroscopy. The results exhibited that this exchange process can lead to satisfactory incorporation of tritium into aromatic and heterocyclic rings.

ACKNOWLEDGEMENTS

We thank Mr.J.P.Bloxsidge for running all spectra and University of Surrey for support.

REFERENCES

[1] P.James et al., *J.Label. Compounds Radiopharmaceuticals*, **18** (1980), 1141.

[2] E.Buncel and C.C.Lee, eds., Isotopes in organic chemistry, Elsevier, Amsterdam, 1978, Vo.4, Capter, 1.

[3] J.Bloxsidge et al., *Org. Magnetic Resonance*, **3** (1971), 127.

[4] A.John et al., *J.Label. Compounds Radio pharmaceuticals*, **15** (1978), 141.

[5] J.A.Eividge et al., *J.Pharm. Pharmacol.*, **31** (1979), 508.

[6] J.P.Bloxsidge et al., *Org. Magnetic Resonance*, **12** (1979), 574.

[7] Sadtier standard spectra, No. 10529- 1, No. 6148- 5, No.8225- 9, No. 10393- 11, No.13485- 12, No.9170- 17, No.10330- 18, No.6715- 20, No.5- 24.

[8] Jackman and Sternhell, Application of NMR spectroscopy in organic chemistry, 2nd ed, 1969, p.209.

[9] P.J.Black and M.C.Heffernan, *Aust. J.Chem.*, **8** (1965), 353.

[10] *Progr. NMR spectroscopy*, **5** (1969), 336.

[11] P.J.Black and M.C.Heffernan, *Aust. J.Chem.*, **17** (1964), 558.

[12] J.P.Bloxsidge et al., *J.Chem. Research(s)*. 1977, p.258.