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A new method for the determination of the absolute stereochemistry of aromatic and heteroaromatic alkanols using Mosher's esters

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Abstract

A list of the ^{1}H NMR chemical shifts of the methoxy group of α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's) esters of α- and β-(hetero)aromatic secondary alkanols has been compiled. Methoxy groups which are orientated *syn* to the (hetero)aromatic group in Mosher's conformational model have lower chemical shift values than those in the *anti*-orientation. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, Mosher's) esters have emerged as the standard reagent for the determination of the enantiomeric excesses of alcohols and amines. The advantages of a derivative that cannot undergo racemisation, which is thermally stable and can be analysed by chromatography or NMR (^{1}H, ^{13}C and ^{19}F) are well known.[1]

Mosher developed models which could be used to predict the absolute stereochemistry of diastereomeric MTPA esters based on the ^{19}F NMR chemical shift differences of the trifluoromethyl group[2] and the ^{1}H NMR chemical shift differences of protons adjacent to the methine centre[3] (Fig. 1). In MTPA esters prepared from (*S*)-MTPA, the protons in substituent L^3 are shielded relative to those in the ester derived from (*R*)-MTPA. Similarly, for the MTPA ester derived from (*R*)-MTPA, the protons in substituent L^2 are shielded relative to those in the ester derived from (*S*)-MTPA. Thus the chemical shift difference between corresponding protons in (*S*)-MTPA and (*R*)-MTPA esters (ie. $\delta_S-\delta_R$) is negative for those located in substituent L^3 and positive for those in substituent L^2. By identical reasoning, the absolute configuration of enantiomeric alcohols can be deduced from their diastereomeric MTPA esters derived from either (*S*)-MTPA or (*R*)-MTPA. The shielding effect can be rationalised as due to the anisotropic effect of the

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phenyl ring on the *syn*-substituents in the conformation shown in Fig. 1. However, the conformation properties of MTPA esters are complicated and the populations of the various rotomers have not been firmly established.[4] Consequently, the structure shown in Fig. 1 should be viewed as a working model rather than the predominant observable conformation.

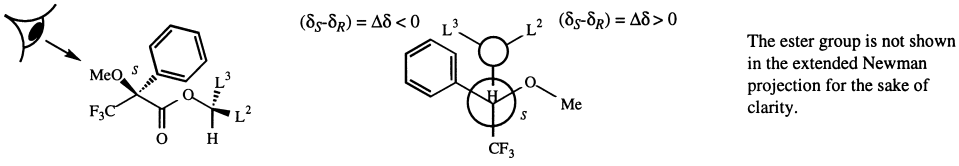


Figure 1.

With the development of high field NMR instruments the proton chemical shift difference method was shown to be applicable to virtually all of the hydrogens in the alkoxyl moiety of MTPA esters. The effect is routinely observed with protons attached to the β, γ and δ carbons and in favourable cases, with protons attached to centres up to 10 carbon atoms away from the carbon bearing the MTPA ester.[5] However, this so called 'modified Mosher's method' often gives anomalous results if α-(hetero)aromatic groups are present.[6–8] Exploitation of the proton chemical shift difference method as a means to determine absolute stereochemistry is often compromised by poor dispersion, particularly if the protons concerned are part of a methylene group. We experienced this recently when examining the MTPA esters of racemic and partially resolved 1-phenyl-1-pentanol. Only the methoxy groups and the methine hydrogens had distinguishable ^{1}H NMR shifts on a 400 MHz instrument.[9]

Prediction of the ^{1}H NMR shifts of the methine hydrogens has not proved to be feasible[10] and the chemical shifts of the methoxy groups are frequently very similar, although the use of lanthanide shift reagents is beneficial for resolving them.[11] Recently, ^{13}C chemical shift differences have also been utilised.[12] Our experience with the MTPA esters of 1-phenyl-1-pentanol, suggested that the methoxy groups of diastereomeric MTPA esters of α-aromatic alkanols might have predictable chemical shift differences. Trends in the chemical shift of the methoxy group of MTPA esters of α-aromatic alkanols have been reported sporadically in the literature[10,13,14,30] but have not been exploited or generalised. This is the purpose of this paper.

2. Methodology

Structure searches in Beilstein (release BS9901AB) were made with the Beilstein Commander/CrossFire system. The MTPA ester moiety linked to a methine group was defined with no free sites, whereas the variable moiety was defined with all free sites. Searches were made for aryl, 2- and 3-furans, -pyrroles or -thiophenes and 2-, 3- and 4-pyridines attached to the methine centre (α-(hetero)aromatic) and separated by a further carbon atom (β-(hetero)aromatic). Compounds containing two MTPA esters were excluded from the listings due to ambiguity in the assignments. Citations were checked manually using the library at Cardiff. All structures were included, for which the stereochemistry was defined unambiguously[15] and for which the chemical shifts of the methoxy groups were reported. On this basis, about one paper in five gave valid data.[16]

3. Results and discussion

The data in Tables 1–5 was interpreted with the model shown in Fig. 2. The absolute configuration of the alkanol moiety of 'normal' MTPA esters of hetero(aromatic) alkanols as defined by the Cahn–Ingold–Prelog (CIP) rules, is assigned from the sequence O>(hetero)aryl>alkyl>H. On this basis, MTPA esters of hetero(aromatic) alkanols in which the absolute configuration of the MTPA moiety matches that of the alkanol moiety (*R,R* or *S,S=l*, like), have the methoxy group in an orientation in which it can be shielded by the hetero(aromatic) group. Whereas if either of the configurations are inverted (*R,S* or *S,R=u*, unlike) this is not the case. Hence for this group of MTPA esters (Table 1) the chemical shift difference ($\Delta\delta$) between the *u*-diastereoisomer and the *l*-diastereoisomer is predicted to be positive. The data for the benzylic alcohols **1**–**5**, **7**–**9** all show a $\Delta\delta$ of +0.08–0.11 ppm and the cyclopropyl analogue **6** shows a similar, but smaller effect ($\Delta\delta$=+0.06) presumably due to shielding by the cyclopropane ring.

The same trend is seen with the homo-allyl derivatives **10**, **14** and the difference ($\Delta\delta$=+0.21) for the latter is the largest in this table and the third largest difference overall. The methine esters **17**, **22**, **23** all have a small, but nevertheless positive chemical shift difference and together with the furylpentanol derivative **21** show that this effect is applicable to furans as well as phenyl derivatives. The 2-pyridyl derivatives **20**, **24**, **26**, **28** all show the effect although the sign is changed for the fluoro-derivatives **26**, **28** because of the effect of the fluoro-group on the CIP priority order and the effect is negligible for the *t*-butyl **25** and difluoro **27** derivatives. The heterogeneous group of benzylic phosphonates **29**–**41** in Table 2 is particularly significant, because they are not easily amenable to the 'modified Mosher's method' for assigning absolute configuration. The expected positive shifts are observed and there is a corresponding but non-parallel upfield shift of the signals in the ^{31}P NMR spectrum (0.22–0.56 ppm), which is due to shielding by the phenyl group of the MTPA moiety (Fig. 2, R=phosphonate).[12]

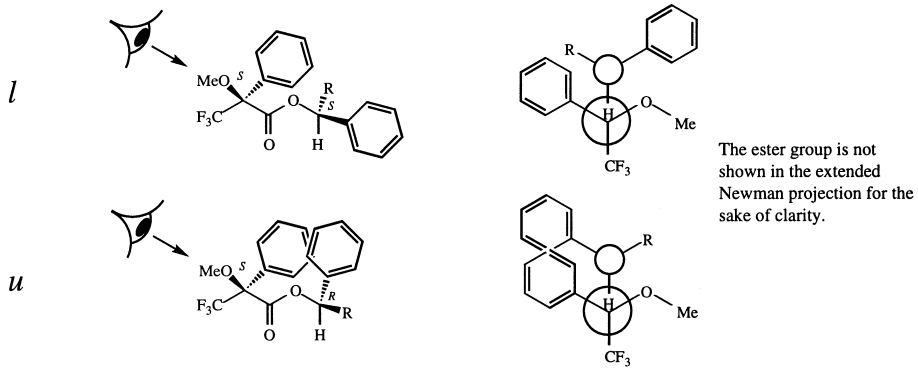
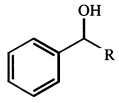
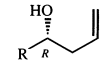
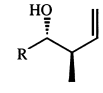
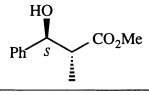
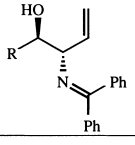
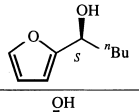
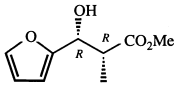
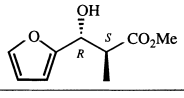
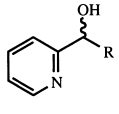


Figure 2.

The 'inverted preference' α-aromatic alkanols in Table 3 present additional complications for interpretation because both the ester (cf. **43**) and the nitrile (cf. **45**–**49**) group act to deshield the methoxy group of MTPA esters.[11] If this deshielding effect and the shielding effect of the phenyl ring act in concert some of the largest negative $\Delta\delta$ values should be seen for this data set. The benzylic ester **43** ($\Delta\delta$ −0.16) and the benzylic nitrile **49** ($\Delta\delta$ −0.16) have absolute chemical shift differences which are at the upper end of those found in Tables 1 and 2 and higher than those of non-aromatic nitriles **45**–**47** ($\Delta\delta$ −0.10).

The anthracene derivative **50** shows the largest absolute chemical shift difference ($\Delta\delta$ −0.39) in the entire data set and other polyaromatic systems also show large chemical shift differences e.g. α-1-naphthalenes **33**, **34** ($\Delta\delta$ +0.17 and +0.14), the α-2-naphthalene **35** ($\Delta\delta$ +0.16) and the β-1-naphthalene

Table 1
'Normal priority' α-(hetero)aromatic alkanols (underlined data has an 'inverted' CIP sequence, doubly underlined data is shown for comparison purposes only, NR=not reported)

No.	Alcohol	R	MTPA	δ ArRHCO *u*, *l*	δ OMe *u*	δ OMe *l*	Δδ = *u* - *l*	Solvent	Ref.
1		Me	*R*	6.08, 6.14	3.54	3.46	+0.08	NR	18
2		Me	*R*	-, -	3.59	3.49	+0.10	$CDCl_3$	19,20
3		Me	*R*	-, -	3.53	3.43	+0.10	CCl_4	11
4		Et	*R*	-, -	3.54	3.43	+0.11	CCl_4	11
5		^{i}Pr	*R*	-, -	3.52	3.42	+0.10	CCl_4	11
6		^{c}Pr	*S*	5.38, 5.46	3.61	3.55	+0.06	$CDCl_3$	21
7		^{n}Bu	*R*	-, -	3.538	3.447	+0.091	NR	22
8		^{n}Bu	*S*	5.86, 5.92	3.52	3.43	+0.09	$CDCl_3$	9
9		(*S*)-$^{n}C_9H_{19}$	*R*,*S*	5.85, 5.92	3.53	3.43	+0.10	$CDCl_3$	19
10		Ph	*R*	-, -	3.42	3.30	+0.12	All	23
11		^{t}Bu	*R*	-, -	3.47	3.38	+0.09	C_6D_6	
12		$^{c}C_6H_{11}$	*R*	-, -	3.48	3.43	+0.05		
13		Bn	*R*	-, -	3.44	3.38	+0.06		
14		Ph	*R*	-, -	3.43	3.22	+0.21		
15		$^{c}C_6H_{11}$	*R*	-, -	3.22	3.15	+0.07		
16		Bn	*R*	-, -	3.03	2.99	+0.04		
17			*S*	5.93, 5.99	3.37	3.33	+0.04	$CDCl_3$	24
18		$^{c}C_6H_{11}$	*R*	-,-	3.51	3.64	-0.13	All	25
19		Ph	*R*	-, -	3.44	3.57	-0.13	$CDCl_3$	
20		2-Pyridyl	*R*	-, -	3.57	3.44	+0.13		
21			*S*	-, -	3.53	3.46	+0.07	$CDCl_3$	20
22			*R*	6.350, -	3.505	3.453	+0.052	Both $CDCl_3$	26
23			*R*	6.158, -	3.442	3.397	+0.045		
24		^{i}Pr	*S*	-, -	3.55	3.49	+0.06	All	27
25		^{t}Bu			3.52	3.52	0	$CDCl_3$	
26		CH_2F			3.53	3.64	-0.09		
27		CHF_2			3.55	3.55	0		
28		CF_3			3.50	3.61	-0.11		

52 (Δδ +0.26). It is well known that polyaromatics have a greater intrinsic shielding effect,[17] but for the effect to operate the correct conformation must be attained, as seems to be the case here.

β-(Hetero)aromatic alkanols were investigated in order to discover if the deshielding effect was maintained over a longer distance, but the data set was particularly limited. The benzyl homoallyl ester **13**, showed the expected positive chemical shift difference (Δδ +0.06), but the methyl derivative **16**

Table 2
α-(Hetero)aromatic phosphonate alkanols (all 'normal' CIP sequence)

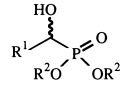
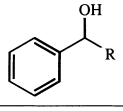
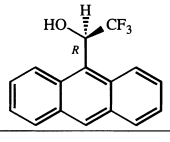
No.	Alcohol	R^1	R^2	δ OMe *u*	δ OMe *l*	Δδ = *u* - *l*	Solvent	Ref.
29	 (*R*)-MTPA	2-MePh	*i*Pr	3.60	3.47	+0.13	All	14
30		2-MePh	Me	3.59	3.49	+0.10	$CDCl_3$	
31		2-MeOPh	*i*Pr	3.61	3.50	+0.10		
32		3-MeOPh	*i*Pr	3.63	3.50	+0.13		
33		1-Naphthyl	*i*Pr	3.65	3.48	+0.17		
34		1-Naphthyl	Me	3.64	3.48	+0.14		
35		2-Naphthyl	*i*Pr	3.56	3.40	+0.16		
36		2-Thienyl	*i*Pr	3.58	3.45	+0.13		
37		2-Thienyl	Et	3.58	3.48	+0.10		
38		3-Thienyl	*i*Pr	3.61	3.47	+0.14		
39		2-Furyl	*i*Pr	3.58	3.47	+0.11		
40		2-Pyridyl	*i*Pr	3.64	3.57	+0.07		
41		3-Pyridyl	*i*Pr	3.61	3.49	+0.12		

Table 3
'Inverted priority' α-aromatic alkanols (doubly underlined data is shown for comparison purposes only, NR=not reported)

No.	Alcohol	R	MTPA	δ ArRHCO *u*, *l*	δ OMe *u*	δ OMe *l*	Δδ = *u* - *l*	Solvent	Ref.
42		CF_3	*R*	-, 6.30	3.45	3.539	-0.089	NR	28
43		CO_2Me	*R*	-, -	3.56	3.72	-0.16	CCl_4	11
44		CH_2OAc	*R*	-, -	3.47	3.58	-0.11	$CDCl_3$	29
45		Me	*S*	4.68, 4.75	3.20	3.30	-0.10	All	30
46		Et		4.69, 4.77	3.22	3.32	-0.10	$CDCl_3$	
47		*i*Pr		4.74, 4.82	3.24	3.34	-0.10		
48		Bn		5.10, 5.17	3.06	3.25	-0.19		
49		Ph		6.03, 6.04	3.16	3.31	-0.16		
50			*R,S*	6.32, 6.37	3.28	3.67	-0.39	$CDCl_3$	19

showed a small positive shift difference (Δδ +0.04), although a negative one is predicted. The benzylic nitrile **48** exhibited a much larger absolute shift difference (Δδ −0.19), due in part to the deshielding effect of the nitrile group.

The cyclohexanol derivatives **51**–**55** all showed significant chemical shift differences, except the 2,4,6-trimethylphenyl derivative **56**. In the heterocyclic example **58** a minute chemical shift difference (Δδ +0.03) was observed which can be rationalised as due to the phenyl rather than the pyridine ring.

It was noted above, that data for bis(MTPA) esters was excluded from consideration for inclusion in Tables 1–5 because of ambiguities in assigning the ^{1}H NMR signals for the methoxy groups to the individual esters. However Ichikawa's data[8] has full listing for all signals and a number of favourable coincidences render it amenable to analysis.

There is no explicit data to distinguish the ^{1}H NMR shifts of the two methoxy groups in each molecule,

Table 4
β-(Hetero)aromatic alkanols (doubly underlined data is shown for comparison purposes only)

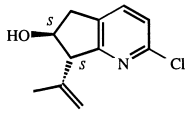
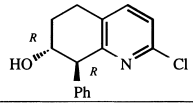
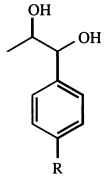
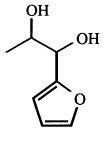
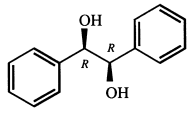
No.	Alcohol	R	MTPA	δ ArRHCO *u*, *l*	δ OMe *u*	δ OMe *l*	Δδ = *u* - *l*	Solvent	Ref.
51		Ph	*R*	5.08-5.48	3.21	3.10	+0.11	$CDCl_3$	31
52		1-Naphthyl		5.48-5.70	3.10	2.84	+0.26		
53		4-Me-Ph		5.16-5.36	3.25	3.15	+0.1		
54		4-OMe-Ph		5.10-5.34	3.28	3.18	+0.1		
55		4-Br-Ph		5.10-5.39	3.38	3.22	+0.16		
56		2,4,6-tri-Me-Ph		5.60-5.98	3.20	3.20	0		
57			*R,S*	-,-	3.50	3.52	-0.02	Both $CDCl_3$	32
58			*R,S*	-,-	3.45	3.42	+0.03		

Table 5
α-(Hetero)aromatic alkan-diols (underlined data has an 'inverted' CIP sequence)

No.	Alcohol	R and/or stereochemistry	MTPA *u* *l*	δ H-1, H-2	δ OMe C-1 or C-2	δ OMe C-2 or C-1	Δδ = *u* - *l*	Solvent	Ref.
		R = H							
59		1*R*,2*S*	*S*	6.09, 5.45	3.30	3.38	-0.02 to	All	8
60		1*R*,2*S*	*R*	6.09, 5.46	3.46	3.40	-0.16	$CDCl_3$	
		R = OMe							
61		1*R*,2*S*	*S*	6.01, 5.43	3.30	3.37[a]	-0.03 to		
62		1*R*,2*S*	*R*	6.00, 5.44	3.45	3.40[b]	-0.15		
63		1*S*,2*S*	*R*	6.14, 5.64	3.45	3.41	+0.01 to	All	8
64		1*S*,2*S*	*S*	6.14, 5.62	3.32	3.40	+0.13	$CDCl_3$	
65		1*S*,2*R*	*R*	6.09, 5.70	3.45	3.40	-0.02 to		
66		1*S*,2*R*	*S*	6.11, 5.62	3.42	3.40	+0.05		
67			*S*	6.32	3.36		-0.03	Both $CDCl_3$	8
68			*R*	6.21	3.39				

[a] **61** δ ArOMe 3.81; [b] **62** δ ArOMe 3.79; These signals are assigned on the basis of their higher chemical shift and by comparison with the data for the phenyl analogues **59**, **60**.

however the chemical shift effect may be demonstrated by deduction. Recall that for MTPA esters of α-(hetero)aromatic alkanols which follow the 'normal' CIP sequence (O>(hetero)aryl>alkyl>H), the methoxy group of the *l*-diastereoisomer is shielded and hence the expression $\Delta\delta=\delta(u\text{-OMe})-\delta(l\text{-OMe})$ is positive. In the arguments that follow only the configuration of C-1 and the MTPA ester moiety are relevent to the sign of the chemical shift difference. The MTPA esters of the phenyl alkan-diols **59**, **60** have an 'inverted' CIP sequence at C-1 and hence a negative chemical shift difference

is predicted. Fortuitously, the ^{1}H NMR chemical shifts of both the methoxy groups of the (1*R*,2*S*,*S*′)-*u*-diastereoisomer are upfield of those of the (1*R*,2*S*,*R*′)-*l*-diastereoisomer. Hence the chemical shift difference must be in the range −0.02 to −0.16. By identical reasoning, the MTPA esters of the *p*-anisyl alkan-diols **61**, **62** have chemical shift differences which must be in the range −0.03 to −0.15.

The MTPA esters of the (1*S*,2*S*)-furanyl alkan-diols **63**, **64** follow the 'normal' CIP sequence and have the predicted positive chemical shift difference ($\Delta\delta$=+0.01 to +0.13), whereas the (1*S*,2*R*)-diastereoisomers **65**, **66** have poorly dispersed ^{1}H NMR signals for the methoxy groups. The four possible chemical shift differences are −0.02, 0.0, 0.0 and +0.05 and the best that can be said is that the data is insufficient to support or refute the proposed trend.

The MTPA esters of the bibenzyl diols **67**, **68** have a C_2 axis and hence 'C-1' and 'C-2' are identical in an achiral environment. A negative (albeit small) chemical shift difference ($\Delta\delta$=−0.03), is observed as predicted. In summary, for all data for which unambiguous assignments of chemical shift difference can be made, the predicted trend is observed.

4. Conclusion

Tables 1–4 contain 50 examples of mono(MTPA esters) of α- and β-hetero(aromatic) alkanols (plus eight sets of comparison data). In 46 cases the expected shift difference was observed (absolute range 0.03–0.39 ppm, absolute average 0.11 ppm). In three cases **25**, **27**, **56** no difference was present and the β-aromatic MTPA ester **16** had a chemical shift difference contrary to that predicted. Four examples of bis(MTPA esters) of α-hetero(aromatic) alkan-diols (Table 5) also had chemical shift differences in accord with the predicted trend.

There can be no doubt that a complete set of chemical shift differences for a pair of MTPA esters provides a convincing body of evidence for the assignment of absolute configuration. However when time, resources or lack of dispersion do not permit such an investigation, the method presented here provides a quick, easy and reliable alternative for α- and β-hetero(aromatic) alkanols.

I commend this method as an extension of the 'modified Mosher's method' and invite researchers who have data which supports or refutes these generalisations to send it to me for inclusion in a future publication.

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