Synthesis of highly hindered oxepins and an azepine from bis-trityl carbenium ions: structural characterisation by NMR and X-ray crystallography

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Reactions of the bis-carbenium ion 2,2′-bis[bis(*p*-methoxyphenyl)methyl]biphenyl ditetrafluoroborate with ammonia, *n*-propylamine and benzylamine have been studied with the aim of developing an acid-labile protecting group for primary amines that masks both hydrogen atoms of the NH_2 group. Although the parent 5,5,7,7-tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]azepine was isolated and fully characterised, the corresponding azepines could not be obtained in a pure state from the reactions with the primary amines. The bis-carbenium ion was prepared from the treatment of 2,2′-bis[bis(*p*-methoxyphenyl)hydroxymethyl]biphenyl with fluoroboric acid. Attempts to prepare the corresponding diphenyl analogue were unsuccessful using either fluoroboric acid or boron trifluoride. The only product isolated from these reactions was 5,5,7,7-tetraphenyl-5,7-dihydrodibenzo-[*c*,*e*]oxepin. The oxepin and its phenyl-*p*-methoxyphenyl and bis(*p*-methoxyphenyl) analogues were efficiently obtained by dehydration of the corresponding diol, *e.g.* 2,2′-bis[bis(*p*-methoxyphenyl)hydroxymethyl]biphenyl, in the presence of 3 Å molecular sieves or Amberlite IR-200 resin. The compounds 2,2′-bis[bis(*p*-methoxyphenyl)-hydroxymethyl]biphenyl, (*R*,*R*/*S*,*S*)-2,2′-[bis(phenyl-*p*-methoxyphenyl)hydroxymethyl]biphenyl, 5,5,7,7-tetraphenyl-5,7-dihydrodibenzo[*c*,*e*]oxepin, 5,5,7,7-tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]oxepin and 5,5,7,7-tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]azepine were characterised by crystal structure analyses. 2,2′-Bis[bis(*p*-methoxyphenyl)hydroxymethyl]biphenyl and 5,5,7,7-tetrakis(*p*-methoxyphenyl)-5,7-dihydro-dibenzo[*c*,*e*]oxepin exhibited dynamic NMR properties, and free energy barriers have been determined.

Introduction

The need for the protection of amino groups is commonplace in the synthesis of natural products, *e.g.* amino acids[1,2] and peptides,[3,4] polyamines,[5–7] and antibiotics.[8] Varied protecting strategies have been described for amino functions, including the use of *N*-alkyl (*e.g.* benzyl), acyl (*e.g.* acetyl), alkoxycarbonyl (*e.g.* BOC), silyl (*e.g.* trimethylsilyl),[9–11] and metallo groups (*e.g.* cobalt(III) derivatives).[12] Most protecting groups for primary alkylamines (RNH_2), however, mask only one of the hydrogen atoms connected to nitrogen. The remaining N–H is susceptible to removal by strongly basic reagents, which can cause problems in multistage synthesis because the derived nitrogen-based anion is intrinsically reactive as a base and a nucleophile. Furthermore, the salt formed by deprotonation of an amine may be insoluble in organic solvents. Various possible solutions to this problem have been presented, including the use of phthalimide, dichloro-[13] and tetrachlorophthalimides,[14] dithiasuccinoyl,[15] dimethylmaleoyl,[16] diphenylsilyldiethylene groups,[17] and other silicon-containing protecting groups such as STABASE (tetramethyldisilylazacyclopentane),[18] benzostabase[19,20] and TEDI (tetraethyldisilaisoindoline).[21] Primary amines have also been protected as *N*-substituted 2,5-dimethylpyrroles,[22] 2,5-bis[tris(isopropylsilyl)oxy]pyrrole (BIPSOP) derivatives,[23] triazones,[24] and *N*,*N*-dibenzylformamidines;[25] diprotected primary amines have also been prepared from 3,5-dinitro-1-(*p*-nitrophenyl)-4-pyridone.[26]

We have recently described the use of substituted triphenylmethyl (trityl) groups for the protection of primary and secondary amines.[27] The substituted trityl protecting groups, however, do not solve the problem posed above, *i.e.* one N–H remains unblocked. We therefore considered the possibility that a suitable bis-trityl dication, which would be regenerated under acidic conditions,[27–29] could be used to mask both hydrogen atoms of a primary amine. We now present results of an investigation into the use of bis-trityl dications as their ditetrafluoroborate salts **1**, Fig. 1, as possible new protecting groups for primary amines. This led to a study of the highly hindered oxepins **2** and azepine **3**, Fig. 1, derived from these bis-trityl dications. Although a satisfactory procedure for protecting a primary amine by reaction with **1** was not achieved, several of the compounds derived from **1** exhibited interesting structural features which are described herein.

Results and discussion

Synthesis of diols 4

Diols **4a** and **4b**, Fig. 2, were prepared by reaction of an aryl lithium with diphenic acid dimethyl ester.[30,31] The yield of **4a** was 73% using phenyllithium freshly prepared from bromobenzene and *n*-butyllithium. The identity of the product was confirmed by comparison of the ^1H and ^{13}C NMR spectra with those of an authentic sample (kindly supplied by Professor Toda). The tetraanisyl diol **4b**[32] was prepared in a similar manner in 72% yield from *p*-methoxyphenyllithium, which was generated *in situ* from *p*-bromoanisole and *n*-butyl-

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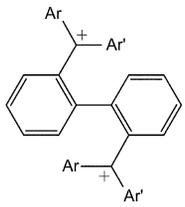
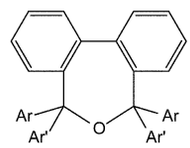
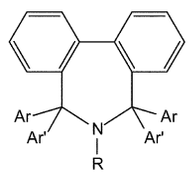


1a Ar = Ar' = Ph
1b Ar = Ar' = 4-MeOC$_6$H$_4$

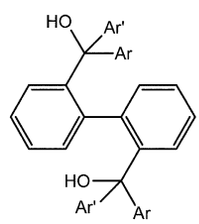


2a Ar = Ar' = Ph
2b Ar = Ar' = 4-MeOC$_6$H$_4$
2c Ar = Ph, Ar' = 4-MeOC$_6$H$_4$



3a R = H, Ar = Ar' = 4-MeOC$_6$H$_4$

Fig. 1



4a Ar = Ar' = Ph
4b Ar = Ar' = 4-MeOC$_6$H$_4$
4c Ar = Ph, Ar' = 4-MeOC$_6$H$_4$

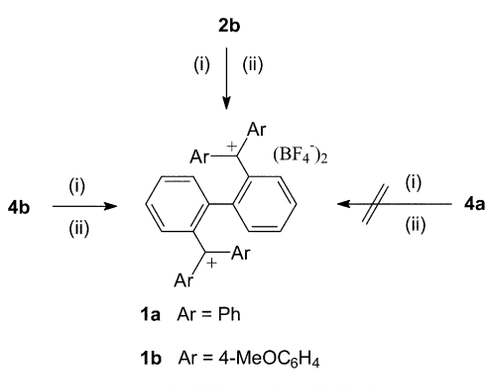
Fig. 2

lithium by a modification of the method of Rapoport and co-workers.[33]

The nature of diol **4c** did not allow it to be prepared by the method employed for **4a** and **4b**, and no synthesis of it had been previously reported. The compound was prepared by reaction of 2,2′-dilithiobiphenyl (freshly prepared from 2,2′-dibromobiphenyl and *n*-butyllithium) with an excess of 4-methoxybenzophenone. There is, of course, little or no stereocontrol in the generation of the two stereogenic centres in this reaction. The ^{1}H NMR spectrum of the crude reaction mixture showed two methoxy signals of almost equal intensity indicating that **4c** was a 1 : 1 mixture of *RR*/*SS* and *meso* forms.

Synthesis of dications 1

Tetramethoxy diol **4b** was converted into **1b** in 98% yield using the Dauben procedure[34] Scheme 1. Salt **1b** was also prepared from oxepin **2b** in 57% yield using the same procedure. Soon after the completion of our work, Suzuki and co-workers[32] reported the preparation from **4b** of the ditetrafluoroborate and diantimony hexachloride salts of dication **1b** and analysed their structures by X-ray crystallography.



1a Ar = Ph
1b Ar = 4-MeOC$_6$H$_4$
(i) HBF$_4$, Ac$_2$O (ii) Et$_2$O

Scheme 1 Synthesis of dications.

Attempts to obtain the methoxy-free analogue **1a** from the corresponding diol **4a** were unsuccessful so, following a report by Olah and co-workers[35] on rearrangements induced by protic acids in related systems, we investigated an alternative procedure using boron trifluoride.[36] This was considered to be superior to the previously used method in that it could be performed under anhydrous conditions, under nitrogen, and the product would precipitate out of solution without the need for addition of more ether. The procedure was first investigated using 4,4′,4″-trimethoxytrityl alcohol (TMTrOH) and trityl alcohol (TrOH), which gave 99% and 60% yields of the tetrafluoroborates of the (substituted) trityl cations, respectively. The tetraphenyl diol **4a** was subjected to the same procedure. A green colour was observed on addition of BF_3–diethyl ether and a white compound precipitated out of solution, which was identified as oxepin **2a** by ^{1}H NMR and TLC comparison with an authentic sample. The diethyl ether–BF_3 phase was hydrolysed, worked up, and was shown to contain further oxepin **2a**. The total yield of oxepin was about 70% with no isolable salt of the dication. Hart and co-workers had previously studied reactions of diols related to and including **4a** and **4b**.[37] They reported that, when the two hydroxy groups can achieve the correct proximity, formation of a relatively stable oxonium ion after the first ionisation prevents formation of the dication from compounds without carbocation-stabilising substituents. Salts with diphenylmethyl cationic groups at *para* positions on the biphenyl system have been isolated.[38]

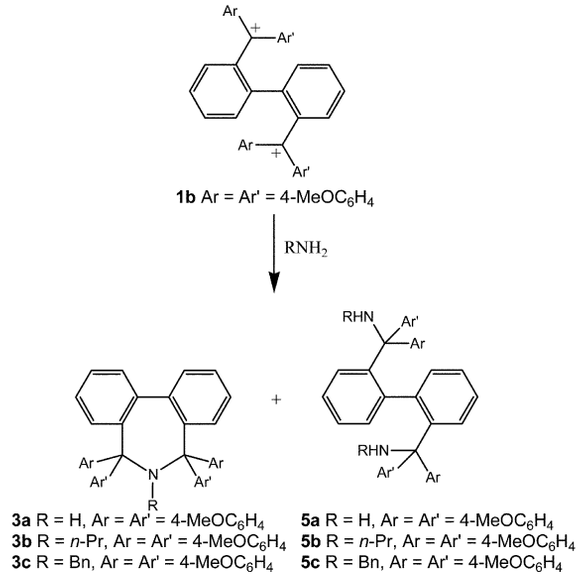
Synthesis of oxepins 2

The oxepins **2a**–**c** were prepared by dehydrating the corresponding diols, and the ease of these reactions reflects the relative stabilities of the intermediate cations. Tetramethoxy diol **4b** was simply stirred with 3 Å molecular sieves in dichloromethane at room temperature for 24 days to give oxepin **2b** quantitatively. This transformation occurred overnight when Amberlite was used in place of molecular sieves. Diol **4c** was converted to oxepin **2c** in 6 days under the same conditions. Reaction of diol **4a** by the same procedure gave isolated yields of oxepin **2a** (70%) and starting material (20%) after two weeks, or overnight by refluxing in toluene with Amberlite, using a Dean–Stark apparatus.

Synthesis of azepines 3

Dication ditetrafluoroborate **1b** was reacted with ammonia according to a literature procedure[27] to give 5,5,7,7-tetrakis-(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]azepine **3a** (40%) and the corresponding diamine, **5a** in a 2 : 1 ratio, Scheme 2. The azepine decomposed during attempted separation of these compounds on silica. Chromatography on Florisil proved effective in terms of separating efficiency and recovery. Dication ditetrafluoroborate **1b** was also reacted with *n*-propylamine and benzylamine. ^{1}H NMR spectra of the crude reaction mixtures indicated the presence of both the desired ring closed protected amines **3** along with the diamines **5**, Scheme 2, in approximately equal amounts. It was not possible to separate these compounds by chromatography. The instability of the bis-tritylated alkylamines on silica is not too surprising in the light of results published by Maskill and coworkers[29] on the simpler methoxy-substituted *N*-tritylalkylamines. Attempts to isolate the azepines by crystallisation from the crude products also proved unsuccessful.

Given the difficulties of separation of azepines **3** from the diamines **5**, we attempted driving the reaction wholly towards **3** and minimising the formation of diamine by using just one equivalent of primary amine and a highly hindered base.



Scheme 2 Synthesis of azepines and diamines.

Golding and coworkers[39] had reported that the visible spectrum of 4-methoxy- and 4,4′-dimethoxytrityl tetrafluoroborates in acetonitrile remains virtually unchanged when titrated with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). Excess DTBMP was added to a solution of the dication **1b** in acetonitrile and the red colour remained. A stoichiometric amount of *n*-propylamine was added, but the characteristic red colour of the dication did not disappear; it only became less intense, even after addition of more amine and continued stirring for 4 days. The reaction mixture was worked up as described below, but NMR analysis of the crude mixture showed no signals characteristic of the propyl group.

X-Ray crystal structures

Diols

Crystals of a single stereoisomer of **4c** were obtained by chromatography of the crude reaction mixture followed by crystallisation using the vapour diffusion technique. The crystal structures of diols **4b** and racemic **4c** are shown in Fig. 3 and

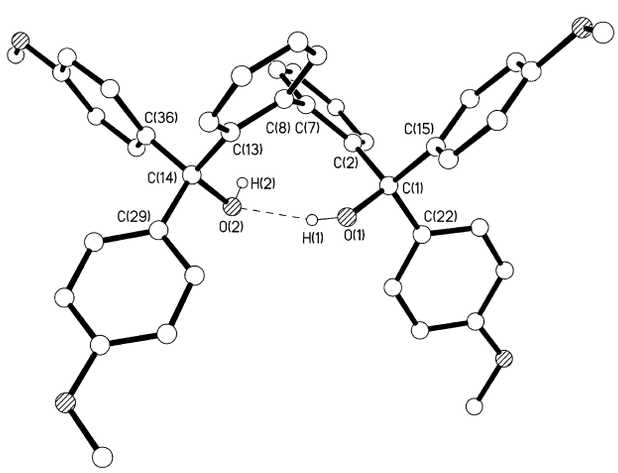


Fig. 3 2,2′-bis[bis(*p*-methoxyphenyl)hydroxymethyl]biphenyl **4b**.

Fig. 4, respectively. Some of the important features are summarised in Table 1 along with relevant data for **4a**[30] and the simple trityl alcohols TrOH[40] and TMTrOH.[41] As can be seen, results for all five compounds are in good agreement. The C–OH bond lengths for the bis-trityl diols are comparable with

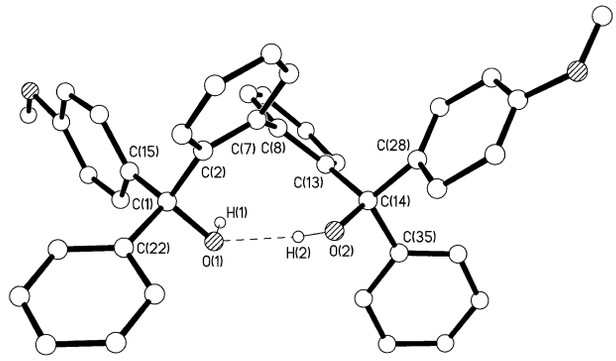


Fig. 4 (*RR*/*SS*)-2,2′-bis(phenyl-*p*-methoxyphenylhydroxymethyl)-biphenyl **4c**.

the mean literature value of 1.43 Å for a C–OH bond.[42] The $C(sp^3)$–C_{Ar} bond lengths are shown in rows 4–6. There are two sets of three for the bis-trityl diols. It is worth noting that the two C–anisyl bonds in diol **4c** are appreciably shorter than the C–Ph bonds in the same molecule, although this relationship does not hold for the tetramethoxy diol **4b**, where all such bonds are the same within experimental error. Also, the relationship is reversed between TrOH and TMTrOH, *i.e.* the $C(sp^3)$–C_{Ar} bonds are shorter in the former, but the effect here is very small. The sums of the bond angles around the tetrahedral carbon (Σ C_{Ar}–C–C_{Ar}) and (Σ O–C–C_{Ar}) are shown in rows 8–11. As can be seen, the values for Σ C_{Ar}–C–C_{Ar} and Σ O–C–C_{Ar} are in good agreement amongst all four compounds, which indicates that there is no unusual crowding in the bis-trityl systems compared with the simpler trityl alcohols.

The biphenyl bond lengths in diols **4b** and **4c** are 1.505 and 1.501 Å, respectively. The biphenyl torsion angles are 84.0 and 83.7°, respectively, which are accompanied by intramolecular hydrogen bonds between the hydroxy groups (there is no intermolecular hydrogen bonding). These are compared with similar compounds, Fig. 5 in Table 2 and, as could be expected, the

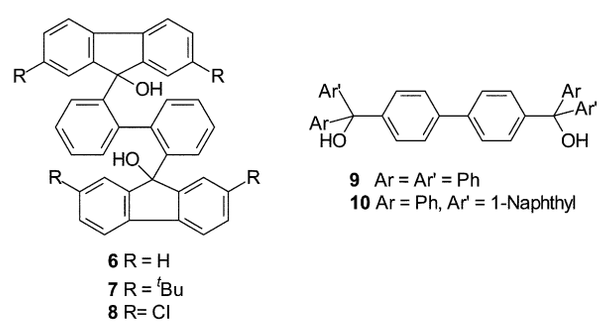


Fig. 5 Literature diols related to **4**.

biphenyl bond length is shorter for the *p*,*p*′-diols, where there is less crowding around the biphenyl bond. The presence of the guest molecules for the literature diols in Table 2 probably affects their ability to form the intramolecular hydrogen bonds, and accounts for the torsion angle of the *o*,*o*′-diols.

Oxepins

The crystal structures of oxepins **2a** and **2b** are shown in Fig. 6 and Fig. 7, respectively. The salient features are summarised in Table 3, along with the data for ditrityl ether[43] (Tr–O–Tr) for comparison. The crystal structure of **2a** shows one molecule of toluene (which has been omitted from Fig. 6 for clarity) for each molecule of oxepin. This is simply solvent of crystallisation rather than a host–guest relationship and there are no evident significant intermolecular interactions. The molecule of **2b** has C_2 crystallographic symmetry. The C–O bond lengths are essentially the same in both oxepins and in ditrityl ether, indi-

Table 1 Structural parameters for **4a**, **4b**, **4c**, TrOH and TMTrOH; standard uncertainties are given in parentheses for individual results obtained in this work, here and in other tables

Compound		**4a**[f]	**4b**	**4c**	TrOH	TMTrOH
Bond length/Å	$C(sp^3)$[a]–OH	1.457	1.429 (2)	1.454 (8)	1.449	1.459
Bond length/Å	$C(sp^3)$[a]–OH	1.451	1.453 (2)	1.435 (8)	—	—
	Mean	1.454	1.441	1.445	—	—
Bond length[c]/Å	$C(sp^3)$[a]–Ar	1.508 1.538	1.542 (3) 1.545 (3)	1.525 (10) 1.542 (10)	1.514	1.525[b]
Bond length[c]/Å	$C(sp^3)$[a]–Ar	1.546 1.548	1.537 (3)[b] 1.536 (3)[b]	1.501 (12)[b] 1.558 (10)	1.514	1.529[b]
Bond length[c]/Å	$C(sp^3)$[a]–Ar	1.532 1.526	1.537 (3)[b] 1.545 (3)[b]	1.482 (11)[b] 1.539 (11)	1.514	1.521[b]
	Mean	—	—	—	1.514	1.525
Σ angles[d]/°	O–$C(sp^3)$[a]–C_{Ar}	322.7	322.9	322.5	324.0	324.8
Σ angles[d]/°	O–$C(sp^3)$[a]–C_{Ar}	322.5	324.8	324.7	—	—
Σ angles[e]/°	C_{Ar}–$C(sp^3)$[a]–C_{Ar}	334.1	333.7	331.9	323.7	331.9
Σ angles[e]/°	C_{Ar}–$C(sp^3)$[a]–C_{Ar}	334.2	331.9	334.2	—	—

[a] Tetrahedral carbon. [b] Anisyl group. [c] C–C bond lengths for the sp^2-sp^3 bonds in the bis-trityl diols and simple trityl alcohols [d] The sum of the three O–$C(sp^3)$–C_{Ar} bond angles around the sp^3 carbon atoms as a measure of the extent of steric crowding. [e] The sums of the three C_{Ar}–$C(sp^3)$–C_{Ar} bond angles around the sp^3 carbon as a measure of the extent of steric crowding. [f] Complex with acetone.

Table 2 Torsion angles and central C–C bond lengths for biphenyls **4a** and **6**–**10**

Compound	**4a**	**6**[a]	**7**[b]	**8**[c]	**9**[d]	**10**[d]	**10**[de]	**10**[da]
Torsion angle/°	78.0	88.1	88.3	89.1	7.2	41.2	37.9	18.0
Biphenyl bond/Å	1.501	1.508	1.510	1.514	1.495	1.492	1.486	1.477

[a] Complex with acetone. [b] Complex with butyronitrile. [c] Complex with cyclohexanone. [d] *p*, *p*′-diol; no simple related *m,m*′-diols were found in the Cambridge Structural Database. [e] Polymorph.

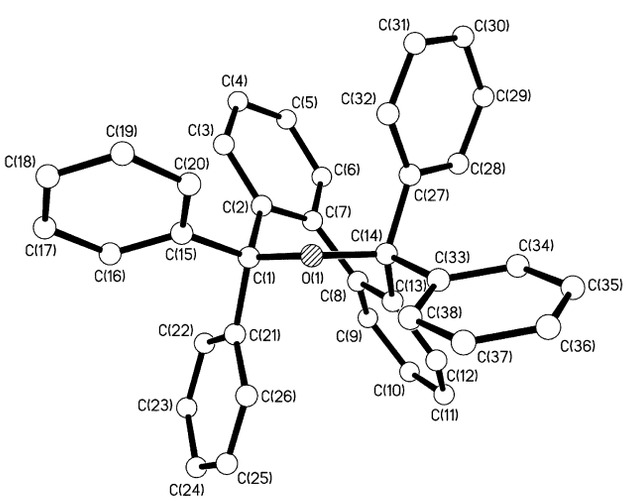


Fig. 6 5,5,7,7-Tetraphenyl-5,7-dihydrodibenzo[*c,e*]oxepin, **2a.**

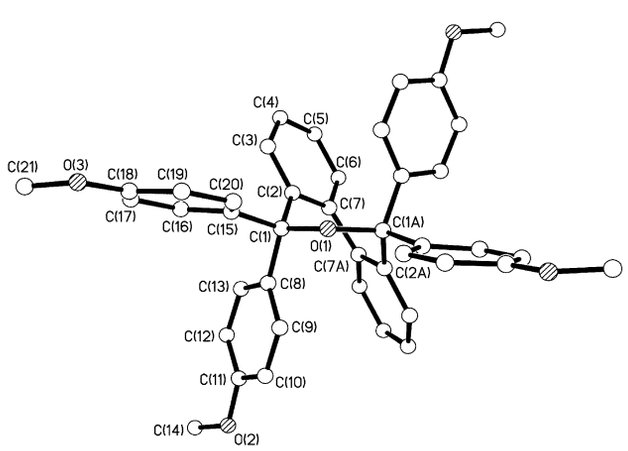


Fig. 7 5,5,7,7-Tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c,e*]-oxepin, **2b.**

cating that the crowding in the *ortho* positions of the biphenyl system does not lead to unusually long C–O bonds. The C–O bond lengths and the mean $C(sp^3)$–C_{Ar} bond lengths for all three compounds in Table 3 are in good agreement with the corresponding bond lengths in the diols, Table 1.

Table 3 Structural parameters for **2a**, **2b** and ditrityl ether

Compound	**2a**	**2b**	Tr–O–Tr
C–O bond/Å	1.448 (2)	1.452 (1)[b]	1.454
C–O bond/Å	1.454 (2)		1.466
Mean	1.451		1.460
$C(sp^3)$[a]–C_{Ar} bond/Å	1.535 (3) 1.531 (3)	1.535 (2)[b]	1.544 1.548
$C(sp^3)$[a]–C_{Ar} bond/Å	1.541 (3) 1.551 (3)	1.540 (2)[b]	1.553 1.541
$C(sp^3)$[a]–C_{Ar} bond/Å	1.546 (3) 1.544 (3)	1.548 (2)[b]	1.541 1.533

[a] Tetrahedral carbon. Rows 1–2, C–O bond lengths for oxepins **2a**, **2b** and trityl ether. Rows 4–6, $C(sp^3)$–C_{Ar} bond lengths. [b] Data for both halves of the C_2 symmetric molecule supplied.

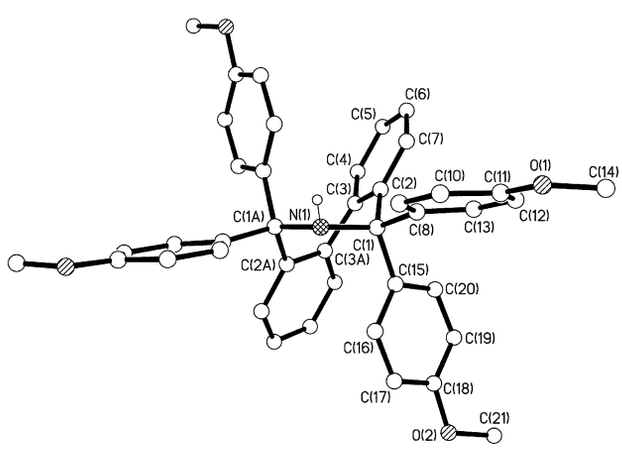


Fig. 8 5,5,7,7-Tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c,e*]-azepine, **3a**

Azepine

The crystal structure of azepine **3a** is shown in Fig. 8 and some features are summarised in Table 4. The amine hydrogen is disordered equally over two positions related by a crystallographic two-fold axis, but only one position is shown. As can be seen in

Table 4 Structural parameters for **3a**, $TrNH_2$, and $TMTrNH_2$

Compound	Azepine **3a**	$TrNH_2$	$TMTrNH_2$
$C(sp^3)$[a]–N bond length/Å	1.480 (2)[b]	1.486	1.484
$C(sp^3)$[a]–Ar bond length/Å	1.537 (2)[b]	1.540	1.537
$C(sp^3)$[a]–Ar bond length/Å	1.551 (2)[b]	1.538	1.539
$C(sp^3)$[a]–Ar bond length/Å	1.558 (2)[b]	1.543	1.540
Mean $C(sp^3)$[a]–Ar bond length/Å	1.549	1.540	1.539
Σ[c] C_{Ar}–$C(sp^3)$[a]–C_{Ar}/°	327.5[b]	331.9	330.6
Σ[d] N–$C(sp^3)$[a]–C_{Ar}/°	329.3[b]	324.7	326.2

[a] Tetrahedral carbon. [b] Data for both halves of the molecule. [c] The sums of the three C_{Ar}–$C(sp^3)$–C_{Ar} bond angles around the sp^3 carbon as a measure of the extent of steric crowding. [d] The sum of the three N–$C(sp^3)$–C_{Ar} bond angles around the sp^3 carbon atoms as a measure of the extent of steric crowding.

Table 4, the C–N bond lengths in azepine **3a** are both 1.480 Å and are in good agreement with those in tritylamine ($TrNH_2$) and trimethoxytritylamine ($TMTrNH_2$).[44] There are no unusual bond lengths; this is analogous to what was observed for the oxepins and trityl alcohols. The $C(sp^3)$–Ar bond lengths (of which there are two sets) and the sums of the bond angles around the tetrahedral carbons (two sets of angles for each carbon, *i.e.* C_{Ar}–C–C_{Ar} and N–C–C_{Ar}) are also shown in Table 4. Results for all three compounds are in good agreement and show that there is no unusual crowding in the azepine system compared to the simpler tritylamines.

Dynamic NMR studies

The ^{1}H NMR spectrum of the tetramethoxy diol **4b** has two striking features. First, there are two signals corresponding to the methoxy groups at δ 3.7; this is ascribed to the two methoxy groups being in different environments due to restricted rotation around the biphenyl central bond. Secondly, there is an upfield signal at δ 6.0, which is ascribed to hydrogens in the 3,3′-positions of the biphenyl system lying in the shielding region of the anisyl rings. Similarly, the ^{1}H NMR spectrum of diol **4c** is complicated, because there is enantiomerism due to the restricted rotation (as for **4b**) as well as two stereogenic sp^3 carbons in the molecule. The ^{1}H NMR spectrum of **4c** shows two signals for the hydroxy groups and two upfield doublets near δ 6.0. In contrast, the spectrum for **4b** shows only one doublet in this region and only one hydroxy signal.

The ^{1}H NMR spectrum of oxepin **2b** also shows two methoxy signals attributed to the anisyl rings occupying *pseudo*-axial and *pseudo*-equatorial positions on the seven-membered oxepin ring, as seen in the crystal structure (Fig. 7). The less different methoxy signals in the diol **4b**, compared with **2b**, could be due to the same phenomenon in a nine-membered ring only weakly held by a hydrogen bond.

The aromatic region of the spectrum of **2b** also shows a considerably wider range of chemical shifts than for the diol **4b**, although the doublet seen at δ 6.0 for **4b** is not present for **2b**. The difference in the aromatic regions of the proton spectra between the alcohols and the oxepins is believed to be due to the conformationally more restricted oxepins fixing protons in different positions, which are exchangeable by rotations in the less restrained diols. The size of the *ortho* substituents causes a substantial barrier to rotation around the biphenyl bond, which endows the alcohols with enantiomerism of the type first recognised by Christie and Kenner.[45] The oxygen bridge in the oxepins adds another dimension to their stereochemistry, and Wittig and Leo[46] were the first to identify molecular asymmetry in such compounds. In principle, it is possible to interchange *pseudo*-axial and *pseudo*-equatorial aryl groups by a ring flip mechanism with a concomitant rotation of the biphenyl bond. A number of other dibenzo[*c*,*e*]oxepins showing this phenomenon have been reported.[47] We attempted to measure the free energy barrier to inversion of oxepin **2b** in d_5-chlorobenzene by locating the coalescence temperature of the methoxy signals, using an established mathematical treatment,[48] but there was no significant change in the methoxy signals between 24 and 120 °C. A minimum value of 79 kJ mol^{-1} for the free energy barrier can be estimated, assuming coalescence at 120 °C.

Although there was no significant change in the methoxy signals of oxepin **2b** upon heating, the aromatic region changed dramatically. The broad signal evident at δ 8.5 at lower temperatures disappears, and (amongst other changes) the doublet at δ 8.1 coalesces into a broad singlet. Attempts to assign the signals in the ^{1}H NMR spectrum at room temperature were unsuccessful, even with the aid of COSY, ROESY, and HETCOR experiments.

^{1}H spectra of oxepin **2b** in deuteriochloroform were also obtained at 10° intervals down to −50 °C. The broad aromatic signal at δ 8.4 at 23 °C separates into a doublet at −50 °C when two extra distinct signals become visible between δ 6.6–7.0, and the broad signal in this region at 23 °C is no longer present. The resolved spectrum indicates that conformational interconversions have been frozen out. The signals in the ^{1}H spectrum of **2b** at −50 °C were assigned with the aid of COSY, HETCOR, and ROESY techniques. Analysis of the aromatic regions for **2b** on warming up from −50 °C showed that 4 signals remain unaffected and 4 change dramatically. These are assigned to the two anisyl rings; one set of ring protons are labelled a,a′,c,c′ and the other b,b′,d,d′ in Fig. 9. Signals of hydrogens a,c

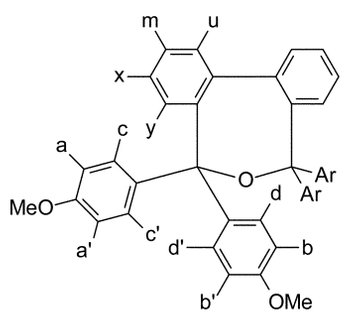


Fig. 9 Signal assignments for oxepin **2b**.

remain unchanged on warming from −50 to 23 °C, because this ring cannot freely rotate, due to unfavourable steric interactions with the hydrogen on C-3 of the biphenyl system. The hindrance to rotation invoked in this interpretation is supported by low level molecular modelling using the Hyper-Chem Lite program. By locating the coalescence temperature of the c,c′ interconversion, the free energy barrier to rotation of the a,c ring has been determined as 67 ± 1 kJ mol^{-1} at 56 °C. If we make the usual assumption that the entropy of activation is zero, this is the value of the enthalpy barrier of the conformational change.

Conclusions

This paper describes an attempt to develop a new protecting group for primary amines, which enables both hydrogen atoms of the NH_2 group to be masked. The strategy adopted using the bis-carbenium ion 2,2′-bis[bis(*p*-methoxyphenyl)methyl]-biphenyl as its ditetrafluoroborate was an extension of that successfully employed to protect primary amines using the dimethoxy- and trimethoxy-trityl groups.[27] However, although the bis-carbenium ion 2,2′-bis[bis(*p*-methoxyphenyl)methyl]-biphenyl reacted with ammonia to give the parent 5,5,7,7-tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]azepine, *N*-substituted azepines were not obtained from *n*-propylamine and benzylamine. The failure of this approach probably derives from the severe steric interactions engendered in such highly hindered systems.

Experimental

n-Butyllithium was titrated with diphenylacetic acid before use. Benzylamine and *n*-propylamine were purified according to literature procedures.[49] Acetonitrile was pre-dried over potassium carbonate and distilled from calcium hydride; tetrahydrofuran was pre-dried by refluxing over sodium wire and was distilled from lithium aluminium hydride. Amberlite refers to Amberlite IR 200 ion exchange resin. Thin layer chromatography was performed using TLC aluminium plates pre-coated with silica gel (Kieselgel 60 F_{254}, 0.2 mm). Silica gel (Kieselgel 60) was used for column chromatography. The ^{1}H NMR spectra were recorded on a Bruker AC-200E (200 MHz) spectrometer for routine work, a Bruker WM-300 WB (300 MHz) spectrometer for high temperature work, and a Jeol JNM-LA500 FT-NMR (500 MHz) for low temperature work. Residual proton signals from the deuteriated solvents were used as references. ^{13}C Spectra were recorded on a Bruker AC-200E (50.3 MHz), the ^{13}C signal from the deuteriated solvent being used as a reference. Infrared spectra were recorded on a Nicolet 20-PC Fourier Transform IR spectrophotometer. Mass spectra [electron impact (EI) mode] were recorded on a Kratos MS80 RF spectrometer. Combustion analysis results are averages of two determinations.

Preparations

2,2′-Bis[bis(*p*-methoxyphenyl)hydroxymethyl]biphenyl 4b

p-Bromoanisole (1.40 cm^3, 10.9 mmol) was added over 5 min to a solution of *n*-butyllithium (2.2 mol dm^{-3} in THF, 5 cm^3, 11 mmol) in THF (10 cm^3) at −78 °C. The mixture was stirred for a further 10 min at −78 °C then dimethyl biphenyl-2,2′-dicarboxylate (0.50 g, 1.9 mmol) in THF (5 cm^3) was added. The solution was stirred for 2 h at −78 °C, allowed to come to room temperature, then stirred overnight before solvents were evaporated and aqueous ammonium chloride (20 cm^3, 0.25 mol dm^{-3}) was added. The mixture was extracted with dichloromethane (3 × 10 cm^3) and the combined extract was dried (sodium sulfate), filtered, and evaporated to dryness under reduced pressure. The product was obtained by recrystallisation using dichloromethane–petrol (0.90 g, 1.4 mmol, 75%); mp 222–223 °C, lit.,[32] 226–228 °C; δ_H (CD_3CN), 6.70–6.77 (m, 12H, Ar), 6.95–7.19 (m, 10H, Ar), 3.74 (s, 6H, OCH_3), 3.75 (s, 6H, OCH_3), 5.99–6.04 (m, 2H, Ar), 4.37 (s, 2H, OH).

2,2′-Bis[bis(*p*-methoxyphenyl)methyl]biphenyl ditetrafluoroborate 1b (from 4b)

Tetrafluoroboric acid (48% w/w aq., 0.50 cm^3, 3.9 mmol) was added dropwise to a cooled solution of 5,5,7,7-tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]oxepin (0.090 g, 0.14 mmol) in acetic anhydride (25 cm^3). The bright red mixture was stirred for 15 min then ether (140 cm^3) was added, whereupon the product precipitated as deep red crystals, which were filtered at the pump, rinsed with ether, and dried under high vacuum (0.060g, 57%).

5,5,7,7-Tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]-azepine 3a

Ammonia (*ca.* 5 cm^3) was condensed into a flask containing 2,2′-bis[bis(*p*-methoxyphenyl)methyl]biphenyl ditetrafluoroborate (0.53 g, 0.68 mmol) at −78 °C under nitrogen; the mixture was stirred for 2 h at −78 °C, then triethylamine (4 cm^3) was added. The excess of ammonia evaporated overnight and the residue was partitioned between aqueous sodium hydroxide (0.5 mol dm^{-3}, 5 cm^3) and dichloromethane (10 cm^3). The aqueous phase was extracted twice more with dichloromethane, then the combined organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was chromatographed (Florisil, ethyl acetate–petrol, 10 : 90 +1% Et_3N) to give the title product as a yellow solid (0.17 g, 0.27 mmol, 40%), which was crystallised from ethyl acetate–petrol to give white crystals; mp 266–268 °C; δ_H ($CDCl_3$) 6.3–7.2 (m, 24H, Ar), 3.67 (s, 6H, OCH_3), 3.78 (s, 6H, OCH_3), 5.28 (s, 1H, NH).

2,2′-Bis(phenyl-*p*-methoxyphenylhydroxymethyl)biphenyl 4c

n-Butyllithium (1.9 mol dm^{-3}, 2.6 cm^3, 4.9 mmol) was slowly added to an ice-cold solution of 2,2′-dibromobiphenyl (0.70g, 2.2 mmol) in THF (25 cm^3), and the mixture was stirred for 1 h at 0 °C. *p*-Methoxybenzophenone (1.0 g, 4.7 mmol) in THF (25 cm^3) was added dropwise and the mixture was stirred for 1 h at room temperature. After refluxing the reaction overnight, solvents were evaporated, saturated aqueous ammonium chloride was added to the cooled residue, and the mixture was extracted with ether (3 × 20 cm^3). The combined ether phase was dried ($MgSO_4$), filtered, and evaporated. The residual orange oil was adsorbed onto alumina and chromatographed (Al_2O_3, ethyl acetate–petrol–Et_3N, 15 : 85 : 1) to give a colourless oil, (0.55 g, 58%). This was crystallised from dichloromethane–petrol to give the title compound as colourless crystals; mp 234 °C; δ_H (200 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.44 (1H, s, OH), 4.47 (1H, s, OH), 5.99 (2H, d, Ar), 6.10 (2H, d, Ar), 6.65–7.35 (24H, m, Ar).

5,5,7,7-Tetrakis(*p*-methoxyphenyl)-5,7-dihydrodibenzo[*c*,*e*]-oxepin 2b

Procedure 1. 2,2′-Bis[bis(*p*-methoxyphenyl)hydroxymethyl]-biphenyl (0.20 g, 0.31 mmol) was dissolved in dichloromethane (5 cm^3) and stirred with 3 Å molecular sieves at room temperature. After 24 days conversion to the oxepin was complete by TLC. The mixture was filtered and solvents evaporated to give the title product (0.13 g, 66%, mp (recryst. CH_2Cl_2–MeCN) 272–275 °C; C, 80.92; H, 5.56; $C_{42}H_{36}O_5$ requires C, 81.25; H, 5.85%; δ_H (500 MHz; $CDCl_3$, −50 °C) 3.55 (6H, s, OCH_3), 3.77 (6H, s, OCH_3), 6.26 (2H, d), 6.38 (2H, d), 6.43 (2H, d), 6.51 (2H, d), 6.55 (2H, d), 6.67 (2H, d), 6.81 (2H, m), 6.99 (2H, d), 7.02 (2H, d), 7.46 (2H, d), 8.41 (2H, d); δ_C (500 MHz; $CDCl_3$, −50 °C) 55.13, 55.31, 85.69, 111.43, 113.15, 126.58, 127.65, 128.27, 129.08, 129.55, 139.12, 140.63, 141.22, 143.16, 157.26, 158.07; *m*/*z* 620 (M^+, 61%), 513 (M^+ −107, 67), 497 (M^+ −123, 100), 378 (M^+ −242, 95) 135 (M^+ −485, 95).

Procedure 2. 2,2′-Bis[bis(*p*-methoxyphenyl)hydroxymethyl]-biphenyl (0.20 g, 0.31 mmol) was dissolved in dichloromethane (5 cm^3) and stirred with Amberlite ion exchange resin at room temperature overnight. The mixture was filtered and solvents removed (rotary evaporator) to give a white solid (0.192 g, 99%); mp (recryst. CH_2Cl_2–MeCN) 272–274 °C. This was confirmed to be the title compound by comparison with an authentic sample (mp, TLC, and ^{1}H NMR).

Crystal structure determinations ‡

Crystals were examined on a Stoe-Siemens four-circle diffractometer with Mo-Kα radiation (λ = 0.71073 Å) for **4b** and with Cu-Kα radiation (λ = 1.54184 Å) for **4c**, **2a**, **2b** and **3a**. Data were collected at 160 K, with on-line profile fitting.[50] Intensity decay ranged from 0 to 5%. Azimuthal-scan absorption corrections were applied. Structure solution was by automatic direct methods, and refinement with full-matrix least-squares.[51] Crystal data and other information are given in Table 5. Hydrogen atoms were placed in ideal positions and constrained with a riding model.

In the structure of **4c**, one of the aromatic substituents is disordered over two orientations, with 54 : 46% occupancy; restraints were applied to geometry and displacement parameters for these atoms. The crystal structure of **2a** is a 1 : 1

‡ CCDC reference numbers 190257–190261. See http://www.rsc.org/suppdata/p1/b2/b207108h/ for crystallographic files in .cif or other electronic format.

Table 5 Crystallographic data for compounds **4b**, **4c**, **2a**, **2b**, and **3a**

Compound	**4b**	**4c**	**2a**	**2b**	**3a**
Molecular formula	$C_{42}H_{38}O_6$	$C_{40}H_{34}O_4$	$C_{38}H_{28}O{\cdot}C_7H_8$	$C_{42}H_{36}O_5$	$C_{42}H_{37}NO_4$
M_r	638.7	578.7	592.7	620.7	619.7
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/n$	$I2$	$I2$
a/Å	10.162(4)	13.017(3)	13.6161(18)	9.656(3)	9.8515(11)
b/Å	12.856(5)	16.298(6)	14.295(2)	9.089(3)	8.9880(10)
c/Å	13.729(5)	15.554(4)	16.520(2)	18.142(6)	17.9926(19)
α/°	74.83(3)				
β/°	71.95(2)	110.699(18)	95.178(18)	91.24(2)	91.406(4)
χ/°	85.00(2)				
U/Å^3	1645.9(11)	3086.7(15)	3202.2(8)	1591.8(9)	1592.7(3)
Z	2	4	4	2	2
D_{calc}/g cm^{-3}	1.289	1.245	1.229	1.295	1.292
Reflections measured	7044	7745	8465	5382	3900
Unique reflections	5799	3881	5563	2680	2785
R_{int}	0.0348	0.0861	0.0470	0.0250	0.0228
Number of parameters	440	469	417	216	220
R (F, $F^2 > 2\sigma$)	0.0455	0.0840	0.0533	0.0245	0.0388
R_w (F^2, all data)	0.1184	0.2787	0.1500	0.0646	0.1051
Goodness of fit on F^2	1.016	1.023	1.054	1.027	1.067
Max, min electron density/Å^{-3}	+0.67, −0.26	+0.16, −0.24	+0.33, −0.28	+0.13, −0.12	+0.21, −0.17

toluene solvate. Compounds **2b** and **3a** are isostructural; for both of them, a crystallographic two-fold rotation axis passes through the ring *O* or *N* atom, so that the asymmetric unit is half a molecule, leading to two-fold disorder of the amine hydrogen atom on either side of the rotation axis in **3a**. These two crystal structures are non-centrosymmetric and chiral; the absolute structure parameter[52] was refined to values of 0.06(15) for **2b** and 0.2(2) for **3a** (ideal value is zero) on the basis of the small degree of anomalous scattering.

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