Preparation of deuterium labelled styrenes and divinylbenzenes

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This paper is dedicated to Professor Arthur N. Bourns

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Specifically deuteriated styrenes (1-*d*, 2,2′-d_2, and ring labelled), perdeuteriostyrene, and specifically deuteriated divinylbenzenes (1,1′-d_2, 2,2,2′,2′-d_4, and ring labelled) have been prepared by transforming suitably labelled phenylacetic (hydride or deuteride reduction and dehydration by solid KOH) and phenylenediacetic acids (esterification, hydride or deuteride reduction, and dehydration by solid KOH), respectively.

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On a préparé des styrènes deutérés d'une façon spécifique (*d*-1, d_2-2,2′ et marqué sur le cycle), du perdeutérostyrène et des divinylbenzènes deutérés d'une façon spécifique (d_2-1,1′,d_4-2,2,2′,2′ et marqué sur le cycle) en transformant respectivement d'acides phénylacétiques (réduction par l'hydrure ou le deutérure et déshydratation par le KOH solide) ou phénylènediacétiques (estérification, réduction par l'hydrure ou le deutérure et déshydratation par le KOH solide) marqués d'une façon appropriée.
[Traduit par la revue]

Introduction

The high temperature – dilute acid (HTDA) method has been used to prepare a wide range of deuteriated and tritiated organic compunds (1–8). In this paper we document its application to the preparation of deuteriated styrenes and divinylbenzenes (DVB's) that were required for solid-state ^{2}Hmr studies of cross-linked styrene polymers (9). Although initial studies established that styrene can be labelled directly at the 2-position under HTDA conditions (*vide infra*), it is not a viable route due to production of dimers and oligomers. Consequently, a general route to the specifically labelled styrenes was developed based on the H–D exchange of phenylacetic acid (PAA). To prepare specifically labelled divinylbenzenes (DVB's), phenylenediacetic acid (PDA) was used as a substrate.

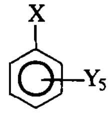
Results and discussion

Attempted direct exchange of styrene and divinylbenzene

When styrene was reacted under HTDA conditions at 165°C, it was found that full equilibration of the C-2 hydrogens with the deuterium pool could be achieved. Unfortunately, although small amounts of styrene-2,2-d_2 (**1***b*) could be isolated by preparative gas chromatography (gc), it appeared that most of the styrene was lost as dimers and oligomers, making this route viable only for preparing **1***b* in relatively small amounts. Treatment of DVB under HTDA conditions resulted in rapid production of polymer, as expected, and this direction was pursued no further.

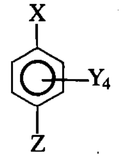
Preparation of deuteriated styrenes

Since direct deuteriation of styrene and DVB[1] was inefficient, PAA and PDA were selected as precursors. Labelled PAA **1***f* (1.90 excess D per molecule) was prepared from **1***e* by refluxing it twice in 1.3 *M* DCl/D_2O. Reduction of this product by LAH, followed by elimination of water by KOH, gave styrene-1-*d* (**1***a*) that contained 0.75 excess D atoms over natural abundance. The ^{2}Hmr spectrum of **1***a* showed signals at 6.6 and 2.7 ppm (<1%), the latter peak indicating that <0.5% of starting material was present. That **1***a* contined substantially less deuterium than expected (1.90/2), based on the deuterium content of the precursor PPA **1***f*, indicates that D–H exchange competes with elimination. Nevertheless, back exchange can be minimized by using KOD and the O–D labelled alcohol.



1

a X = $CD{=}CH_2$; Y = H
b X = $CH{=}CD_2$; Y = H
c X = $CH{=}CH_2$; Y = D
d X = $CD{=}CD_2$; Y = D
e X = CH_2CO_2H; Y = H
f X = CD_2CO_2H; Y = H
g X = CD_2CO_2H; Y = D
h X = CH_2COH_2; Y = D
i X = CD_2CH_2OH; Y = H
j X = CH_2CD_2OH; Y = H
k X = CH_2CH_2OH; Y = D
l X = CD_2CD_2OH; Y = D



2

a X = Z = $CD{=}CH_2$; Y = H
b X = Z = $CH{=}CD_2$; Y = H
c X = Z = $CH{=}CH_2$; Y = D
d X = Z = CH_2CO_2H; Y = H
e X = Z = CD_2CO_2H; Y = H
f X = Z = CD_2CO_2H; Y = D
g X = Z = CH_2CO_2H; Y =D
h X = Z = CH_2CO_2Et; Y = H
i X = Z = CD_2CO_2Et; Y = H
j X = Z = CH_2CO_2Et; Y = D
k X = Z = CD_2CH_2OH; Y = H
l X = Z = CH_2CD_2OH; Y = H
m X = Z = CH_2CH_2OH, Y = D

When PAA was heated at 260°C in 0.26 *M* HCl/D_2O and recycled in 0.26 *M* DCl/D_2O, perlabelled acid **1***g* was obtained. Back exchange at the 2-position by KOH/H_2O (11) yielded ring-deuteriated acid **1***h*. LAH reduction, followed by elimination of water, gave **1***c* that contained 4.75 excess D atoms per molecule. The ^{2}Hmr spectrum of **1***c* exhibited a signal at 7.2 ppm and it was ascertained that <5% of starting alcohol was present.

Reduction of perlabelled PAA **1***g* by LAD, followed by elimination of water from **1***l*, yielded **1***d* (7.17 excess D atoms per molecule). It is evident from the ^{2}Hmr spectrum of **1***d* (Fig. 1) that a substantial amount (~25%) of D–H exchange occurred at the 1-position, as was observed in the preparation of **1***a*.

Reduction of PAA by LAD, followed by elimination of water, gave **1***b* (1.99 excess D atoms per molecule). The ^{2}Hmr spectrum of **1***b* exhibited signals at 5.1 and 5.6 ppm and no signals due to starting alcohol.

Preparation of deuteriated divinylbenzenes

Treatment of PDA 2d with KOH/D_2O at 160°C yielded PDA-1,1,1′,1′-d_4 (**2***e*), and ^{1}Hmr analysis established that

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[1] The commercially available material was a mixture of DVB, diethylbenzene, and the half-dehydrogenated compound.

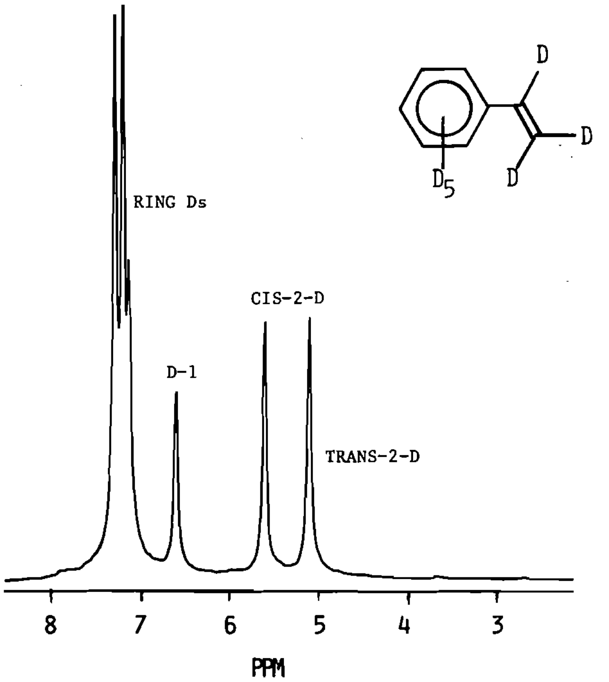

FIG. 1. The ^{2}Hmr (38.4 MHz) spectrum of styrene-d_8 in CHCl$_3$.

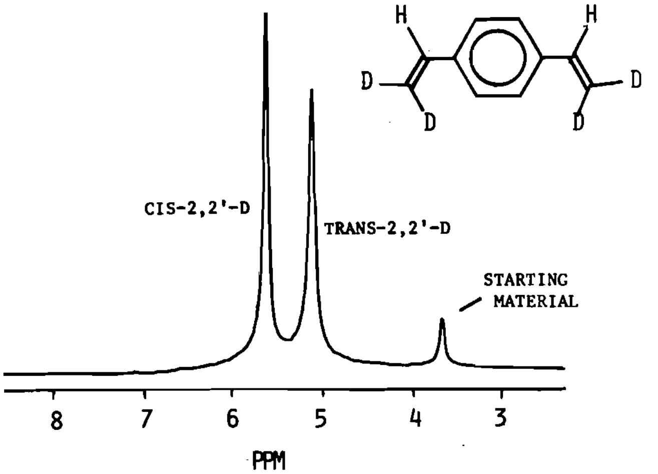

FIG. 2. The ^{2}Hmr (38.4 MHz) spectrum of divinylbenzene-2,2,2′, 2′-d_4 in CHCl$_3$.

exchange was >95% complete. Since direct reduction of the diacid proved to be unsatisfactory, the diethyl ester was prepared and reduced to **2***k* by LAH. KOH-promoted elimination of water from **2***k* gave DVB-1,1′-d_2 (**2***a*) (1.39 excess D per molecule). As observed in the preparation of styrene-1-*d*, **2***k* contained less deuterium (1.39 D) than expected (1.90 D) on the basis of the labelled PDA **2***e* (~3.8 D). As in the case of 2-phenylethanol, D–H exchange competes with elimination of water from **2***k*. The ^{2}Hmr spectrum of **2***a* exhibited signals at 6.6 and 2.8 ppm (6%), the latter establishing that the product contained 3% starting material.

At 260°C in 0.26 *M* DCl/D$_2$O **2***d* was perlabelled. Following back-exchange in aqueous KOH, the acid was converted, as described above, to DVB **2***c* (3.62 excess D atoms per molecule). The ^{2}Hmr spectrum of **2***c* showed, in addition to an intense signal at 7.4 ppm, weak signals at 7.2 (<5%) and 2.7 (<1%) due to starting material. A weak signal (<1%) at 6.7 indicated that a small amount of deuterium was located at the 1,1′-positions of **2***c*.

DVB-2,2,2′,2′-d_4 (**2***b*) (3.89 excess D atoms per molecule) was prepared by reducing diethyl ester **2***h* by LAD and eliminating water from **2***l* in the usual manner. The ^{2}Hmr spectrum (Fig. 2) of **2***b* indicates (signal at 3.7 ppm) that the product contains approximately 6% of **2***l*. The presence of 3–6% of starting material in the DVB's is due to the fact that it was necessary to carry out the elimination reactions at reduced pressure to minimize polymerization.

Conclusions

This study establishes that phenylacetic acid and phenylenediacetic acid are convenient starting materials for the preparation of specifically deuteriated styrenes and *p*-divinylbenzenes as well as the perlabelled compounds, even though the yields of the dehydration steps are modest as a consequence of the reactivity of the compounds. Although styrene-1,2,2′-d_3 was not prepared, its synthesis from PAA would be a simple matter. It should be possible to prepare a wide range of deuteriated substituted styrenes and the isomeric divinylbenzenes using the methodology documented in this paper. Furthermore, the corresponding tritiated compounds can be prepared using this approach as well.

In conclusion, we wish to comment on the facile elimination of water from the alcohols by solid KOH. Although base-promoted dehydration of alcohols is not discussed in general organic chemistry texts, it appears that it may be a very useful method for dehydrating fairly high-boiling alcohols that have an acidic hydrogen β to the hydroxyl group.

Experimental

Mass spectral deuterium analyses were carried out with a VG Micromass 7070F spectrometer at low ionizing voltage (12–15 eV) to minimize fragmentation. The nmr spectra were obtained on Varian EM-390 and Brüker WM-250 spectrometers; gc analyses were performed on a Tracor Model 560 gas chromatograph with a Varian Model 485 electronic integrator using a 6 ft × 4 mm id 3% OV-1 on 100–120 mesh Supelcoport column. For preparative gc a Varian A-700 gas chromatograph fitted with a 5 ft × 1/4 in. 15% SE-30 on 80–100 mesh Chromosorb W column was used. Ether for the hydride reductions was dried by distillation from LAH.

H–D exchange of styrene

Styrene (0.20 g), decalin (2 mL), and 0.26 *M* DCl/D$_2$O (5 mL) were sealed under vacuum in a medium-walled glass tube after degassing by three freeze–pump–thaw cycles. The tube was sealed in a Parr high pressure apparatus containing water to equalize pressure, and was heated at 165°C for 12 h. The organic solution was decanted from the frozen aqueous layer and styrene collected by preparative gc (5 ft × 1/4 in. 15% SE-30 on 80–100 mesh Chromosorb W). Mass spectral analysis indicated the incorporation of 1.94 excess D atoms per molecule (0.7% d_0, 4.3% d_1, 95.1% d_2); ^{1}Hmr (CDCl$_3$) showed that the C-2 Hs had been fully exchanged (δ:6.72 (m, H-1), 7.2–7.5 (m, aromatic Hs)). Gas chromatographic analysis indicated the presence of substantial amounts (~35%) of dimeric products; gc analysis of styrene was found to be inconsistent and unreliable, presumably due to reactivity of styrene on the column and injector block.

An attempt to distill styrene from a large-scale reaction (4.2 g styrene) resulted in the collection of no styrene. Using decalin as an internal standard, gc analysis indicated that only ~20% of the styrene was left in the product with dimeric material comprising ~10% more.

Phenylacetic acid-1,1-d_2 *(***1f***)*

Phenylacetic acid (12.0 g) was refluxed for 142 h in 2.6 *M* HCl/D$_2$O (50 mL), the product was extracted with ether (50 mL, 3 × 20 mL), dried over anhydrous Na$_2$SO$_4$, and solvent removed on a roto-evaporator to yield 11.8 g of **1***f* (97%, 1.57 excess D per molecule). This product (11.8 g) was then refluxed with 1.3 *M* DCl/D_2O (50 mL) for 72 h and extracted as above (yield 11.6 g, 98%; 1.90 excess D atoms per molecule).

Phenylethanol-2,2-d_2 (*1*i)

Phenylacetic acid-2,2′-d_2 (11.6 g) in dry ether (100 mL) was slowly added to a magnetically stirred slurry of LAH (3.0 g) in dry ether (100 mL) and refluxed for 2 h. More LAH (0.5 g) was added and reflux continued for 3 h. The reaction was quenched by careful addition of water (75 mL), then was acidified with concentrated HCl until most of the solid dissolved. The aqueous layer was saturated with NaCl and extracted with ether (4 × 40 mL) after removal of the organic layer. The extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and filtered. The ether was removed by distillation through a 25-cm glass helices column and the last traces were removed under rotatory-pump vacuum to yield 9.9 g (95%) of **1***i*.

Styrene-1-d (*1*a)

Phenylethanol-2,2-d_2 (9.9 g) was heated with KOH pellets (4.3 g) (10) and styrene was rapidly distilled through a 15-cm Vigreux column into a Dry Ice – acetone cooled flask. Styrene-1-*d* was separated from water and dried over anhydrous Na_2SO_4 (yield 2.9 g, 35%). A considerable amount of polymer was produced. Mass spectral analysis indicated incorporation of 0.75 excess D atoms per molecule (27.5% d_0, 70.2% d_1, and 2.0% d_4 species) and ^{2}Hmr ($CHCl_3$) showed two resonances at 6.6 and 2.7 ppm (<1%). This analysis was confirmed by ^{1}Hmr ($CDCl_3$), δ:5.21 (m, *trans*-H-2), 5.72 (m, *cis*-H-2), 6.69 (q, H-1, po.3H), 7.1–7.5 (m, aromatic Hs).

Phenylacetic acid-d_7 (*1*g)

Phenylacetic acid (13.5 g) was heated at 260°C with 0.26 *M* HCl/D_2O (100 mL) for 72 h in a 600-mL Parr high pressure apparatus containing a glass liner. The product was extracted with ether (100 mL, 4 × 50 mL), the extracts were washed with saturated aqueous NaCl (25 mL), ether was removed on a roto-evaporator, and the remaining solvent was removed under vacuum to yield 11.2 g (83%) of **1***g*. The partially deuterated phenylacetic acid (10.9 g) was reacted with 0.26 *M* DCl/D_2O (100 mL) using the same procedure (yield 9.5 g, 87%). Mass spectral analysis showed the presence of 6.81 excess D atoms per molecule (0.5% d_4, 4.0% d_5, 20.2% d_6, 64.3% d_7, 11.0% d_8). The results indicate that not all of the carboxyl deuterons were exchanged during the work-up procedure.

Phenylacetic acid-d_5 (*1*h)

The deuteriated phenylacetic acid obtained above (9.2 g) was back-exchanged (11) by heating with H_2O (50 mL) and KOH (4.1 g) in a 600-mL Parr high pressure apparatus at 160°C for 24 h. The solution was acidified with concentrated HCl and extracted with ether (100 mL, 4 × 25 mL). The extracts were washed with saturated aqueous NaCl (25 mL), dried over anhydrous Na_2SO_4, decolorized with carbon, and the ether was stripped on a roto-evaporator and pumped off under vacuum to yield 9.0 g (98%) of **1***h*. Mass spectral analysis indicated that 4.9 excess D atoms per molecule remained (1.5% d_3, 16.6% D_4, 72.5% d_5, 7.9% d_6, 1.5% d_7); ^{1}Hmr ($CDCl_3$) confirmed that back exchange was essentially complete (δ:3.62 (2, H-2), 7.3–7.4 (residual aromatic Hs), 11.8 (s, —O—H).

Phenylethanol-d_5 (*1*k)

Phenylacetic acid-d_5 (8.9 g) in dry ether (150 mL) was added slowly to a magnetically stirred suspension of LAH (1.2 g) in dry ether (50 mL) and the mixture was refluxed for 5 h. The reaction was quenched by careful addition of water (75 mL), then acidified with concentrated HCl until the precipitates were disolved. After separation of the ether, the solution was further extracted with ether (5 × 20 mL), and the extracts were dried over anhydrous Na_2SO_4 and decolorized with carbon. The ether was stripped on a roto-evaporator and the remainder was removed under vacuum to yield 6.5 g (81%) of **1***k*; ^{1}Hmr ($CDCl_3$), δ:2.80 (t, H-1), 3.60 (s, —O—H), 3.80 (t, H-2), 7.3 (residual aromatic Hs).

Styurene-d_5 (*1*c)

Phenylethanol-d_5 (5.7 g) was heated with KOH (3.2 g, pellets) and styrene rapidly distilled through a 15-cm Vigreux column into a flask cooled in Dry Ice – acetone. The styrene was separated from water and dried over anhydrous Na_2SO_4 to yield 3.2 g (65%) of **1***c*. Mass spectral analysis indicated the presence of 4.75 excess D atoms per molecule (0.6% d_2, 4.0% d_3, 19.4% d_4, 72.1% d_5, 3.8% d_6, 0.1% d_7); ^{2}Hmr ($CHCl_3$) showed a resonance at 7.2 ppm; ^{1}Hmr ($CDCl_3$), δ:5.21 (d, *trans*-H-2), 5.72 (d, *cis*-H-2), 6.73 (q, H-1), 7.3 (residual aromatic Hs).

Phenylethanol-d_9 (*1*l)

To a slurry of LAD (3.0 g) in dry ether (100 mL) was slowly added perdeuteriated phenylacetic acid (10.2 g) in dry ether (100 mL). After refluxing for 2 h a further portion of LAD (0.5 g) was added and reflux continued for 6 h. After careful quenching of the reaction with wet ether (25 mL) and water (50 mL) and acidification with concentrated HCl, the aqueous layer was saturated with NaCl and extracted with ether (5 × 30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), dried over anhydrous Na_2SO_4, decolorized with carbon, filtered, and solvent was removed by distillation through a 15-cm glass helices column. Traces of ether were removed under vacuum to yield 8.3 g (88.5%) of **1***l*.

Styrene-d_8 (*1*d)

Phenylethanol-d_9 from the previous reaction (8.2 g) was heated with KOH (3.7 g) and the styrene was distilled through a 15-cm Vigreux column into a Dry Ice cooled receiver as it was produced. After separation from water, the product was dried over anhydrous Na_2SO_4 and distilled through a 15-cm Vigreux column at reduced pressure (~10 Torr; 1 Torr = 133.3 Pa) to yield 5.4 g (77%) of **1***d*.

Mass spectral analysis indicated the incorporation of 7.17 excess D atoms per molecule (0.5% d_4, 6.0% d_5, 12.6% d_6, 37.0% d_7, 44.0% d_8); ^{2}Hmr ($CHCl_3$) (Fig. 1), δ:5.1 (*trans*-D-2), 5.6 (*cis*-D-2) 6.6 (D-1) 7.1–7.4 (aromatic Ds). Electronic integration established the following deuterium distribution; 1.88 D at C-2, 0.73 D at C-1, and 4.56 D in the aromatic ring.

Phenylethanol-2,3-d_2 (*1*j)

Phenylacetic acid (5.0 g) in dry ether (100 mL) was slowly added to a magnetically stirred slurry of LAD in dry ether (100 mL) and the mixture was refluxed for 4 h. The reaction mixture was carefully quenched with water, then acidified with concentrated HCl until precipitates were dissolved. The ether layer was separated, and the aqueous layer was saturated with NaCl and extracted with ether (4 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4, ether was stripped on a roto-evaporator, and the last traces were removed under vacuum to yield 4.2 g (95%) of **1***j*; ^{1}Hmr (CCl_4), δ:2.69 (s, H-1) 4.15 (s, —O—H), 7.0–7.3 (m, aromatic H5).

Styrene-2,2-d_2 (*1*b)

Phenylethanol-2,2-d_2 (3.6 g) was heated with KOH (2.0 g, pellets) and the styrene rapidly distilled through a 15-cm Vigreux column into a Dry Ice – acetone cooled receiver. The styrene was separated from water and dried over anhydrous Na_2SO_4 to yield 2.6 g (84%) of **1***b*. Mass spectral analysis indicated that 1.99 excess D atoms per molecule (2.5% d_1, 96.0% d_2, 1.5% d_3) were incorporated in the styrene; ^{2}Hmr, δ:5.1 (*trans*-D-2), 5.6 (*cis*-D-2).

Attempted H–D exchange of divinylbenzene

Divinylbenzene (0.20 g), decalin (2 mL), and 0.26 *M* DCl/D_2O (5 mL) in a medium-walled glass tube were degassed via three freeze–pump–thaw cycles and the tube was sealed under vacuum. Reaction was carried out at 160°C for 19 h in a Parr high pressure apparatus containing water to equalize pressure. A solid mass of polymer was formed and this deuteration approach was abandoned.

Phenylenediacetic acid-2,2,2′,2′-d_4 (*2*e)

The potassium salt of phenylenediacetic acid (9.6 g) was prepared by reaction with KOH (3.0 g) in water (20 mL). Water was removed with heating on a roto-evaporator and the salt was reacted with D_2O (50 mL) and KOH (1.0 g) in a 600-ML Parr high pressure apparatus with a glass liner at 160°C for 28 h. The solution was acidified with concentrated HCl and the solid removed by filtration to yield 9.3 g (95%) of **1*e***; ^{1}Hmr (DMSO-d_6), δ:7.25 (s, aromatic Hs), 11.8 (s, —O—H), 3.53 (residual H-2).

Phenylenediacetic acid diethyl ester-2,2,2′,2′-d_4 (2i)

Phenylenediacetic acid **2*e*** (8.9 g) was refluxed with absolute ethanol (38 mL), benzene (63 mL), and concentrated H_2SO_4(10 mL) with magnetic stirring in a Dean–Stark apparatus. After 12 h reaction, saturated aqueous NaCl (75 mL) was added and the mixture extracted with ether (50 mL, 3 × 20 mL). the combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried over anhydrous Na_2SO_4, decolorized with carbon, and the ether was removed on a roto-evaporator, then with heating under vacuum. Removal of all the ethanol was difficult, to yield 9.6 g (84%) of **2*i***; ^{1}Hmr (CCl_4), δ:1.18 (t, CH_3), 4.07 (q, ethyl CH_2), 7.20 (s, aromatic Hs), 3.47 (residual 2,2′ Hs).

Benzenediethanol-2,2,2′,2′-d_4 (2k)

Phenylenediacetic acid diethyl ester (9.2 g) from the above reaction in dry ether (100 mL) was slowly added to a magnetically stirred suspension of LAH (1.9 g) in dry ether (50 mL). After a 6-h reflux, the reaction mixture was quenched by careful addition of water (50 mL) and acidified with concentrated HCl to dissolve the precipitate. Extraction with ether (9 × 50 mL) yielded 5.1 g (83%) of **2*k***; ^{1}Hmr (CDCl), δ:1.87 (s, —O—H), 2.82 (m, 1,1′ Hs), 3.97 (s, residual 2,2′ Hs), 7.20 (s, aromatic Hs).

Divinylbenzene-1,1′-d_2 (2a)

Benzenediethanol **2*k*** (4.9 g) was heated rapidly with KOH pellets (2.5 g) and divinylbenzene (2.3 g, 62%) was quickly distilled through a 15-cm Vigreux column at ~60 Torr. Mass spectral analysis indicated the presence of 1.39 excess D atoms per molecule (11.6% d_0, 41.2% d_1, 45.0% d_2, 1.4% d_3, 0.9% d_4); ^{2}Hmr ($CHCl_3$), δ:6.6 (D-1), 2.8 (6%) (2,2,2′,2′-Ds) of **2*k***; ^{1}Hmr (CCl_4), δ:5.17 (m, *trans*-2,2′ Hs), 5.63 (m, *cis*-2,2′ Hs), 6.63 (residual 1,1′ Hs, 0.64H), 7.30 (s, aromatic Hs).

Phenylenediacetic acid-d_8 (2f)

Phenylenediacetic acid (10.0 g) was reacted with 0.26 *M* DCl/D_2O (100 mL) in a 600-mL Parr high pressure apparatus fitted with a glass liner at 260°C for 88 h. The solid was filtered off, washed with water (2 × 15 mL), and dried to yield 9.35 g (89.9%) of **2*f***. Mass spectral analysis disclosed the presence of 8.29 excess D atoms per molecule (0.9% d_5, 4.5% d_6, 16.2% d_7, 34.3% d_8, 31.2% d_9, 12.8% d_{10}); apparently not all of the carboxyl deuterons were washed out during isolation.

Phenylenediacetic acid-d_4 (2g)

Phenylenediacetic acid **2*f*** (7.9 g) was reacted with KOH (5.0 g) in water (50 mL) to form the salt, and the water was removed on a roto-evaporator with heating and then with heating under vacuum. The salt was reacted in a glass-lined 600-mL Parr high pressure apparatus with KOH (1.0 g) and water (50 mL) at 160°C for 24 h. The reaction mixture was acidified, the precipitate filtered off, washed with water (4 × 15 mL), and dried by heating under vacuum to yield 7.4 g (96%) of **2*g***; ^{1}Hmr (DMSO-d_6), δ:3.56 (s, H-2,2′), 7.24 (s, residual aromatic Hs), 11.7 (s, —O—H).

Phenylenediacetic acid diethyl ester-d_4 (2j)

Phenylenediacetic acid **2*g*** (7.2 g) was refluxed with magnetic stirring with absolute ethanol (35 mL), benzene (65 mL), and concentrated H_2SO_4 (12 mL) in a Dean–Stark apparatus for 18 h. To the reaction mixture was added ether (50 mL) and saturated aqueous NaCl and the organic solution separated. The aqueous layer was further extracted with ether (5 × 30 mL) and the combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and saturated aqueous NaCl (20 mL). After drying over anhydrous Na_2SO_4 and decolorizing with carbon, ether was stripped on a roto-evaporator, then with heating under vacuum, to yield 8.3 g (90%) of **2*j***. Mass spectral analysis demonstrated the presence of 3.75 excess D atoms per molecule (3.7% d_2, 23.5% d_3, 66.5% d_4, 5.9% d_5, 0.4% d_6); ^{1}Hmr ($CDCl_3$), δ:1.20 (t, CH_3), 3.60 (s, 2,2′ Hs) 4.18 (q, ethyl CH_2), 7.30 (s, residual aromatic Hs).

Benzenediethanol-d_4 (2m)

A solution of **2*j*** (8.0 g) in dry ether (100 mL) was added slowly to a magnetically stirred suspension of LAH (1.3 g) in dry ether (50 mL) and the mixture refluxed overnight. The reaction was quenched by careful addition of water (50 mL) and then acidified by addition of concentrated HCl to dissolve the precipitate. The organic layer was separated, the aqueous phase extracted with ether (10 × 30 mL), and the combined extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and decolorized with carbon. Ether was stripped on a roto-evaporator, then under vacuum, to yield 5.2 g (97%) of **2*m***; ^{1}Hmr ($CDCl_3$) δ:1.89 (s, O Hs), 2.81 (dt, 2,2′ Hs), 3.82 (t, 1,1′ Hs), 7.20 (s, residual aromatic Hs).

Divinylbenzene-d_4 (2c)

Benzenediethanol-d_4 **2*m*** (5.0 g) was heated with KOH pellets (2.5 g) and the divinylbenzene (1.0 g, 26%) quickly distilled through a 15-cm Vigreux column at ~60 Torr. In this reaction the divinylbenzene polymerized very rapidly in the reaction flask. Mass spectral analysis indicated 3.62 excess D atoms per molecule (0.5%, d_0, 0.9% d_1, 5.7% d_2, 26.1% d_3, 63.0% d_4, 3.5% d_5, 0.3% d_6). The ^{2}Hmr spectrum showed, in addition to an intense peak at 7.4 ppm, weak signals at 7.2 (<5%) and 2.7 (<1%) due to starting material. A weak signal at 6.7 (<1%) indicated that a small amount of the deuterium was located at the 1,1′-positions of **2*c***. ^{1}Hmr (CCl_4), δ:5.11 (d, *trans*-2,2′ Hs), 5.59 (d, *cis*-2,2′ Hs), 6.66 (q, 1,1′ Hs), 7.30 (s, residual aromatic Hs, 0.35H).

Benezenediethanol-1,1,1′,1′-d_4 (2l)

The diester of PDA (11.0 g) in dry ether (150 mL) was slowly added to a magnetically stirred suspension of LAD (2.2 g) in dry ether (50 mL). After refluxing for 5 h, the reaction mixture was carefully quenched with water (50 mL) and acidified with concentrated HCl to dissolve the precipitate. After separation of the organic layer, the aqueous solution was extracted with ether (10 × 50 mL), and the combined extracts were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na_2SO_4. Ether was stripped on a roto-evaporator, then the last traces were removed under vacuum to yield 7.5 g (88%) of **2*l***; ^{1}Hmr ($CDCl_3$), δ:1.58 (s, O Hs), 2.84 (s, 2,2′ Hs), 7.20 (s, aromatic Hs).

Divinylbenzene-2,2,2′,2′-d_4 (2b)

Benzenediethanol **2*l*** (7.2 g) was heated with KOH pellets (2.6 g) and the divinylbenzene (2.5 g, 46%) was quickly distilled through a 15-cm Vigreux column at ~65 Torr. Mass spectral analysis showed that the product contained 3.89 excess D atoms per molecule (2.9% d_2, 6.6% d_3, 89.3% d_4, 1.1% d_5, 0.1% d_6 species). The ^{2}Hmr ($CHCl_3$) (Fig. 2) showed signals at 5.10 and 5.60 ppm corresponding to the 2,2′ deuterons and a signal at 3.7 pm that was due to starting material; ^{1}Hmr ($CDCl_3$), δ:6.67 (br s, 1,1′ Hs), 7.35 (s, aromatic Hs). Only a very small signal (<1%) was present for the 2,2 protons.

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