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Unexpected dimeric products from the amidomethylation of pentasubstituted benzenes☆

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Abstract—An isomeric series of unexpected diarylmethane products with flexible substituents, isolated from amidomethylation reactions of *p*-dimethoxybenzene derivatives, was analyzed by X-ray crystallography to reveal novel solid-state structures, two of which have identical elemental cell parameters.

1. Introduction

We have been studying amidomethylation reactions[1] of *p*-dimethoxybenzene derivatives in order to gain entry into aminomethylated quinone systems. In two previous cases, we reacted trimethylhydroquinone dimethyl ether and also toluhydroquinone dimethyl ether with *N*-(hydroxymethyl)trifluoroacetamide in chloroform–trifluoroacetic acid solution.[2] The primary product in each case was the expected trifluoroacetamide adduct. However, in each case we also isolated a diarylmethane product that was not expected.

Only a few earlier reports suggest that a diarylmethane product would be formed in such a reaction. These all involved more electron-rich aromatic systems, rather than substituted benzene derivatives, in amidomethylation reactions with reagents different than those used here. In one example, β-naphthol formed an analogous dinaphthylmethane derivative when reacted with various methylenebisamides.[3] We have since expanded our investigation of the diarylmethane forming reaction and report here a more thorough description of the synthetic pathway as well as important X-ray data on an isomeric series of dimeric products.

2. Results and discussion

We studied this reaction further with *p*-dimethoxybenzene derivatives that have a deactivating chlorine group, namely the three isomers of chlorodimethyl-1,4-dimethoxybenzene. These three isomeric precursors were prepared by addition[4] of anhydrous hydrogen chloride[5] to dimethyl-1,4-benzoquinones (xyloquinones) followed by *O*-methylation with dimethyl sulfate under phase transfer conditions.[6]

The amidomethylation reactions were carried out as before[2] using *N*-(hydroxymethyl)trifluoroacetamide in chloroform–trifluoroacetic acid solution. In contrast to our early report with systems that did not have the deactivating chlorine group, only very small amounts of dimeric products were isolated when the reactions were carried out under ambient pressure. When we instead conducted the same reactions at higher temperatures in sealed tubes, diarylmethane products were formed more readily in each case (Scheme 1). For example, in the reaction with 2-chloro-1,4-dimethoxy-3,6-dimethylbenzene approximately 40% of the expected amidomethylation product, 25% of dimer **1a**, and 20% starting material were recovered (the latter two as a mixture that could be resolved by differential crystallization) after silica gel chromatography of the crude reaction mixture; the reactions of the other two chlorodimethoxydimethylbenzene isomers gave similar yields of products.

The nature of the dimer forming pathway was probed by reacting a trifluoroacetamide product with *N*-(hydroxymethyl)trifluoroacetamide under our reaction

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Keywords: Amidomethylation reactions; Diarylmethanes; X-ray crystallography.

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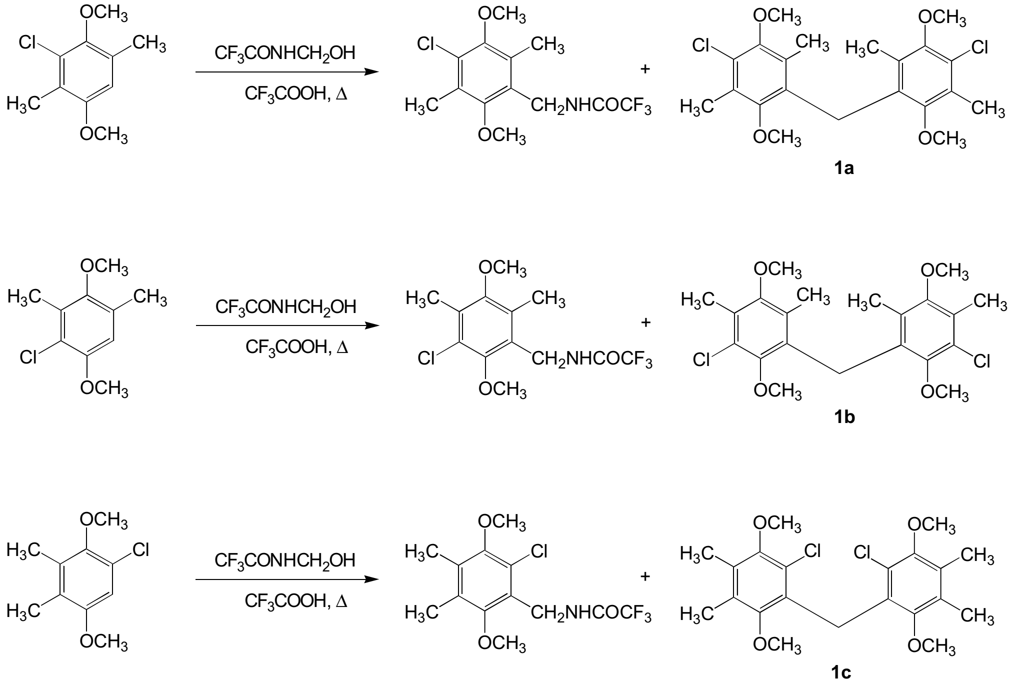

Scheme 1. Amidomethylation reactions studied. In each case, a mixture of dimeric product, amidomethylation product and starting material was obtained.

conditions. Only the unchanged trifluoroacetamide was recovered in this reaction. Thus, we believe that the trifluoroacetamide is the primary product in our dimer forming sequences and that it can react further with the starting dimethoxybenzene species. It is likely that the C–N bond of the trifluoroacetamide can reversibly cleave under the reaction conditions to form a benzylic cation type species; such a species could either reform the trifluoroacetamide or react with a dimethoxybenzene derivative in an electrophilic aromatic substitution reaction.[7] It is also possible that *N*-(hydroxymethyl)trifluoroacetamide reverts to the acetamide and formaldehyde, which then reacts electrophilically with two molecules of starting material to produce the observed dimers.

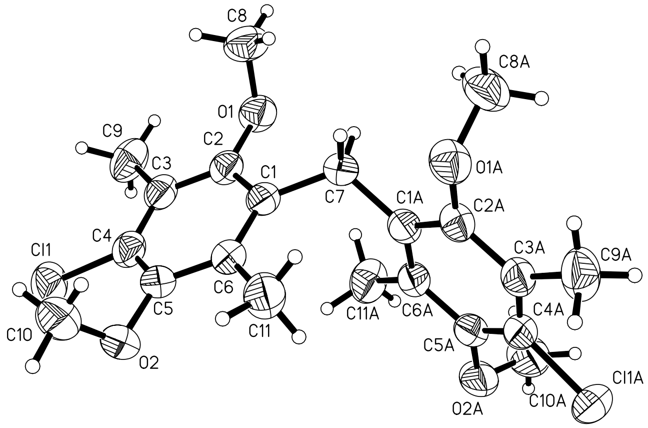

Figure 1. View of dimer **1a** with the atom-numbering scheme. The non-H atoms are shown with thermal ellipsoids drawn at the 50% probability level. H atoms are drawn as circles of arbitrary small radius for clarity.

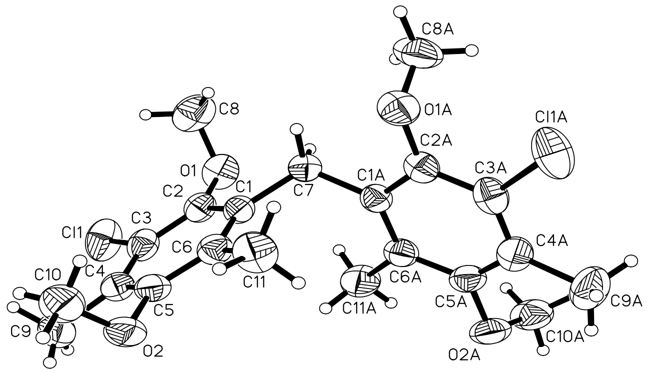

Figure 2. View of dimer **1b** with the atom-numbering scheme. The non-H atoms are shown with thermal ellipsoids drawn at the 50% probability level. H atoms are drawn as circles of arbitrary small radius for clarity.

The three dimeric isomers were fully characterized and their structures investigated by X-ray analysis (Figs. 1–3). Dimer **1c** crystallized in the triclinic space group *P-1* and the molecules occupy a general position in the crystal. In contrast, both compounds **1a** and **1b** crystallized in the orthorhombic space group *Pbcn* and these molecules occupy a special position in the crystal (two-fold axis passing through the methylene group). Remarkably, the elemental cells of **1a** and **1b** have identical parameters despite the presence of flexible methoxy groups in each species.

Comparison of results for the three dimeric isomers reveals that **1c** has a higher density than the other two, reflecting better packing in this isomer. Examination of the geometries of the three isomers reveals that the most

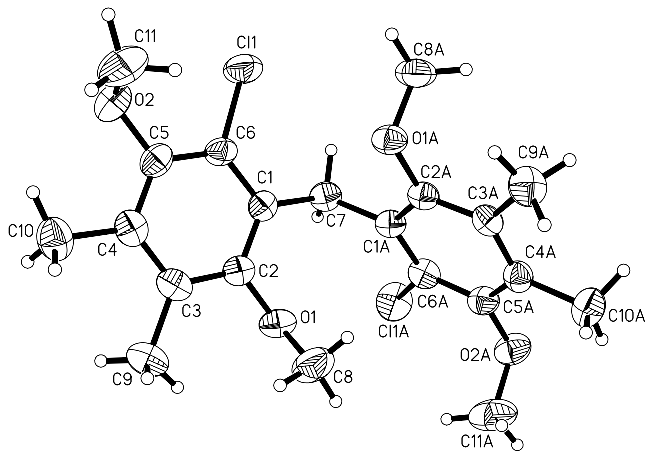

Figure 3. View of dimer **1c** with the atom-numbering scheme. The non-H atoms are shown with thermal ellipsoids drawn at the 50% probability level. H atoms are drawn as circles of arbitrary small radius for clarity.

obviously significant differences in packing appear to be in the orientations of the methoxy substituents with respect to the aromatic rings and also in the dihedral angles between the aromatic rings.

In every case here, the methoxy substituent is almost perpendicular to the aromatic ring. However, the relative orientations of the two methoxy groups with respect to the ring vary in an interesting manner. For the isomers **1a** and **1b**, the methoxy groups have a *syn* orientation (Figs. 1 and 2), in concert with the fact that these molecules have identical elemental cell parameters (isostructural). The methoxy group orientations for dimer **1c** are striking. In this case, the orientation of the methoxy substituents with respect to the ring is different for each aromatic ring; namely, the methoxy groups have a *syn* orientation with respect to one ring and *anti* with respect to the other (Fig. 3). It is interesting to mention that in our previous work[2] with a similar fully substituted molecule, which also lies on a twofold axis, the methoxy groups adopt an *anti*-orientation about the aryl ring. In all cases we have examined, the methoxy group parameters are always in good agreement with literature data.[8]

The dihedral angle between the aryl rings in **1c** is 101.7 (3)°. In the other isomers, the dihedral angles are significantly smaller, namely 79.8 (3)° for **1a** and 81.3 (2)° for **1b**.

The values of bond angles around the bridging methylene group are larger than usual and equal to 117.1 (2)°, 117.2 (2)° and 116.4 (2)°, for **1a**–**c**, respectively. This constant bond angle is similar to that found in two related cases.[2] Nevertheless, the C–C bond lengths around the central methylene group are only slightly elongated compared to the usual value[9] in every case.

The crystal packing was standard for each species except for an intermolecular halogen contact displayed by **1a**. Thus, a very short intermolecular contact Cl1$\cdots$Cl1 ($-x$, $-y$, $1-z$) exists that has a distance of 3.269 (2) Å. This distance is less than the doubled radii of the chlorine atoms.[10] We ascribe the difference in melting points observed for **1a** and **1b** (ca. 34° greater for **1a**) to the presence of these contacts in **1a**, but not **1b**. These contacts apparently do not distort the geometry of **1a** significantly within the elemental cell, since **1a** and **1b** display identical cell parameters.

3. Conclusions

We make the following major conclusions from this study: (1) unexpected dimeric products are common in amidomethylation reactions of aromatic species with *N*-(hydroxymethyl)trifluoroacetamide, (2) an isomeric series of fully substituted aromatic dimers has been fully characterized and described here, (3) the dimeric products arise from the primary reaction mixture, (4) the rare phenomenon was observed that two of the isomers, **1a** and **1b**, have identical elemental cells, (5) the major geometrical differences between **1c** and the other two isomers in the solid state are the different dihedral angles between aryl rings and the different orientations of the methoxy groups with respect to the aromatic rings.

Notes:

Crystallization of the compounds **1a**–**c** from hexanes–ethyl acetate gave X-ray quality crystals. We did grow crystals of **1a**–**c** under other conditions (using different solvents), but obtained identical parameters for each molecule in each case.

The structures of all isomers were investigated using an Enraf–Nonius CAD4 diffractometer[11] at 295 K. The structure solution and refinement were usual.[12–14]

Crystal data for **1a**: $C_{21}H_{26}Cl_2O_4$, $M = 413.32$, orthorhombic, space group *Pbcn*, $a = 11.412(2)$, $b = 7.623(2)$, $c = 23.796(5)$ Å, $V = 2070.1(7)$ Å^3, $Z = 4$, $D_c = 1.326\ \mathrm{g\,cm^{-3}}$, $\mu(\mathrm{Mo\,K_\alpha}) = 0.337\ \mathrm{mm^{-1}}$, $\lambda = 0.71073$ Å, $F(000) = 872$, $2\theta_{\max} = 52°$, 3930 reflections measured, 2028 unique ($R_{\mathrm{int}} = 0.067$). Final residuals for 131 parameters were $R_1 = 0.0456$ against 1430 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1365$ for 2028 unique reflections.

Crystal data for **1b**: $C_{21}H_{26}Cl_2O_4$, $M = 413.32$, orthorhombic, space group *Pbcn*, $a = 11.469(2)$, $b = 7.577(2)$, $c = 23.820(5)$ Å, $V = 2070.0(7)$ Å^3, $Z = 4$, $D_c = 1.326\ \mathrm{g\,cm^{-3}}$, $\mu(\mathrm{Mo\,K_\alpha}) = 0.337\ \mathrm{mm^{-1}}$, $\lambda = 0.71073$ Å, $F(000) = 872$, $2\theta_{\max} = 54°$, 4415 reflections measured, 2237 unique ($R_{\mathrm{int}} = 0.047$). Final residuals for 131 parameters were $R_1 = 0.0551$ against 1513 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1692$ for 2237 unique reflections.

Crystal data for **1c**: $C_{21}H_{26}Cl_2O_4$, $M = 413.32$, triclinic, space group *P-1*, $a = 8.807(2)$, $b = 9.193(2)$, $c = 13.847(3)$ Å, $\alpha = 107.17(3)°$, $\beta = 105.95(3)°$, $\gamma = 96.02(3)°$, $V = 1008.6(4)$ Å^3, $Z = 2$, $D_c = 1.361\ \mathrm{g\,cm^{-3}}$,

$\mu(\mathrm{Mo\,K_\alpha}) = 0.346\,\mathrm{mm^{-1}}$, $\lambda = 0.71073\,\text{Å}$, $F(000) = 436$, $2\theta_{\max} = 54°$, 4632 reflections measured, 4342 unique ($R_{\text{int}} = 0.034$). Final residuals for 252 parameters were $R_1 = 0.0612$ against 2788 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1774$ for 4342 unique reflections.

Supporting information available: Detailed experimental procedures and NMR data for compounds **1a–c** and their precursors, as well as X-ray crystallographic collection and refinement details and structural data. Crystal data for **1a–c** have been deposited with the Cambridge Crystallographic Data Center (CCDC 234469-234471).

Acknowledgements

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