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Hydrogen–deuterium exchange of aromatic amines and amides using deuterated trifluoroacetic acid

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ABSTRACT

The H–D exchange of aromatic amines and amides, including pharmaceutically relevant compounds such as acetaminophen and diclofenac, was investigated using CF_3COOD as both the sole reaction solvent and source of deuterium label. The described method is amenable to efficient deuterium incorporation for a wide variety of substrates possessing both electron-donating and electron-withdrawing substituents. Best results were seen with less basic anilines and highly activated acetanilides, reflecting the likelihood of different mechanistic pathways.

Introduction

Increasing demand for deuterated compounds, especially due to a renewed interest in the therapeutic prospects of so-called 'heavy drugs',[1] has spurred development of novel methods for hydrogen–deuterium exchange. One group of compounds with significant research interest for H–D exchange is the aromatic amines and amides, due to the presence of these moieties in numerous clinically important pharmaceuticals, including such mainstays as acetaminophen (paracetamol), diclofenac, and acebutolol. The former two compounds are of particular importance with respect to aromatic isotopic exchange due to their metabolism to potentially toxic ring-oxygenated metabolites in the liver by cyctochrome P450 and related enzymes. Several in vitro and in vivo studies performed using deuterated analogs of these compounds have had profound mechanistic implications.[2] As a result, various syntheses of ring-deuterated variants of acetaminophen[3] and diclofenac[4] have been reported. However, these methods generally require several synthetic steps from expensive deuterated starting materials. Efforts have been made toward exploring the direct aromatic H–D exchange of both of these compounds to varying degrees of success.[5] In particular, a rapid, direct, and metal-free method for labeling acetaminophen with deuterium has proven elusive.

Acid-catalyzed H–D exchange conditions encompass some of the most powerful and efficient methods for incorporating deuterium into an aromatic ring.[6] While these methods can employ a wide variety of acidic catalysts, including heterogeneous and Lewis acids, homogeneous Brønsted systems are the most common. Under these conditions, reactivity typically proceeds through an electrophilic aromatic substitution mechanism and the aromatic ring is selectively deuterated at the most electron-rich positions. Commonly-used systems for H–D exchange include a solvent, usually D_2O, as well as a deuterated mineral acid catalyst such as DCl, DBr, or D_2SO_4. However, the use of these harsh reagents has several disadvantages, including unwanted side reactions, low substrate solubility in aqueous solution, and potential substrate decomposition.

The use of deuterated trifluoroacetic acid (CF_3COOD) has several benefits over other acidic H–D exchange methods, including its ease of preparation, simple removal in vacuo, low nucleophilicity, and high solubility properties for a wide variety of substrates. CF_3COOD can be prepared quantitatively from trifluoroacetic anhydride and D_2O in essentially anhydrous fashion. Since the pioneering efforts of Lauer et al.,[7] CF_3COOD has found use as a highly versatile and effective deuterating agent for hormones,[8] natural products,[9] and various other biologically relevant aromatic systems.[10] We considered the viability of this reagent for the deuteration of aromatic amines and amides such as acetaminophen. A handful of examples can be found in the chemical literature, including the CF_3COOD-catalyzed H–D exchange of tryptophan and its derivatives[11] along with a single report each regarding H–D exchange of naphthalene-diamines,[12] reserpine,[13] and pteroylglutamic acid.[14] However, to the best of our knowledge, the H–D exchange of other aromatic amines and amides in CF_3COOD has not been studied extensively. Herein we report on the generalized

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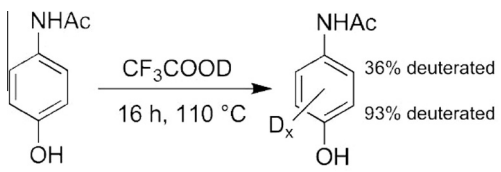
use of CF_3COOD as a source of deuterium and reaction solvent for the preparation of several deuterated aromatic amine and amide derivatives.

Results and discussion

While investigating palladium-catalyzed H–D exchange of pharmaceutically relevant compounds, we found CF_3COOD be highly effective at deuterating acetaminophen without any metal catalyst at 110 °C (Scheme 1). Since efficient and direct H–D exchange of this compound has only been conducted using the assistance of rhodium salts[5c] we decided to investigate this unexpected transformation further. At reflux without any additional catalyst or co-solvent, acetaminophen was deuterated extensively at the aromatic positions *ortho* to the hydroxyl substituent and more slowly at the positions *ortho* to the amide. The selectivity of deuteration is opposite that observed in the previously reported metal-catalyzed example and is unprecedented in the direct H–D exchange of acetaminophen.

Encouraged by these results, we endeavored to determine the scope of this methodology[16] and subjected simple aniline and acetanilide, as well as aniline derivatives substituted only at nitrogen, to the same CF_3COOD conditions used for acetaminophen (Fig. 1). Aniline **1** and *N*-ethylaniline **2** underwent H–D exchange smoothly under these conditions at the positions *ortho* and *para* to the nitrogen atom, a result consistent with a standard EAS mechanism. However, the H–D exchange of *N*,*N*-diethylaniline **3** under the same conditions was poor despite the enhanced induction from the alkyl substituents on nitrogen. This low rate of exchange was also observed in previous work on the acid-catalyzed proton exchange of *N*,*N*-diethylaniline[17] and attributed to its high basicity and at least partially to steric interference from the ethyl groups. Interestingly, 1-phenylpiperazine **4** was even more reactive toward CF_3COOD–catalyzed H–D exchange than aniline, indicating that dialkylation of the amine is not inherently detrimental toward the exchange process. Acetanilide **5** was similarly reactive toward H–D exchange as aniline, suggesting that acetylation of the nitrogen does not necessarily deactivate the aromatic ring toward reaction with CF_3COOD.

To test the effect of various ring substituents, *para*-substituted substrates were then investigated under the reaction conditions (Fig. 2). The reactivity of *p*-toluidine **6** was similar but not enhanced compared to aniline, despite the presence of an activating methyl substituent on the ring. However, the reactivity of both *p*-anisidine **7** and *p*-aminophenol **8** was significantly lower than that of *p*-toluidine, and deuteration of both of these substrates proceeded with very low selectivity. Interestingly, 4-nitroaniline **9** underwent H–D exchange analogously to *p*-toluidine despite the very different electronic properties of these aromatic systems. Thus a strong correlation between the basicity of the amine and the rate of H–D exchange can be seen, with more basic anilines reacting somewhat less efficiently and with lower selectivity. Acid-catalyzed H–D exchange of aromatic anilines can proceed via aromatic substitution of either the protonated anilinium ion (slow) or its free-base counterpart (fast) which exists in equilibrium. In strongly acidic solution, electron-rich anilines are more



Scheme 1. CF_3COOD-catalyzed H–D exchange of acetaminophen.[15]

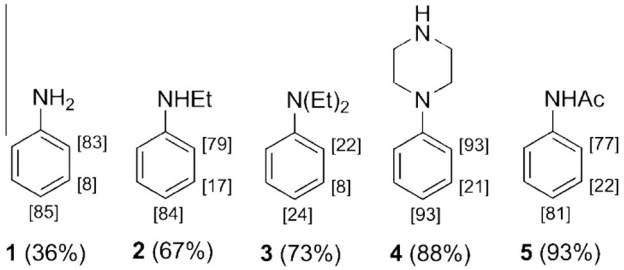


Figure 1. H–D exchange of anilines and acetanilide without ring substituents.[15]

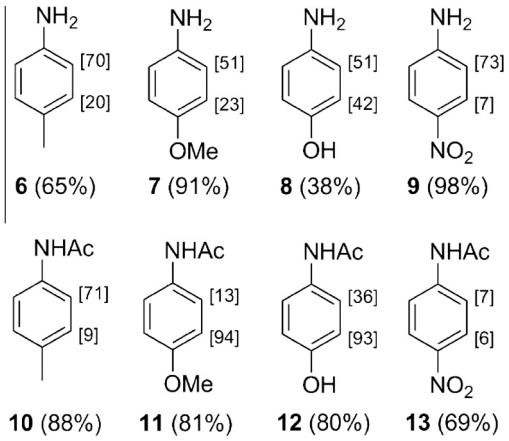


Figure 2. H–D exchange of *para*-substituted anilines and acetanilides.[15]

likely to react through the former pathway, and with deactivated anilines, the latter pathway predominates.[18] The observed selectivity differences in this experiment likely reflect these mechanistic differences.

Further support of this hypothesis can be drawn from the reactivity of the N-acetylated derivatives of each compound. Acetylation of the amine inhibits protonation at nitrogen, essentially eliminating one of the two possible H–D exchange pathways from consideration. The reactivity of 4′-methylacetanilide **10** was comparable to its non-acetylated counterpart **6**, reflecting a minor inductive effect from the methyl substituent. In contrast, the H–D exchange of 4-methoxyacetanilide **11** was very efficient and highly selective compared to *p*-anisidine **7**, and the observed H–D exchange pattern was opposite that of 4′-methylacetanilide. The reactivity and deuteration selectivity of acetaminophen **12** was analogous to that of 4-methoxyacetanilide and similarly improved relative to 4-aminophenol **8**. The reactivity of **11** and **12** revealed the strong directing influence of the hydroxy and methoxy functional groups in the absence of protonation at nitrogen. However, the more-deactivated 4-nitroacetanilide **13** barely reacted at all compared to 4-nitroaniline **9**. Thus, while optimal H–D exchange results occur with less electron-rich anilines, acetanilides react with greater efficiency with an activating substituent on the aromatic ring.

We then considered the effect of the substitution pattern of the ring on H–D exchange by reacting the other anisidine isomers with CF_3COOD (Fig. 3). The influence of the amine group dominated the H–D exchange selectivity of *o*-anisidine **14**, and the positions *ortho* and *para* to the amine exchanged rapidly under these conditions while the positions *ortho* and *para* to the methoxy group had significantly lower deuterium incorporation. A similar pattern was observed in *m*-anisidine **15**, which underwent rapid exchange throughout the ring except the single position *meta* to both the

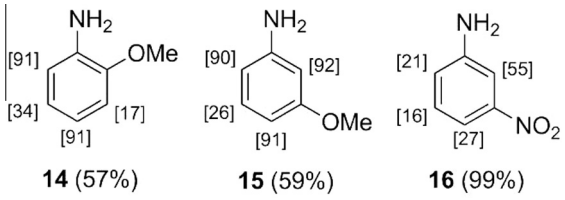
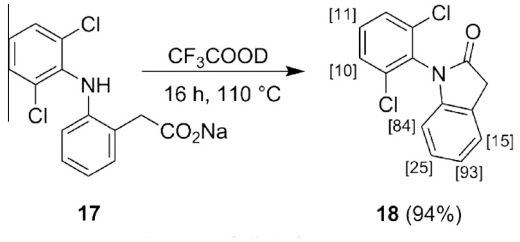


Figure 3. H–D exchange of ortho and meta-substituted anilines.[15]



Scheme 2. H–D exchange of diclofenac.[15]

amine and methoxy substituents. The effect of an electron-withdrawing substituent nitro substituent in place of the methoxy was pronounced, as 3-nitroaniline **16** exchanged at a much lower rate than *m*-anisidine.

The applicability of this method to more complex pharmaceutical compounds was investigated using diclofenac as an example (Scheme 2). Like acetaminophen, diclofenac is an aromatic amine or amide-containing NSAID with wide-ranging therapeutic applications. Upon subjecting the sodium salt of diclofenac to the described experimental conditions, cyclization was observed to the amide derivative **18**. This transformation was precedented in another acid-catalyzed H–D exchange experiment of diclofenac, and the original sodium salt can be recovered using a simple base-catalyzed procedure.[5a] Significant H–D exchange was observed in the ring annulated to the newly-formed lactam at the positions *ortho* and *para* to nitrogen. However, little H–D exchange was observed at the other aromatic positions.

Conclusion

Using deuterated trifluoroacetic acid, the rapid and efficient H–D exchange of a wide variety of aromatic amines and amides was achieved without the need for metal salts or other co-catalysts. Direct H–D exchange of valuable pharmaceutically relevant compounds such as acetaminophen and diclofenac was conducted, engendering the possibility of applying this technique toward deuteration of other biologically active compounds. The exchange reaction generally proceeded according to typical EAS patterns, but was inhibited by strongly basic amines or highly deactivated acetanilides.

Acknowledgments

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15. Deuterium incorporation in all experiments was verified using ^{1}H, ^{2}H, and ^{13}C NMR and a 1,3,5-trimethoxybenzene internal NMR standard. The bracketed numbers adjacent to each aromatic position in the figures represent deuterium incorporation at that position, and are averaged in the case of a symmetrical structure. Yields are given in parentheses.
16. General conditions: To the aniline or acetanilide (0.2 mmol) in a 2 dram vial was added CF_3COOD (1.0 mL, 12.98 mmol). A stir bar was added and the sealed vial was heated to 110 °C for 16 h. The solvent was evaporated in vacuo and the residue was stirred in 2 M KOH solution (0.5 mL) for 0.1–4.0 h. The deuterium-labeled substrate was extracted using CH_2Cl_2, Et_2O, or EtOAc and purified using flash column chromatography with silica gel (hexanes/EtOAc).
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