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Reaction of N,N-Dimethyltryptamine with Dichloromethane Under Common Experimental Conditions

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ABSTRACT: A large number of clinically used drugs and experimental pharmaceuticals possess the N,N-dimethyltryptamine (DMT) structural core. Previous reports have described the reaction of this motif with dichloromethane (DCM), a common laboratory solvent used during extraction and purification, leading to the formation of an undesired quaternary ammonium salt byproduct. However, the kinetics of this reaction under various conditions have not been thoroughly described. Here, we report a series of experiments designed to simulate the exposure of DMT to DCM that would take place during extraction from plant material, biphasic aqueous work-up, or column chromatography purification. We find that the quaternary ammonium salt byproduct forms at an exceedingly slow rate, only accumulates to a significant extent upon prolonged exposure of DMT to DCM, and is readily extracted into water. Our results suggest that DMT can be exposed to DCM under conditions where contact times are limited (<30 min) with minimal risk of degradation and that this byproduct is not observed following aqueous extraction. However, alternative solvents should be considered when the experimental conditions require longer contact times. Our work has important implications for preparing a wide-range of pharmaceuticals bearing the DMT structural motif in high yields and purities.

1. INTRODUCTION

A wide-variety of bioactive compounds contain the N,N-dimethyltryptamine (DMT) structural motif (Figure 1). The parent compound DMT (1) is the primary hallucinogenic component of ayahuasca— an Amazonian tisane used in traditional medicine and for religious purposes.† There is a growing interest in the therapeutic potential of DMT because of recent clinical data demonstrating that ayahuasca produces rapid antidepressant effects in humans that resemble those of the prototypical fast-acting antidepressant ketamine.‡—§ Furthermore, DMT is capable of producing behavioral effects in rodents relevant to the treatment of depression and post-traumatic stress disorder.‖ Other psychedelics possessing the DMT structural core, such as psilocybin (2) and ibogaine (3), have also demonstrated therapeutic potential for treating various neuropsychiatric disorders including depression, anxiety, and addiction.¶‖ Taken together, these data suggest that psychedelics possessing the DMT core structure may have value as medicines and cannot simply be labeled as drugs of abuse.¶

In addition to the classical serotonergic psychedelics, a variety of other bioactive compounds contain the DMT structural motif. These include the triptan drugs sumatriptan (4), zolmitriptan (5), and rizatriptan (6) (Figure 1)— compounds that are widely prescribed for treating migraines and cluster headaches as well as the 5-HT6 ligands EMDT (7), MS-245 (8), and ST1936 (9).† The latter compounds are still in the experimental phase but have shown great promise in preclinical models and in clinical trials for improving cognitive deficits associated with Alzheimer’s disease and depression.† Paul Because of the ubiquity of the DMT structural motif in molecules of medicinal importance, it is imperative to identify methods for their preparation and purification that maximize yield and purity while minimizing cost.

During the course of our studies regarding the synthesis and biological evaluation of DMT derivatives, we became aware of reports detailing the reaction of DMT with dichloromethane (DCM) to form N-chloromethyl-N,N-dimethyltryptamine chloride 10 (Scheme 1).‡—§ These findings have caused some chemists to question the appropriateness of using DCM in the synthesis, work-up, or purification of DMT derivatives, despite the fact that DCM possesses many desirable traits like being one of the only commercially available low boiling solvents that is nonflammable.¶ One common alternative to...
DCM is diethyl ether, but the latter can be quite hazardous due to its low flash point (−45 °C), low autoignition temperature (180 °C), and ability to form peroxides. Chloroform is another solvent commonly used as a replacement for DCM, but it is far from perfect. In the presence of a base, it can form dichlorocarbene, which is known to react with indoles and amines. Additionally, it causes a variety of adverse health effects that are less likely to be caused by DCM. Finally, both diethyl ether and chloroform are significantly more expensive than DCM (circa 1.5×). Therefore, despite the possibility of amines reacting with DCM through an S_N2 reaction, this solvent remains attractive from safety and economic standpoints.

While there have been several studies reporting the reactivity of DCM with amines, such reactions are highly substrate dependent. Tertiary amines appear to be the most susceptible to reactions with DCM, though the reactivity of secondary amines has also been reported. Secondary amines stored in DCM transiently form an N-chloromethyl-N,N-dimethyltryptamine chloride 10.

2. RESULTS AND DISCUSSION

2.1. Synthesis of Analytical Standards. First, we prepared pure DMT and 10 as described previously for use as analytical standards. For reference, the 1H NMR and LC–MS (liquid chromatography–mass spectrometry) spectra are presented in Figure 2. Characterization data for 1 and 10 were consistent with previous reports.

2.2. DMT Degradation in Pure Solvent. Alkaloids are commonly extracted from plant material using DCM. To mimic such conditions, we dissolved a DMT free base in DCM and observed the formation of 10 via 1H NMR as a function of time. While previous reports have described the formation of 10 after extended reaction times, the rate of its formation was previously unknown. By comparing the integrations of the peaks corresponding to DMT (1) with those corresponding to 10, we could determine the rate of the reaction. In a pure solvent, the reaction of 1 with DCM is quite clean yielding 10 as the only observable product by 1H NMR (Figure 3A) or LC–MS (data not shown). After 1 h, the percentage of 10 in the mixture was 0.8%, and it reached 38% after 4 days (Figure 3B). Crystals of 10 were observed to precipitate around day 2 when the starting concentration of DMT was 10 mg/mL. The pseudo-first-order rate constant k, for this reaction was calculated to be 1.21 × 10^−5 s^-1 and is comparable to that previously reported for the reaction of DCM with trimethylamine. Like trimethylamine, DMT reacts approximately 35× faster with DCM than triethylamine, but only 2X as fast as the secondary amine piperidine. Compared with the bulkier tertiary amine N-methylpiperidine, DMT reacts nearly 10X as fast highlighting the importance of steric effects in the reaction of amines with DCM.

Though DMT and trimethylamine react faster with DCM than most amines (with the exception of quinuclidine), this reaction is still quite slow when compared with their reaction with methyl iodide. For example, trimethylamine reacts with methyl iodide approximately 3000× faster than it does with DCM. Notably, when chloroform was used as the solvent, no appreciable decomposition of DMT was observed (data not shown). When the reaction between DMT and DCM was carried out at −20 °C, the amount of 10 formed was less than 1% as determined by NMR after 4 days. While the rate of formation of 10 is quite slow in DCM, care should be taken when lengthy extraction protocols are required. In such cases, chloroform may be a more appropriate solvent choice.

2.3. DMT Degradation under Biphasic Basic Work-Up Conditions. While the rate of formation of 10 in DCM is relatively slow, appreciable amounts were observed after several days. However, it is quite uncommon for reactive tertiary amines to be left in solvent for multiple days at a time. Therefore, we were interested in assessing the formation of 10 under more typical experimental conditions, namely, those corresponding to a biphasic aqueous work-up. Because of the partitioning between the organic and aqueous phases, one might expect to form 10 at an accelerated rate because of the dynamic removal of the ammonium salt product from the organic layer where the S_N2 reaction occurs. In fact, Brandt and co-workers have reported that a basic aqueous work-up using DCM following the synthesis of DMT resulted in the formation of 10, which constituted 4% of the total peak area in the LC-UV trace.

As Brandt and co-workers did not precisely
quantify the formation of 10, we subjected DMT to DCM/NaOHaq biphasic work-up conditions and monitored the formation of 10 in both layers as a function of time using LC–MS with selective ion monitoring (SIM). In our hands, we observed that the rate of DMT degradation under biphasic conditions is comparable to that in pure DCM (Figure 4A,B). By 24 h, 5% of 10 was observed in the aqueous layer, comparable to the 4% observed in pure DCM conditions. Importantly, we discovered that 10, likely because of its ionic nature, partitions almost exclusively into the aqueous phase, resulting in undetectable amounts of 10 contaminating the DMT dissolved in the organic phase (Figure 4B).

Because of fear of forming impurity 10, others have preferred the use of chloroform to DCM for extracting DMT free base. However, chloroform is known to form dichlorocarbene under basic conditions, such as those employed in aqueous work-ups involving amines. Therefore, we wished to directly compare the yields and purities of synthetic DMT subjected to basic biphasic work-up conditions utilizing either DCM, chloroform, or diethyl ether. The work-ups were carefully timed such that the solvent was completely removed 30 min following the initial exposure of DMT to solvent. Inspection of the unpurified 1H NMRs revealed that 10 was unobservable following aqueous

Figure 2. Characterization data for purified DMT/fumarate (2:1) and 10. 1H NMR spectra taken in DMSO-d6 for DMT (A) and 10 (B). Insets depict LC–MS traces and mass spectra for each compound.

Figure 3. Formation of 10 in pure solvent. (A) Reaction of DMT (1) with DCM to produce 10 monitored by 1H NMR over time. The peaks highlighted in gray were used to quantify the molar ratio of 1 to 10. (B) Quantification of the peaks in A demonstrates that 10 reaches 38 mol % after 4 days.
work-up regardless of the organic solvent employed (Figure 4C). This fact makes it unlikely that 10 can be used as a diagnostic impurity when trying to identify DMT produced by clandestine laboratories using DCM in their syntheses. After crystallization as the fumarate salt, the synthetic DMT produced using these three distinct work-up conditions was judged to be analytically pure (via 1H NMR, and LC−MS). Furthermore, the yields of the final product were comparable (79−86%), regardless of the solvent used during the work-up. Isolated yields following crystallization as the fumarate salt (2:1 DMT/fumarate) are indicated.

### 2.4. DMT Degradation Following Purification via Chromatography.

Basic amines such as DMT (1) are often purified via flash chromatography with the most common solvent system being 9:1 DCM/MeOH with 1% NH4OHaq. In fact, similar conditions produced 10 from an extract of Acacia confusa, and the authors concluded that its formation was an artifact of the isolation conditions.12 Following chromatography using this solvent system, amines are often left to sit in the collected fractions for a period of time, and thus, we were interested to measure the conversion of DMT to 10 in 9:1 DCM/MeOH with 1% NH4OHaq.12 Following chromatography using this solvent system, amines are often left to sit in the collected fractions for a period of time, and thus, we were interested to measure the conversion of DMT to 10 in 9:1 DCM/MeOH with 1% NH4OHaq (Figure 5A,B). After 1 h, the percentage of 10 in the mixture was 2% and had reached 6% by 24 h, comparable to previously seen quantities at 24 h. The reaction proceeded under pseudo-first-order conditions at a comparable rate to that of DMT in pure DCM, and thus, it would appear that the addition of MeOH and NH4OHaq has very little effect on the rate of the reaction of DMT with DCM. However, we recommend that fractions containing DMT be concentrated within 1 h or stored at −20 °C following column chromatography using 9:1 DCM/MeOH with 1% NH4OHaq as the solvent system to minimize any potential for degradation.

### 3. CONCLUSIONS

Here, we have demonstrated that 1 will form 10 in the presence of DCM as described previously.12−14 However, the rate of this reaction is exceedingly slow under most common experimental conditions, and significant amounts of this impurity do not accumulate when contact times are limited (<30 min) or when cryogenic temperatures are used. Therefore, concerns regarding the use of DCM during the preparation of DMT (and likely other related dimethyltryptamine analogs) are not warranted. It has been previously suggested that forensic teams could use 10 as a diagnostic impurity to identify clandestine laboratories using DCM in their syntheses of DMT. However, we think that this possibility is unlikely due to the readily extractable nature...
of 10 in water as well as the slow rate of reaction between 1 and DCM. Although there are still environmental concerns with using chlorinated solvents such as DCM, this study has shown that its use has no effect on the purity or yield of the final DMT product as compared to other common laboratory solvents. Dimethyltryptamine and related analogs have high medicinal value, and our work answers some fundamental questions regarding their economical preparation in excellent yields and purities.

4. METHODS

4.1. Materials. The DCM (ACS reagent grade, stabilized), chloroform (HPLC grade), and all other reagents used in these studies were purchased from Fisher Scientific and used without purification. The concentration of the ammonium hydroxide used in the chromatography experiments was 28—30%.

4.2. Synthesis of DMT (1). To an ice-cold solution of tryptamine (0.60 g, 3.1 mmol) and glacial acetic acid (0.88 mL, 15 mmol, 5.0 equiv) in MeOH (48 mL) was added sodium cyanoborohydride (0.40 g, 6.4 mmol, 2.1 equiv) followed by 37% formaldehydeaq (0.64 mL, 7.9 mmol, 2.6 equiv). The reaction was stirred at room temperature for 5 h, at which time the mixture was transferred equally to three separate vials. Concentration under reduced pressure afforded an unpurified solid, which was dissolved in either DCM, diethyl ether, or CHCl3 (5 mL) and diluted with 1.0 M NaOHaq (75 mL). The precipitate that had formed was dried under reduced pressure to yield a colorless oil. The unpuriﬁed samples were dissolved in acetone (15 mL). A precipitate formed immediately. The oil was dissolved in acetone (5 mL) and added dropwise to a boiling solution of fumaric acid (0.059 g, 0.50 mmol, 0.50 equiv) in acetone (15 mL). A precipitate formed immediately. The solution was allowed to cool to room temperature and ﬁltered. The white solid was dried under reduced pressure to yield the pure compound as the fumarate salt (2:1 DMT/fumarate) (0.20 g, 0.82 mmol) was basiﬁed using 1.0 M NaOHaq (30 mL) and extracted twice with diethyl ether (20 mL). The organic extracts were combined, dried over Na2SO4, and concentrated under reduced pressure to yield DMT free base (0.11 g, 0.58 mmol, 71%).

4.4. Conversion of DMT/Fumarate (2:1) to the Free Base. DMT/fumarate (2:1) (0.20 g, 0.82 mmol) was basiﬁed using 1.0 M NaOHaq (30 mL) and extracted twice with diethyl ether (20 mL). The organic extracts were combined, dried over Na2SO4, and concentrated under reduced pressure to yield DMT free base (0.11 g, 0.58 mmol, 71%).

4.5. DMT Degradation in Pure Solvent. The free base of DMT (as prepared above) was dissolved in DCM or CHCl3 to give a concentration of 10 mg/mL (0.05 M). The vial was blanketed with N2 and stored in the dark. Aliquots were taken at various time points (1 h, 1 day, 2 days, 3 days, and 4 days) and concentrated under reduced pressure. Care was taken to ensure that the mixture was homogenious before aliquots were taken. The unpuriﬁed samples were dissolved in 0.6 mL of DMSO-d6 and 1H NMR spectra were obtained. The aliquot taken after 4 days was also subjected to analysis by LC−MS to conﬁrm the formation of 10.

4.6. DMT Degradation under Biphasic Basic Work-Up Conditions. The free base of DMT (as prepared above) was dissolved in 9:1 DCM/MeOH with 1% NaOHaq to give a concentration of 10 mg/mL (0.05 M). To this solution was added an equal volume of 1.0 M NaOHaq. The vial was blanketed with N2 and stored in the dark. Aliquots were taken at 5 min, 15 min, 30 min, 1 h, and 1 day from the aqueous layer, neutralized with 2.0 M HClaq, and subjected to analysis by SIM LC−MS using caffeine as an internal standard. Aliquots from the organic layer were taken at the same time points, concentrated under reduced pressure, diluted with methanol, and subjected to analysis by SIM LC−MS using caffeine as an internal standard. Standard curves were prepared by comparing SIM peak integrations for increasing concentrations of puriﬁed DMT/fumarate (2:1) or 10 relative to a constant concentration of caffeine as an internal standard.

4.7. DMT Degradation under Column Chromatography Conditions. The free base of DMT (as prepared above) was dissolved in 9:1 DCM/MeOH with 1% NaOHaq to give a concentration of 10 mg/mL (0.05 M). The vial was blanketed with N2 and stored in the dark. Aliquots were taken at 5 min, 15 min, 30 min, 1 h, and 1 day, and then concentrated under reduced pressure. The unpuriﬁed samples were dissolved in 0.6 mL of DMSO-d6 and 1H NMR spectra were obtained. An aliquot taken after 1 day was also subjected to analysis by LC−MS to conﬁrm the formation of 10.

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Notes

The authors declare no competing ﬁnancial interest.

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