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A novel approach to the synthesis of acetylsalicylic acid *via* H/D substitution

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ABSTRACT

This study introduces a unique technique for synthesizing acetylsalicylic acid (aspirin) with a hydrogen-deuterium (H/D) exchange, by using a hydrothermal autoclave device, for the first time. Aspirin was subjected to deuterium substitution by dissolving it in deuterium oxide and allowing it to react with K_2PtCl_4 in a hydrothermal autoclave. The reaction conditions (temperature, stress, and time) were optimized in order to facilitate the H/D exchange. The characterization of the synthesized deuterium-substituted aspirin was performed through the employment of ^{1}H-nuclear magnetic resonance (NMR) spectroscopy and ^{13}C-NMR spectroscopy, confirming a hit substitution at particular hydrogen sites. The findings were validated after full-size adjustments in NMR spectra, indicating a powerful incorporation of deuterium, which enhances aspirin's pharmacokinetic properties and decreases its metabolic liabilities. This study highlights the ability of H/D change to improve drug efficacy.

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used globally. These drugs include NSAIDs containing a carboxylic acid moiety, those with enolic acid systems, and compounds that lack carboxylic acid or different acidic corporations. Aspirin is a famous NSAID, celebrated for its ability to relieve pain and inflammation. Introduced in 1899, aspirin became the first effective remedy for rheumatic illnesses[1], and is also used as an anticoagulant so as to treat headaches related to the hyperviscosity of the blood. Aspirin is one of the earliest drugs to be categorized inside identified therapeutic classes, with its use dating back to the Sumerians and the Egyptians that used to apply willow bark as a medication[2].

Prostaglandins (PGs), inclusive of PGG_2 and PGH_2, are bioactive mole-

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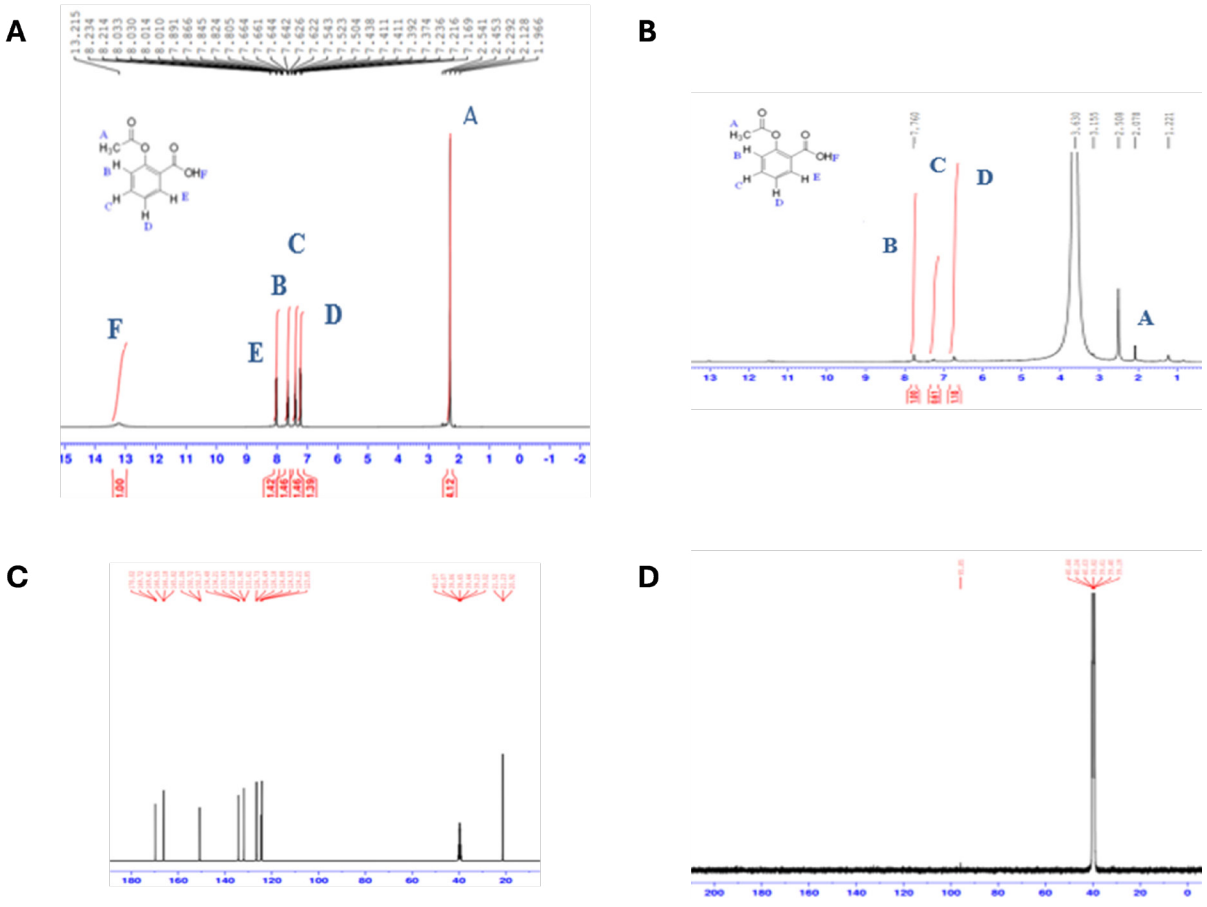

Figure 1. *(A): The [1]H-nuclear magnetic resonance (NMR) spectroscopy chart for aspirin before deuteration. (B): The [1]H-NMR spectroscopy chart for aspirin after deuteration. (C): The [13]C-NMR spectroscopy chart for aspirin before deuteration. (D): The [13]C-NMR spectroscopy chart for aspirin after deuteration.*

cules synthesized through cyclooxygenase (COX), in particular COX-1 and COX-2, in the course of inflammatory responses. Aspirin exerts its consequences by inhibiting COX-1, thereby influencing platelet activation. Moreover, high doses of aspirin also suppress COX-2 by covalently binding to the Ser516 residue at its active site[3].

The hydrogen-deuterium exchange (H/D exchange) refers back to the chemical method in which a hydrogen atom in a covalent bond is changed by means of a deuterium atom. This trade takes place with the participation of hydrogen and deuterium compounds, and is normally catalysed by way of platinum (Pt) or palladium. The response charge is stimulated through factors which include temperature and pressure[4]. The H/D exchange is a crucial method in chemical research, providing insights into molecular interactions. It is an essential tool in pharmaceutical research, particularly for the identification of precise drug binding sites and the assessment of their distribution and effects. Additionally, the H/D exchange is employed in order to investigate the stability, folding, and characteristics of proteins and nucleic acids[5]. The approach also aids at studying metabolic tactics and changes in various factors, thereby contributing to a higher knowledge of biomolecular

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dynamics[6]. This technique is particularly beneficial for analysing the steadiness and conformational modifications of biomolecules, shedding light on their shape and function. By substituting hydrogen with deuterium, one can influence drug excretion and oxidative metabolism, as enzymes within the cytochrome P450 (CYP) alter many drugs[7]. However, oxidative metabolism can cause several unwanted outcomes, inclusive of the production of poisonous, reactive metabolites, variations in bioavailability because of genetic variations, and drug–drug interactions. Therefore, the substitution of hydrogen with deuterium by using the kinetic isotope effect (KIE) has been employed by pharmaceutical developers in order to lessen the CYP-mediated metabolism and its related disadvantages[8].

2. Methodology

For our study, we have used deuterium oxide (Merck, USA), aspirin (Sigma-Aldrich, USA), potassium tetrachloroplatinate(II) (Fisher Scientific, UK), dichloromethane (BDH, UK), magnesium sulfate (BDH, UK), and ethanol (Sigma-Aldrich, USA) of the purest grade. Deuterium-substituted aspirin was synthesized in a new way for the first time by using a hydrothermal autoclave device, by way of dissolving 1.5 g of aspirin in 25 mL of deuterium oxide (D_2O). The solution was stirred magnetically, and 0.1 g of the catalyst (K_2PtCl_4) were added whilst preserving continuous stirring. The solution was then transferred into a hydrothermal autoclave reactor, which was securely sealed before being placed in the autoclave. The reactor was heated for 120 min at 300 W power, 150 psi pressure, and a temperature variety of 170°C to 180°C. After this step, the reactor was allowed to cool completely. Subsequently, the contents were transferred gradually to a separation funnel, wherein the organic phase was extracted. The natural segment was washed three times with 10 mL of dichloromethane (CH_2Cl_2; three times × 10 mL). After discarding the aqueous layer, the organic segment was obtained, was dried with 0.05 grams of magnesium sulfate ($MgSO_4$), was filtered, and then collected with the use of a rotary evaporator (Büchi R-205 Rotavapor).

The characterization of both aspirin and deuterium-substituted aspirin was performed by using ^{1}H-nuclear magnetic resonance (NMR) spectroscopy (Bruker Avance Neo 400, Germany) at a frequency of 400 MHz, and DMSO-d_6 as the solvent. The pulse program used was zg30, with the probehead identifier z163739-0420. The FID resolution (FIDRES) was 0.250144 Hz. Additionally, the ^{13}C-NMR spectra were recorded, at a frequency of 100 MHz.

3. Results and Discussion

When comparing the ^{1}H-NMR spectra of aspirin before and after deuterium substitution (Figures 1A and 1B), a marked decrease in peak intensity at 7–8 ppm was observed in spectra B, C, and D. In spectrum E, this peak is completely absent, suggesting that protons at more sterically hindered sites were replaced by deuterium, facilitated by the platinum catalyst (K_2PtCl_4) under elevated pressure and temperature. Additionally, a reduction in peak intensity at 2 ppm is noted in spectrum A, with the corresponding signal disappearing entirely in spectrum F, which represents the deuterium-substituted aspirin. These observations further support the occurrence of H/D exchange, promoted by the platinum catalyst, high pressure, and thermal activation. The findings are consistent with those reported in previous studies[9].

Significant differences are also evident when comparing the ^{13}C-NMR spectra of standard aspirin and deuterium-substituted aspirin. In the spectrum of unmodified aspirin, carbon atoms C1–C9 exhibit chemical shifts at 170, 168, 150, 134, 132, 126, 123, 122, and 21 ppm, respectively (Figure 1C). In contrast, the spectrum of deuterium-treated aspirin (Figure 1D) shows the merging and disappearance of several peaks, indicating the replacement of hydrogen atoms bound to carbon with deuterium. This substitution alters the local magnetic environment, leading to the attenuation or loss of specific carbon signals. The observed spectral changes are consistent with the expected effects of deuterium incorporation and align with those of previous reports[10].

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4. Conclusion

The comparative analysis of the ^{1}H-NMR and ^{13}C-NMR spectra of aspirin before and after deuterium substitution provides compelling evidence for the successful incorporation of deuterium atoms. The identified spectral alterations are consistent with those reported by previous studies, thereby reinforcing the reliability of the applied methodology. Collectively, our findings highlight the critical role of catalytic and environmental conditions in enabling efficient H/D exchange in aspirin, representing a significant advancement in isotopic labelling techniques for organic compounds.

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Conflicts of interest

None exist.

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