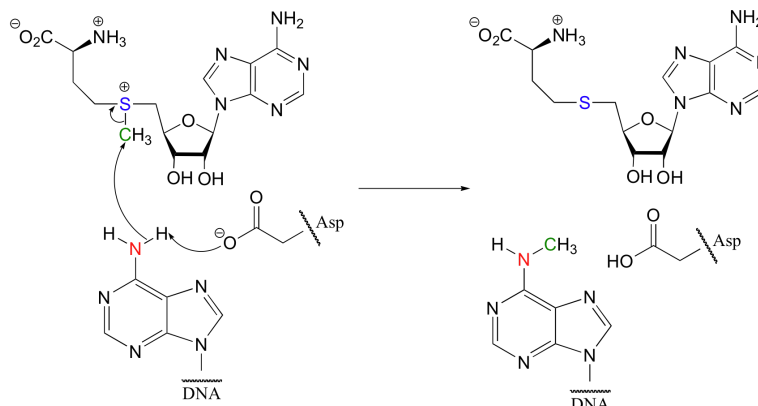


7.12: Application- Useful S_N2 Reactions

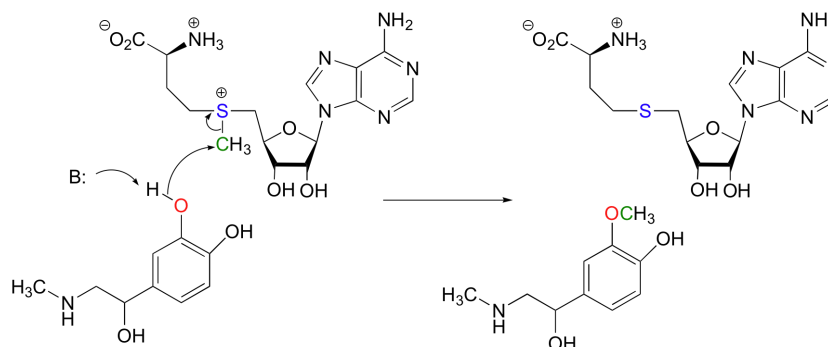
SAM methyltransferases

Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



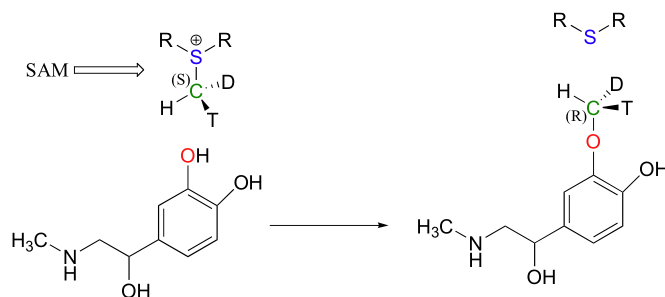
(*Nucleic Acids Res.* **2000**, 28, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1 -like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2 . Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^3H , T) and deuterium (^2H , D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an $\text{S}_{\text{N}}2$ displacement (*J. Biol. Chem.* **1980**, 255, 9124).

Example

Exercise 9.1: SAM is formed by a nucleophilic substitution reaction between methionine and adenosine triphosphate (ATP). Propose a mechanism for this reaction.

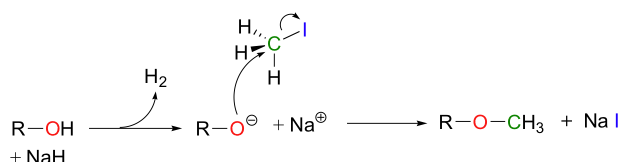
Solution



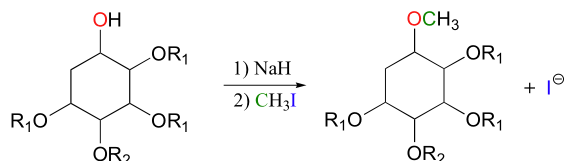
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([click for details](#))

9.1B: Synthetic parallel – the Williamson ether synthesis

Synthetic organic chemists often use reactions in the laboratory that are conceptually very similar to the SAM-dependent methylation reactions described above. In what is referred to as "O-methylation", an alcohol is first deprotonated by a strong base, typically sodium hydride (this is essentially an irreversible deprotonation, as the hydrogen gas produced can easily be removed from the reaction vessel).



The alkoxide ion, a powerful nucleophile, is then allowed to attack the electrophilic carbon in iodomethane, displacing iodide in an $\text{S}_{\text{N}}2$ reaction. Recall (section 7.3A) that iodide ion is the least basic - and thus the best leaving group - among the halogens commonly used in the synthetic lab. CH_3I is one of the most commonly used lab reagents for methyl transfer reactions, and is the lab equivalent of SAM. In the synthesis of a modified analog of the signaling molecule *myo*-inositol triphosphate, an alcohol group was methylated using sodium hydride and iodomethane (*Carbohydrate Research* **2004**, 339, 51):



Methylation of amines (N-methylation) by iodomethane is also possible. A recent study concerning the optimization of peptide synthesis methods involved the following reaction (*J. Org. Chem.* **2000** 65, 2309):

