Reaction of Iodoethane with Sodium Saccharin, an Ambident Nucleophile

Scenario

Saccharin is a nonnutritive sweetener, meaning that it is not metabolized by the body to produce energy. But saccharin is usually mixed with fructose or other Calorie laden sweeteners to mask its bitter aftertaste, giving the mixture about half as many Calories as sucrose and thus making it less attractive as a sugar substitute. Dulcinea Petty IV directs a product development team at Sweet Nothings Ltd., which manufactures saccharin. She has learned that substances with N—H bonds often have bitter tastes, so she wonders if converting the N—H bond of saccharin to an N—C bond by alkylating it will mask the bitter taste and thus yield a better sweetener. Saccharin is converted to its more nucleophilic sodium salt prior to alkylation, but resonance structures of the salt reveal that it is an ambident nucleophile; that is, it has two potentially nucleophilic atoms, the nitrogen atom and an oxygen atom.

Before their quest for a better sweetener can be pursued, Sweet Nothings needs to know whether or not alkylation will occur mainly on the nitrogen atom. Your assignment is to carry out the alkylation of sodium saccharin with iodoethane and analyze the product mixture to determine the structure of the major product.

Applying Scientific Methodology

The scientific problem can be stated as “Will the alkylation of sodium saccharin with iodoethane produce N-ethylsaccharin as the major product?” You will not taste the product, but you can ask your instructor about its taste after the experiment.

Saccharin, an Accidental Sweetener

One rule that most chemists follow scrupulously is to never, ever, taste anything they make in the laboratory. A chemist should not even eat or drink anything else while working in the lab because of possible contamination by toxic chemicals. During the nineteenth century, however, chemists were not so fastidious. It was a common practice to perform a “taste test” on any new chemical, sometimes with unfortunate results; but occasionally an accidental or deliberate tasting paid off with a new discovery.

Ira Remsen, a Johns Hopkins University chemistry professor, studied chemistry under a student of the “father of organic chemistry,” Friedrich Wöhler, and became the most famous American chemist of the nineteenth century. In 1878 a German student working in Remsen’s research group, Constantin Fahlberg, prepared some white crystals of a previously unknown compound from o-toluensulfonamide. He later ate a piece of bread and was astonished to find that it tasted intensely sweet. It didn’t take Fahlberg long to trace the sweet taste to the new compound he had just handled, which he named saccharin after the Latin word for sugar, *saccharum*.

Saccharin is about 500 times sweeter than sucrose, common table sugar. Its sweetness came as a surprise because no one was looking for a synthetic sweetener at the time—most scientists believed that only natural compounds could be sweet. Fahlberg recognized the commercial possibilities of a nonfattening sweetener, so he applied for a patent and began to manufacture saccharin. Despite its somewhat bitter aftertaste, saccharin was the most popular artificial sweetener during most of the twentieth century, outselling other synthetic sweeteners such as dulcin (from the Latin *dulcis*, meaning sweet), which was discovered just six years after saccharin.

Concerns about the safety of saccharin cropped up from time to time, inspiring Theodore Roosevelt to proclaim, “anyone who says saccharin is injurious to health is an idiot.” Roosevelt, who liked to sweeten his chewing tobacco with saccharin, was no authority on the safety of commercial products, but his words must have reassured many Americans about saccharin. Then in 1977 a Canadian study showed that some rats developed bladder tumors when they were fed a diet containing 5% saccharin. Although the rats’ diet was equivalent to a human consuming about 1000 cans of diet soda per day, saccharin was promptly removed from the GRAS (generally recognized as safe) list and later banned in the United States. Reacting to protests by diabetics and overweight Americans, for whom consuming sugar was a far greater health risk than the remote possibility of saccharin-induced cancer, Congress suspended the ban in 1979. As a result, you can still buy Sweet ‘n Low at your local grocery store, but the packets carry a mandatory warning label.

Because of the cancer scare and competition from aspartame (Nutrasweet), saccharin use has declined sharply in recent years. Lacking the bitter aftertaste of saccharin, aspartame has become our most popular artificial sweetener, but it may also face some tough competition before long. A French sweetener called superaspartame is 300 times sweeter than aspartame and—unlike aspartame—can be used in baking and frying. The natural sweetener thaumatin, which is extracted from the west African plant ketemfe, is reported to be nearly 100,000 times sweeter than sucrose, making it the sweetest natural substance ever discovered. It is also (like aspartame) a flavor enhancer, so it has been used to persuade farm animals to eat more—pigs gain up to 10 percent more weight when thaumatin is added to their feed!

**Understanding the Experiment**

In this experiment you will carry out the reaction of sodium saccharin with iodoethane in the solvent N,N-dimethylformamide (DMF). This is a nucleophilic substitution reaction in which the nucleophile atom can be either nitrogen or oxygen and the leaving group is iodide ion (I⁻). The rate of a nucleophilic substitution reaction can be very sensitive to the solvent used. Polar protic solvents (solvents capable of hydrogen bonding) such as water and ethanol form bulky solvation shells around a charged nucleophile, reducing its nucleophilic strength. Polar aprotic solvents such as DMF do not solvate the nucleophile strongly, leaving it free to attack the substrate. Thus they accelerate the rates of many substitution reactions, particularly *S_N2* reactions in which the strength of the nucleophile has a large effect on the reaction rate.
The composition of the product will depend on whether nitrogen or oxygen acts as the nucleophilic atom most of the time. As shown in the “Reactions and Properties” section, nucleophilic attack by nitrogen will yield N-ethlysaccharin, while nucleophilic attack by oxygen will yield O-ethlysaccharin. Predicting the major product is not easy because a number of competing factors may come into play. N-Ethlysaccharin is more stable than O-ethlysaccharin so it should be the major product if the reaction reaches thermal equilibrium. But the oxygen atom of sodium saccharin has a higher partial negative charge than the nitrogen atom (oxygen is more electronegative than nitrogen), so a reaction involving oxygen as the nucleophile might occur faster than one involving nitrogen. For example, the reaction of potassium saccharin with 2-bromopropane in N,N-dimethylformamide yields mainly O-isopropylsaccharin.

Reactions and Properties

Table 20.1 Physical properties

<table>
<thead>
<tr>
<th></th>
<th>M. W.</th>
<th>b. p.</th>
<th>m. p.</th>
<th>d</th>
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<tr>
<td>sodium saccharin</td>
<td>205.2</td>
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<tr>
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<td>156.0</td>
<td>72</td>
<td></td>
<td>1.950</td>
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<td>N,N-dimethylformamide</td>
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<tr>
<td>N-ethlysaccharin</td>
<td>211.2</td>
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<td></td>
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</tr>
<tr>
<td>O-ethlysaccharin</td>
<td>211.2</td>
<td></td>
<td>211</td>
<td></td>
</tr>
</tbody>
</table>

Note: m. p. and b. p. are in °C, density is in g/mL

Directions

This procedure is adapted from an article published in the Journal of Chemical Education, 1990, 67, 611.

Safety Notes

Iodoethane severely irritates the eyes, skin, and respiratory tract and it may be carcinogenic. Wear gloves to avoid contact and do not breathe vapors.

N,N-Dimethylformamide is harmful by inhalation, ingestion, and absorption through the skin. Avoid contact, do not breathe vapors.

Deuterocloroform is harmful by ingestion, or absorbed through the skin, and it may be carcinogenic. Avoid contact and do not breathe vapors.
Take Care! Avoid contact with DMF, do not breathe its vapors.

Take Care! Wear gloves, avoid contact, do not breathe vapors.

Take Care! Do not taste the product.

Waste Disposal: Put the filtrate in a designated solvent recovery container.

Stop and Think: Is the product a single compound or a mixture? How can you tell?

Reaction. Carry out the reaction under the hood. Weigh out 10.0 mmol of sodium saccharin and add it to 5.0 mL of N,N-dimethyl formamide in a 125-mL Erlenmeyer flask. Heat the mixture in an 80°C water bath with swirling until the solid dissolves, then add 0.80 mL (~10 mmol) of iodoethane using a dispenser or an automatic pipet. Seal the flask with Parafilm and heat the mixture in the water bath for 10 minutes, keeping the temperature around 80°C.

Separation. Let the reaction mixture cool to room temperature, add 75 mL of water, and shake the stoppered flask until any liquid residue that forms has solidified. Cool the flask in an ice water bath, break up the solid with a stirring rod if necessary, and collect the product by vacuum filtration [OP-12], washing it twice with 5-mL portions of cold water.

Analysis. Dry the product and measure its mass and melting point range. You should also obtain an IR spectrum of your isolated compound. How/what will help in the IR to correctly assign the major product?
One objection raised to the use of aspartame is that it decomposes in the presence of moisture to produce phenylalanine, which must be avoided by people who have the genetic condition phenylketonuria, and methanol, which can have an effect on mental behavior. Write an equation for the hydrolysis of aspartame yielding both of these products.

(a) Assuming that the reaction was $S_N2$ and that the major product was the one that formed faster, which atom appears to be more nucleophilic, N or O? (b) Write a mechanism showing the transition state of the reaction that led to your major product.

Most compounds containing N—H bonds are basic but saccharin is acidic. Explain why, using resonance structures.