

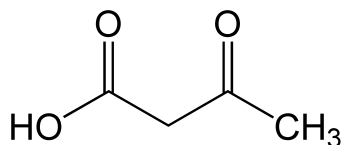
### Group Exercise

(adapted from Henderson (1998) *Biochemical Education* 26: 141-142.)

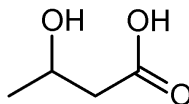
Diabetes mellitus affects 2-3% of people in many populations, close to 8% in the US. It is one of the top 10 causes of death in this country. The disease was described as early as the 2<sup>nd</sup> century: "Diabetes is a remarkable disorder. It consists of a moist and cold wasting of the flesh and limbs into urine... The disease is chronic in nature and is slowly engendered, though the patient does not survive long when it is completely established.." (Aretaeus)

Animals, including household pets, can also suffer from diabetes. Consider the case of a pet Schnauzer. She had been a normal, fun-loving and loyal dog, a bit overweight. Recently, she had begun to urinate often and drink water more frequently and in larger quantities. She was losing weight and acting lethargic.

Sometimes she seemed disoriented and unsteady on her feet. It was on one such occasion, when she also experienced unusual breathing, that the dog was rushed to the vet. It was determined that she had excessive glucose in her urine, her breath smelled sweet, and she was dehydrated. Lab tests confirmed that she was suffering from diabetes. Her blood pH was low, glucose concentrations high, osmolarity high, and ketone concentrations high. She was placed on insulin injections and her owners given instructions to feed her small, regular meals avoiding simple sugars.



acetoacetic acid



$\beta$ -hydroxybutyric acid

1. Shown above are acetoacetic acid and  $\beta$ -hydroxybutyric acid. These substances are among the ketone bodies, generated during ketosis.

a.) These compounds are moderately strong acids, stronger than acetic acid,  $\text{CH}_3\text{COOH}$ . The  $\text{pK}_a$  of acetic acid is 4.75. Will the  $\text{pK}_a$  of these acids be greater or less than 4.75? Why should these be stronger acids than acetic acid?

b.) Look at the structure of acetoacetate. Where would a nucleophile react with it?

c.) In the metabolic reactions,  $\beta$ -hydroxybutyrate is converted to acetoacetate.

What kind of reaction is this?

2. One of the major buffer systems in the body is the bicarbonate system. It is governed by the following equilibria:



Predict what will happen to these equilibria when acetoacetic acid and  $\beta$ -hydroxybutyric acid increase during ketosis.

3. One of the dog's symptoms was deep, rapid breathing. Use the information in the case and the equilibria in question #2 to explain why this symptom was observed.
4. Why should high blood glucose levels result in withdrawal of water from cells and thus cause the symptoms of excessive thirst, excessive dehydration and excessive urination?