Potassium Hydrogen Malonate: Remarkable Crystal and Molecular Structure

Abstract. *X-ray crystallographic investigations of potassium hydrogen malonate crystals reveal a very unusual structure in which malonic acid molecules and doubly ionized malonate ions exist in equal numbers. These two species are connected by strong hydrogen bonds in one direction and by potassium ions in the other directions. This seems to be the first observation of the simultaneous presence in a crystal of the two species dicarboxylic acid molecules and their doubly charged ions.*

Recent studies (*1*) of potassium hydrogen malonate crystals ($KC_3O_4H_3$) using electron spin resonance techniques revealed a very unusual electron spin resonance spectrum. These studies indicate that there is dipole-dipole coupling between pairs of radicals. In order to facilitate the understanding of these electron spin resonance spectra, a detailed x-ray study of the crystal structure of potassium hydrogen malonate was undertaken.

The crystal structure was solved with the use of approximately 860 x-ray reflections. The crystallographic data (*2*) for potassium hydrogen malonate are: monoclinic, C2, a = 9.477 (±.002) Å, b = 11.561 (±.002) Å, c = 4.730 (±.002) Å, $\beta = 91.45°$ (±.04°) T (°C) = 22° (±3°), Z = 4, density = 1.81, observed (1.82 calculated) g/cm^{-3}, MoKα = 0.7093 Å. A General Electric XRD-6, equipped with a scintillation counter and MoKα radiation, monochromatized by a balanced pair of Zr and Y Ross filters, was used for the intensity measurements. The positions of the K atoms were obtained from the Harker section Y = 0 of the three-dimensional Patterson function, and the structure was solved by the heavy atom method. The structure was refined by the least-squares technique, including individual anisotropic thermal parameters. Electron density difference maps were used to obtain the positions of hydrogen atoms. The present value of the residual R is 0.07.

From the density measurements it was expected that one asymmetric unit of the cell would contain one K^+ atom and one molecule of $COO^-{\cdot}CH_2{\cdot}COOH$. Actually, it was found that the asymmetric unit contains one half of a malonic acid, $COOH{\cdot}CH_2{\cdot}COOH$ molecule and one half of a doubly ionized malonate ion $COO^-{\cdot}CH_2{\cdot}COO^-$, in addition to the one K^+ ion. The malonic acid molecule, and the doubly ionized malonate ion, are located on twofold axes (see Fig. 1). The bond distances indicate that molecule A (Fig. 1) is the un-ionized malonic acid molecule and that molecule B is the doubly ionized malonate ion.

These conclusions are primarily based on the carboxyl C–O distances, unequal in the un-ionized carboxyl groups and nearly equal in the ionized. It is found that, in addition to the differences in the carboxyl groups, the molecules A and B also differ in other aspects. For example, C(1)–C(2) is 1.559 ± 009 Å, whereas C(3)–C(4) is 1.498 ± 008 Å; also, the angles C(2)–C(1)–C(2′) and C(3)–C(4)–C(3′) are different (Fig. 1). The primes in C(2′) and C(3′) denote that these atoms are related to C(2) and C(3) by a twofold rotation axis.

The two species, namely, the malonic acid and the malonate ions, are strongly linked together by a strong hydrogen bond of length 2.461 (±.006) Å. The hydrogen atom H(3) has not been quite well located in the electron density difference map, although the hydrogen atoms H(1) and H(2) could be fixed more easily. At the expected position of H(3) between the O(1) and O(4) rather diffuse cloud of electron density.

The K^+ atom has an eightfold coordination. The ligand distances are, respectively, 2.735 Å to O(1), 2.904 Å, 2.801 Å, 2.827 Å to the O(2) atoms (*3*), 2.862 Å, 2.921 Å, 2.802 Å to the O(3) atoms (*3*), and 2.807 Å to O(4).

Note added in proof: Another crystal structure determination of potassium hydrogen malonate by G. Ferguson, J. G. Sime, J. C. Speakman, and R. Young has recently appeared in *Chem. Commun.* (1968), p. 162. In

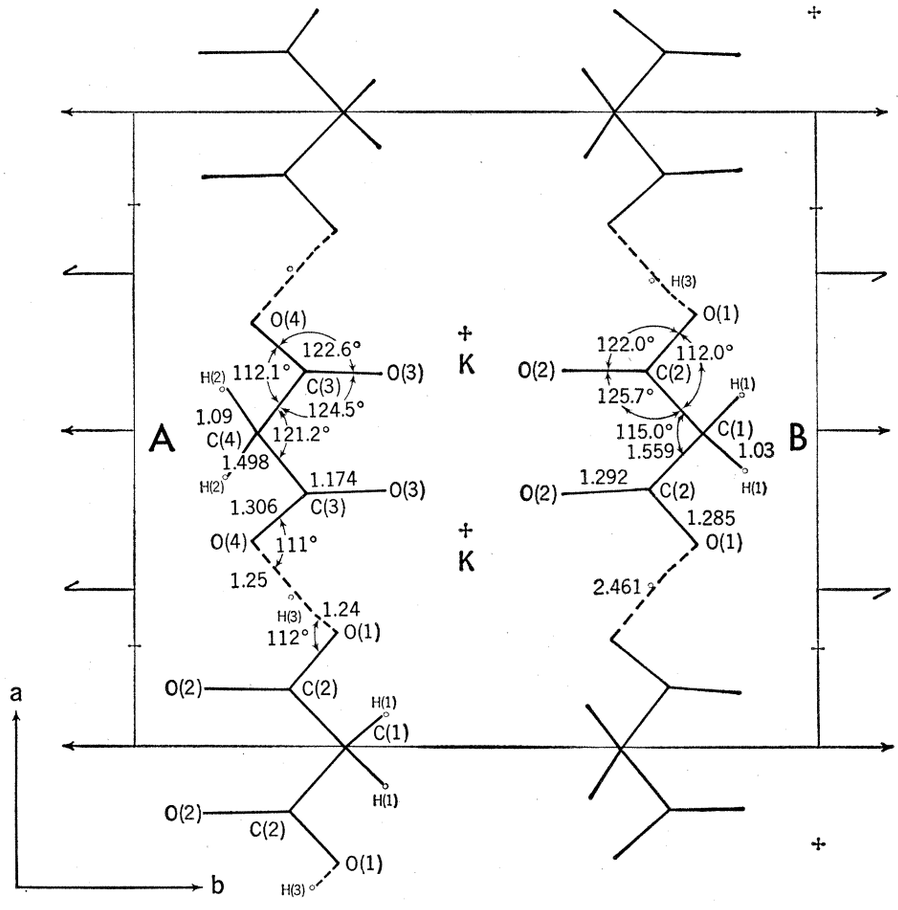

Fig. 1. A projection of the crystal structure of potassium hydrogen malonate on the *ab* plane. The malonic acid molecule is denoted by A and the doubly charged malonate ion is denoted by B. Molecules A and B are linked by a strong hydrogen bond across O(4)—O(1) in one direction and are connected by K^+ ions in other directions.

this work, the structure is solved by using the space group $C2/m$, and the atomic coordinates are nearly equal to the average values of the corresponding quantities of the two molecules A and B.

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References and Notes

1. H. C. Box, private communication.
2. Crystallographic data are in agreement with those reported by M. P. Gupta and W. H. Barnes, *Can. J. Chem.* **34**, 563 (1956).
3. In these cases, three oxygen atoms of the same kind, but from different asymmetric units, are in contact with the same K^+.
4. I thank Professor D. Harker for enlightening discussions. Financial support by NIH-A-3942 and NSF-GB-4056 is gratefully acknowledged. A complete description of the structure determination is in preparation.

12 March 1968

Aspirin: Action on Receptor in the Tooth

Abstract. *Impulse frequency recorded from dentinal receptors in the cat's tooth provided an indication of sensory excitation. Topical application of aspirin to the dentin promptly inhibited both steady-state discharge and response to a brief heat stimulus. When the drug was washed out, the initial excitability was restored in 15 minutes.*

The control or reduction of pain through ingestion of aspirin is a common observation, but its site of action has long been a matter of debate. If its action were primarily peripheral, it would be expected to decrease the excitability of the receptor structure which originates the "pain" signal or to increase selectively the threshold of those fibers which conduct nerve impulses from such receptors. Recent study of the dentinal receptor in the tooth has made possible the clear demonstration of the action of aspirin on the peripheral receptor.

The sensation aroused by excitation of the tooth with thermal, tactile, or chemical stimuli has been described by many investigators as primarily painful in character. Although pain may mask other modalities present in lesser degree, there is little evidence to support such a concept and there is little doubt that pain is the primary conscious response. The electron-microscopic study of the ultrastructure of a gradually tapering sensory nerve terminal located within the dentinal canal has been described by Frank (*1*), who observed the terminals to extend beyond the predentin and for short distances into the calcified portion of the dentinal tubule in human teeth. Our electrophysiologic evidence indicates the presence of single receptors distributed infrequently in the dentin of the canine teeth of cats, which respond to stimulation by heat, cold, distortion, and certain chemical agents (*2*). The fact that the electrical signals from these receptors could be obtained only when the recording electrode was between 0.15 and 0.20 mm from the pulp strongly suggests an identity between these units and those described by Frank. Reflex aversive movements of the tongue could be elicited by moderate stimulation of these receptors involving any one of these methods. Stimulation of these receptors probably gives rise to the sensation of pain in the animal.

Experiments were conducted on the canine teeth of cats, whose sensory axons follow the axis of the pulp and, turning abruptly, reach the odontoblast layer, where they branch extensively. Such a terminal branch may then enter a dentinal canal (*1*). No great differences exist in the sensory innervation of mammalian teeth except for those which are continuously erupting, as in rodents. Two cavities were prepared on the lateral aspect of the tooth to overlie the pulp and were separated by 2 to 5 mm. The cavity nearest to the incisal tip was placed in the close vicinity of the pulpal horn where the maximum number of receptors had previously been demonstrated by microapplication of acetylcholine (*3*). Records obtained from silver–silver chloride saline agar electrodes placed in such cavities have shown potentials originating from one to three receptors (*2*, *4*), this result being attributable to the fact that all dentinal receptors are located within dentinal tubules.

Amplification of these potentials by a Grass P-6 preamplifier, followed by a trigger circuit and an Atomic rate meter, provided a continuous record of discharge frequency while visual presentation and photography of the amplified impulse on a Tektronix 565 oscilloscope monitored the identity of the discharging unit. The frequency of impulse discharge is closely related to temperature (*2*). Therefore, the temperature of the bottom of the cavity nearest to the receptor was continuously recorded, and the ambient temperature was maintained by a heat lamp directed at the oral cavity.

This method (*3*) provides a continuous comparison of receptor temperature and discharge frequency. Thermal stimuli consisting of pulses of heat lasting 10 seconds were delivered at intervals by a coil of fine Nichrome wire, 1 mm in diameter, placed 2 mm from the surface of the tooth opposite the incisal electrode. Such pulses raised the temperature of the receptor several degrees Celsius and increased the discharge frequency to more than double its resting value, thus providing a quantitative indication of the irritability of the receptor. Aspirin was applied directly to the incisal cavity in droplets (1 μl) containing 40 ng of unhydrolyzed aspirin in normal Ringer solution.

The steady-state discharge of the dentinal receptor is influenced by its temperature (normal being approximately 34°C). If constant temperature is maintained during cavity preparation with a constant flow of Ringer solution at 39°C over the bur (to offset evaporative cooling), a steady discharge of 10 per second is most frequently obtained, but higher or lower frequencies are not infrequent, depending on conditions of preparation. Since my study concerned a depression of receptor response, a higher initial frequency was desired, and this was obtained by the addition of occasional small (1 μl) single drops of isotonic sodium citrate. The irritability of the receptor as a function of its initial frequency does not distinguish between receptors which have been bathed only with Ringer and those to which a few small drops of citrate have been added to increase their resting excitability.

In a typical experiment (Fig. 1) a steady-state discharge frequency of 20 to 30 per second was obtained, and a 10-second heat pulse was administered to provide a measure of the irritability of the receptor. The maximum frequency observed after the heat stimulus was 73 per second. For the next 2 minutes, both temperature and frequency returned toward their initial values.

At the end of this period, 1 μl of aspirin solution was applied to the incisal cavity between the plastic capillary of the electrode and the dentinal wall. The evaporative cooling resulting from this droplet reduced the temperature to approximately its initial value. The receptor discharge responded to the as-