ered *credible* by a person of ordinary skill in the art" (emphasis in the original). In addition, the guidelines counsel examiners to accept an expert's credible statements that support patentability unless the examiner "can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements." In legal effect this means that the examiner must show that such a one would be more likely to disbelieve than to believe the asserted utility.

Commissioner Bruce Lehman is to be congratulated for taking prompt action to ensure that biotechnology patent applications will now be judged by the same legal standards of utility that are applied to patent applications in other technical fields.

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Low-Barrier Hydrogen Bonds

In our report of 24 June 1994 (p. 1927), Sean A. Whitt, John B. Tobin, and I (*1*) described the spectroscopic evidence implicating a low-barrier hydrogen bond (LBHB) linking $N^{\delta 1}$ of His^{57} with the β-carboxyl group of Asp^{102} in the protonated triad of chymotrypsin. We further described a first approximation to a chemical model for this LBHB. After noting the spectroscopic evidence for an LBHB in a close model of the tetrahedral intermediate in chymotrypsin (*2*), we postulated a mechanism in which the LBHB linking the dyad His^{57} and Asp^{102} facilitates the nucleophilic addition of the β-OH group of Ser^{195} to a substrate by stabilizing the dyad on the enzymatic side of the tetrahedral intermediate. To the extent that the transition state resembles the intermediate, its energy would be lowered by this interaction and the rate would be enhanced.

Richard L. Schowen has pointed out that he and his associates earlier suggested the participation of strong hydrogen bonds in "catalytic proton bridges" that facilitate multiproton catalysis by serine proteases [*3* (p. 119), *4*]. It is true that Showen and his colleagues speculated on the possible importance of "Kreevoy-type" hydrogen bonds in multiproton catalysis. Their suggestions differed from our postulate, however, in several respects. First, they emphasized the possibility that strong hydrogen bonds in putative hydrogen bonding networks might stabilize the transition state as distinguished from the intermediates. Second, they consistently suggested the simultaneous participation of more than one strong hydrogen bond. They did not specify the positions of strong hydrogen bonds, but included the hydrogen bond bridging Asp^{102} and His^{57} in the putative network. Third, their suggestions were inspired by the observation of small isotope effects, which are consistent with, but do not specifically implicate, strong hydrogen bonds.

In this connection, G. Robillard and R. G. Shulman, who described the low-field proton in the catalytic triad and assigned it to $His^{57}(N^{\delta 1})$–Asp^{102} (*5*), later suggested that a hydrogen bond linking $His^{57}(N^{\epsilon 2})$ with the leaving group in a tetrahedral intermediate might be characterized by a single minimum potential, that is, it might be a single-well hydrogen bond (*6*). This suggestion arose from studies of boronate inhibitors. Our postulate is not related to this latter suggestion.

The main purpose of our report was to point out that LBHB's are characterized by spectroscopic signatures, including a low-field nuclear magnetic resonance chemical shift; that a low-field proton appears in the protonated catalytic triad, as well as in a tetrahedral adduct of chymotrypsin with *N*-acetyl-L-Leu-L-Phe trifluoromethylketone and in a simple model for the dyad; that the low-field proton in chymotrypsin exhibits a deuterium isotope effect that is characteristic of protons participating in low-barrier hydrogen bonds; and that the participation of this low-barrier hydrogen bond in catalysis can resolve a long-standing controversy regarding the mechanism of action of serine proteases.

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