

# Correlation between Chemical Reactivity and the Hammett Acidity Function in Amorphous Solids Using Inversion of Sucrose as a Model Reaction

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**ABSTRACT:** The goal was to evaluate the effects of acidity, expressed as the Hammett acidity function, on chemical reactivity in freeze-dried materials (lyophiles). Dextran–sucrose–citrate and polyvinyl pyrrolidone (PVP)–sucrose–citrate aqueous solutions, adjusted to pH values of 2.6, 2.8, and 3.0 were freeze dried, and characterized by X-ray powder diffractometry, DSC, isothermal microcalorimetry, and Karl Fischer titrimetry. Lyophiles were also prepared from identical solutions but containing bromophenol blue (BB). Diffuse reflectance-visible spectroscopy was used to measure the extent of BB protonation from which the Hammett acidity functions were determined. The stability studies were performed at 60°C. All the freeze-dried samples were observed to be X-ray amorphous with <0.15% w/w water content. The  $T_g$  of dextran lyophiles were approximately 20°C higher than that of PVP lyophiles whereas enthalpy relaxation rates at 60°C were similar. The Hammett acidity functions were significantly lower (i.e., higher acidity) for dextran systems (<2.2–2.6) when compared with PVP systems (3.3–3.9). The rate of sucrose inversion was significantly (an order of magnitude) higher in dextran lyophiles. This study showed that in amorphous matrices with comparable water content and structural relaxation times, chemical reactivity could be significantly different depending on the matrix “acidity”. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 97:274–286, 2008

**Keywords:** sucrose inversion; solid state stability; Hammett acidity function; freeze-drying; amorphous; glass transition; UV/Vis spectroscopy; relaxation time

## INTRODUCTION

Amorphous organic materials are ubiquitous in both natural (e.g., dehydrated drought- and frost-

resistant organisms) and man-made (e.g., dried pharmaceuticals and biopharmaceuticals) systems. For example, dehydration of aqueous solutions of sugars and other organic solutes by freeze-drying (lyophilization) usually results in partially or completely amorphous materials. Glasses, at temperatures far below their glass transition temperatures ( $T_g$ ), usually exhibit very low molecular mobility. This has been believed to be responsible for the low rates of physical as well as chemical processes such as crystallization and decomposition.<sup>1–4</sup> In spite of the low molecular mobility, the rates of these processes are not negligible in the time scales of interest, in particular during the

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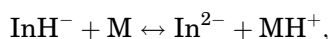
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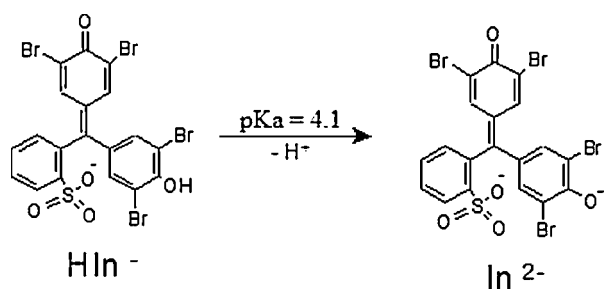
shelf-life of amorphous pharmaceutical products. The reactivity in amorphous systems has been typically correlated with molecular mobility, a reasonable expectation in diffusion-controlled processes. Recently, however, it has been shown that the reaction rates in some systems are significantly higher than would be expected for diffusion-controlled processes.<sup>5</sup> Also, degradation of a protein, insulin, appears to be unaffected by molecular mobility of the matrix under certain conditions.<sup>6-8</sup> To understand the apparent lack of correlations between molecular mobility and chemical reactivity observed in some systems, it has been suggested that other factors need to be considered based on a traditional physical organic chemistry approach. In particular, it has been proposed that medium effects, for example, matrix polarity may influence chemical reactivity in amorphous systems.<sup>9</sup> Furthermore, since many chemical processes are mediated by proton transfer, the matrix proton activity could be a critical determinant of reaction rates in amorphous systems.

A direct measurement of proton activity in solid systems is challenging. It has been proposed recently that acid–base relationships in lyophilized amorphous systems can be studied using pH indicators as probes for determining the Hammett acidity function.<sup>10,11</sup> This approach has found extensive use for measuring acidity in nonideal systems.<sup>12,13</sup> For a weakly acidic indicator, for example, a sulphonphthalein dye, the proton transfer equilibrium reaction in a matrix M can be written as below (see also Scheme 1).



and the Hammett function can be expressed as follows (Eq. 1)

$$H_{2-} = -\log_{10} \left[ a_{\text{H}^+} \frac{f_{\text{In}^{2-}}}{f_{\text{InH}^-}} \right] = \text{p}K_a + \log_{10} \frac{c_{\text{In}^{2-}}}{c_{\text{InH}^-}} \quad (1)$$



**Scheme 1.** Ionization of bromophenol blue indicator.

Here  $c$ ,  $f$ , and  $a$ , represent concentration, activity coefficient, and activity respectively, and  $K_a$  is ionization constant of the indicator. For an ideal solution, when the ratio of activity coefficients is unity, Eq. 1 is reduced to the Henderson–Hasselbalch equation. As the systems deviate from ideality, the ratio of the activity coefficients can no longer be assumed to be unity.

The Hammett acidity function has been extensively used as a measure of medium properties which influence acid–base catalyzed reactions. For example, Hammett acidity function is applied to express surface acidity and catalytic activity of solid acids in heterophase hydrocarbon reactions<sup>14</sup> to describe hydrolysis of carbohydrate derivatives in aqueous acidic solutions<sup>15</sup> and the rate of oxidation of substituted acetic acid by hydrogen peroxide in nonaqueous media.<sup>16</sup> Probe molecules have been used extensively to characterize a variety of systems, for example to study acid–base relationships in concentrated acids and nonaqueous systems<sup>13,17,18</sup> as well as to evaluate Bronsted acidity of solid surfaces.<sup>19,20</sup>

In this study, we have investigated matrix effects on the chemical reactivity in organic glasses. Sucrose inversion, an acid-catalyzed reaction with a well-understood mechanism, was the model system. This reaction involves a rapid preequilibration protonation step leading to the formation of protonated sucrose. This is followed by a unimolecular rate determining splitting of the glycosidic bond. Glycosyl-oxygen cleavage will produce fructose and protonated glucose, whereas fructosyl-oxygen cleavage will produce glucose and protonated fructose.<sup>21</sup> Both processes occur in solution.<sup>22</sup> Water does not participate as a direct reactant in sucrose cleavage but plays a role in the conversion of the carbonium ions (protonated fructose or glucose) into neutral monosaccharides in the final step.

Our overall objective was to correlate chemical reactivity in amorphous lyophiles with the Hammett acidity function using sucrose inversion as the model reaction. Two common polymers, dextran and polyvinyl pyrrolidone (PVP), were used as amorphous matrices. The influence of two matrix properties, that is, molecular mobility and Hammett acidity function, on the sucrose inversion kinetics was evaluated.  $T_g$  and enthalpic relaxation were used to express mobility, while the Hammett acidity function was calculated from the extent of protonation of a probe molecule. Both dextran and PVP are expected to form a single amorphous phase with sucrose in a broad

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