were located did not usually manifest degenerative changes. It is conceivable, nevertheless, that interactions between virus and cell membrane may have induced the formation of accessible, abnormal beta cell immunogenic proteins responsible for the initiation of a cell-mediated immune response (*15*).

Pancreatic insulitis was reported in experimental virus-induced diabetes (*16*), in juvenile diabetics autopsied shortly after onset of clinical symptoms (*17*), and in rare examples of maturity-onset diabetes (*18*). A chronic inflammatory cell infiltrate within the islets of Langerhans was also described after unsuccessful attempts to produce an immune-type diabetes (*19*).

Of independent significance, however, is the observation that SZ, a beta cell toxin, is apparently responsible for the activation of virus replication in mouse beta cells. The genome of the mouse type C virus is present in most if not all strains of laboratory and wild mice (*20*). Furthermore, structures resembling type C virus particles have been observed in the beta cells of certain inbred mice (*21*). 5′-Bromodeoxyuridine and 5′-iododeoxyuridine induce viral genome activation in vitro (*22*), and activation of mouse leukemia virus is induced in vivo by x-irradiation, chemical carcinogens, and steroid hormones (*23*). This report of virus activation in vivo by SZ is important because of the drug's occasional clinical use in the treatment of neoplastic disease. This finding is of more than theoretical importance when one considers the oncogenic potential of SZ (*2*).

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References and Notes

1. J. S. Evans, G. C. Gerritsen, K. M. Mann, S. P. Owen, *Cancer Chemother. Rep.* **48**, 1 (1965); I. M. Murray-Lyon, A. L. Eddleston, R. Williams, M. Brown, B. M. Hogbin, A. Bennett, J. C. Edwards, K. W. Taylor, *Lancet* **1968-II**, 895 (1968); R. W. DuPriest, Jr., M. C. Huntington, W. H. Massey, A. J. Weiss, W. L. Wilson, W. S. Fletcher, *Cancer* **35**, 358 (1975).
2. R. N. Arison and E. L. Feudale, *Nature (London)* **214**, 1254 (1967); N. Rakieten, B. S. Gordon, D. A. Cooney, R. D. Davis, P. S. Schein, *Cancer Chemother. Rep.* **52**, 563 (1968); N. Rakieten, B. S. Gordon, A. Beaty, D. A. Cooney, R. D. Davis, P. S. Schein, *Proc. Soc. Exp. Biol. Med.* **137**, 280 (1971).
3. N. Rakieten, M. L. Rakieten, M. V. Nadkarni, *Cancer Chemother. Rep.* **29**, 91 (1963).
4. P. S. Schein, R. Kahn, P. Gorden, S. Wells, V. T. DeVita, *Arch. Intern. Med.* **132**, 555 (1973).
5. A. Junod, A. E. Lambert, L. Orci, R. Pictet, A. E. Gonet, A. E. Renold, *Proc. Soc. Exp. Biol. Med.* **126**, 201 (1967); G. Brosky and J. Logothetopoulos, *Diabetes* **18**, 606 (1969).
6. L. Orci, M. Amherdt, W. Stauffacher, A. A. Like, C. Rouiller, A. E. Renold, *Diabetes* **21** (Suppl. 1), 326 (1972); L. Orci, F. Malaisse-Lagae, M. Ravazzola, W. J. Malaisse, A. Perrelet, A. E. Renold, *Lab. Invest.* **34**, 451 (1976).
7. A. Junod, A. E. Lambert, W. Stauffacher, A. E. Renold, *J. Clin. Invest.* **48**, 2129 (1969).
8. Each of the five daily injections consisted of 25 percent of the dose of SZ (160 mg/kg) required to induce severe and lasting hyperglycemia when administered as a single injection. Streptozotocin was from lot No. 10508-GGS-37A, a gift of W. E. Dulin of the Upjohn Company.
9. A. A. Rossini, M. Berger, J. Shadden, G. F. Cahill, Jr., *Science* **183**, 424 (1974).
10. R. G. D. Steel and J. H. Torrie, in *Principles and Procedures of Statistics* (McGraw-Hill, New York, 1960), p. 173.
11. A. A. Like and L. Orci, *Diabetes* **21** (Suppl. 2), 511 (1972).
12. Results of intravenous and intraperitoneal injections were essentially equivalent. Only the data from animals given intraperitoneal injections are presented.
13. Mean plasma glucose values for mice receiving citrate buffer alone were 175 to 185 mg/100 ml; those for mice receiving a single injection of SZ (200 mg/kg) were greater than 500 mg/100 ml within 48 hours.
14. We thank A. F. Gazdar of the National Cancer Institute for advice and invaluable assistance in the ultrastructural identification of the type C viruses.
15. G. J. Todaro, *Am. J. Pathol.* **81**, 590 (1975).
16. J. E. Craighead and M. F. McLane, *Science* **162**, 913 (1968); K. F. Wellmann, D. Amsterdam, P. Brancato, B. W. Volk, *Diabetologia* **8**, 349 (1972); H. Münterfering, *Virchows Arch. A* **356**, 207 (1972).
17. W. Gepts, *Diabetes* **14**, 619 (1965).
18. P. M. LeCompte and M. A. Legg, *ibid.* **21**, 762 (1972).
19. A. E. Renold, J. S. Soeldner, J. Steinke, *Ciba Found. Colloq. Endocrinol.* **15**, 122 (1964); P. E. Lacy and P. H. Wright, *Diabetes* **14**, 634 (1965); J. Logothetopoulos and E. G. Bell, *ibid.* **15**, 205 (1966); G. Freytag and G. Klöppel, *Beitr. Pathol. Anat. Allg. Pathol.* **39**, 138 (1969).
20. For a comprehensive review, see: P. S. Sarma and A. F. Gazdar, *Curr. Top. Microbiol. Immunol.* **68**, 1 (1974).
21. A. A. Like and W. L. Chick, *Diabetologia* **6**, 216 (1970).
22. D. R. Lowy, W. P. Rowe, N. Teich, J. W. Hartley, *Science* **174**, 155 (1971); V. Klement, M. O. Nicolson, R. J. Huebner, *Nature (London) New Biol.* **234**, 12 (1971).
23. R. J. Huebner and G. J. Todaro, *Proc. Natl. Acad. Sci. U.S.A.* **64**, 1087 (1969); G. J. Todaro and R. J. Huebner, *ibid.* **69**, 1009 (1972); C. E. Whitmire, R. A. Salerno, L. S. Rabstein, R. J. Huebner, H. C. Turner, *J. Natl. Cancer Inst.* **47**, 1255 (1971); A. Hellman and A. K. Fowler, *Nature (London) New Biol.* **233**, 142 (1971).
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Alternative Transformation Behavior in Sulfides: Direct Observations by Transmission Electron Microscopy

Abstract. *Structural phase transformations in Ni_7S_6 and Cu_7S_4 have been observed dynamically by in situ experiments in a transmission electron microscope. In this way it is possible to demonstrate the possibility of two fundamentally different types of behavior: (i) the ideal transformation from the stable high-temperature form to the stable low-temperature form and vice versa and (ii) alternative metastable processes which operate when the formation of the low-temperature state is impeded.*

The process of inversion from a high-temperature to a low-temperature form is of considerable importance for an understanding of the behavior of crystalline phases. In particular, the situation can arise when the kinetics of the process are such that the formation of the low-temperature form is impeded and hysteresis is introduced, or in the extreme case when the low-temperature form is inaccessible. Although the existence of a metastable, high-temperature polymorph is not uncommon, in some cases processes may operate to reduce the free energy of the system by the formation of some modification of the high-temperature form. These alternative processes lead to structural forms which do not have a stability field at any temperature and whose modes of behavior are determined by the kinetics of the processes involved rather than by thermodynamic considerations alone. Such alternative states may persist for long periods of time and have been shown to be fundamental to a description of the transformation behavior of a number of silicate systems (*1*). In this report I describe experiments in which both the ideal and the alternative behavior can be observed dynamically and the course of the transformations can be directly controlled by variations in the experimental conditions.

Structural phase transformations in a number of sulfides occur at rates which make direct observation possible in a transmission electron microscope (TEM). The transformations are induced by electron beam heating, and the temperature of an individual crystal fragment is controlled by focusing and defocusing or by lateral shifts of the beam, although the temperature cannot be directly measured in this way. Further details of the experimental method are described elsewhere (*2*). The ability to observe these transformations directly makes it possible to examine the ideal and the alternative behavior separately and to study the conditions operative in each case independently. Such information is not readily obtainable by other means, and the method leads to a rigorous definition of the transformation behavior of a material as a function of cooling history.

Several sulfides with known high- and low-temperature polymorphs were investigated, and their modes of behavior were studied dynamically as a function of temperature. The behavior of two of these polymorphs is briefly described here to illustrate the conditions under which ideal and alternative processes take place.

The nickel sulfide Ni_7S_6 (godlevskite) undergoes a high-low transformation at 400°C (*3*). The structure of the high-temperature form has been determined (*4*); although the structure of the low-temperature form is not known, initial investigations suggest that the nickel coordination changes (*5*) and hence a reconstructive transformation must take place between the two forms. In bulk specimens this transformation is sluggish but can be observed dynamically in small grains in the TEM. The hysteresis is appreciable, as would be expected for a reconstructive transformation, but, if the grain is quenched, a sufficient amount of supercooling is achieved to cause the abrupt formation of the low-temperature form. The reverse transformation to the high-temperature form takes place on heating.

If the high-temperature form is cooled slowly below the transformation temperature, conditions are produced where, although the low-temperature form is stable, its formation is impeded by insufficient supercooling and hence provides a small driving force for the transformation. Under these conditions the high-temperature form can be observed to undergo a series of structural modifications leading to the formation of successively larger superstructures. Details of these superstructures, all modifications of the high-temperature structure, have been published elsewhere (*2*), but the important point is that the formation of the superstructure phases is an alternative metastable process and these phases do not have a stability field at any temperature. The conditions under which they form as well as the fact that the low-to-high Ni_7S_6 transformation does not involve the formation of these superstructures as intermediates confirm the metastability of these superstructure phases.

The second example chosen to illustrate alternative behavior is the transformations of the copper sulfide Cu_7S_4 (anilite). Earlier investigators (*6*) have shown that anilite is a stable phase at room temperatures, but that above 70°C the low-temperature cubic form of digenite is stable. At a slightly higher temperature, 76° to 83°C depending on the exact composition, low digenite inverts to a high-temperature cubic form. This series of transformations has been observed dynamically with the same methods as for Ni_7S_6, but with a smaller condenser aperture to keep the heating effect of the electron beam low.

On heating anilite in the beam, a discontinuous transformation directly to high digenite occurs. When this phase is cooled by rapidly moving the beam off the grain, anilite is again formed by an abrupt process. However, if this cooling is carried out slowly, a superstructure based on the high-temperature digenite phase is formed. This superstructure with cell edge $6a$ (a is the cell edge of high digenite) is the low digenite phase referred to above. Careful cycling of the specimen through these transformations has shown that high digenite and anilite have stability fields, but that the formation of low digenite must be regarded as alternative metastable behavior operating under conditions when the transformation to anilite is impeded. In other words, low digenite is not a stable phase in the Cu-S system. This conclusion is based on the evidence that the transformation from anilite to high digenite does not have low digenite as an intermediate product and also on the fact that the formation of low digenite can be equated with a small degree of supercooling.

The possibility that the metastable alternative states described here could have a narrow stability range, and that a transformation from the stable low-temperature phase to the stable high-temperature phase could "jump over" such a narrow stability range has been considered. It is, however, unlikely that, if such a stability range existed, it has never been observed in a low-to-high transformation despite efforts to carry out the transformation by very slow heating. The reproducibility of the transformation behavior over many heating and cooling cycles indicates that the transformations are polymorphic and that compositional changes, such as sulfur loss, do not occur.

The recognition of two broad classes of behavior in these sulfides has a number of important implications for the study of sulfide phase equilibria. The methods generally used for the determination of phase diagrams take no account of the possibility of alternative metastable behavior and are based on the assumption that a phase which appears to be stable has a stability field. The case of low digenite illustrates this point. The phase chemistry of systems in which alternative processes may operate cannot be specified on the usual phase diagram and must be described in terms of the kinetics of the processes taking place. Although the extent to which alternative processes are important in a description of sulfide systems is not fully appreciated at present, our experiments indicate that the possibility cannot be excluded, especially in systems in which the transformation temperatures are relatively low. The dynamic aspects of the transformation behavior of low-temperature sulfide phase equilibria should be investigated, and in situ experiments in a TEM provide an ideal method of studying such materials.

The nature of the alternative processes taking place in Ni_7S_6 and Cu_7S_4 is worthy of note. In both cases the metastable state formed is a large superstructure of the high-temperature form, whereas the stable low-temperature form has a simple, smaller unit cell. Similar behavior has been found in TaS_2 (*7*), in which structural changes in the metastable high-temperature form lead to a series of superstructure phases whereas the stable form has a simple cell. The implication arises that large superstructures based on the high-temperature form may represent alternative transformation behavior. Superstructure formation is a common feature of the low-temperature behavior in many sulfides, and a prima facie case exists for a reexamination of these systems in terms of possible metastability.

The results obtained here further demonstrate the general applicability of the theory of subsolidus behavior in minerals developed by McConnell (*1*). They also illustrate the inadequacy of classical thermodynamics in predicting the course of transformations in crystalline phases.

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References and Notes

1. J. D. C. McConnell, *Mineral. Mag.* **38**, 1 (1971).
2. A. Putnis, *Am. Mineral.* **61**, 322 (1976).
3. G. Kullerud and R. A. Yund, *J. Petrol.* **3**, 126 (1962).
4. M. E. Fleet, *Acta Crystallogr. Sect. B* **28**, 1237 (1972).
5. ——, personal communication.
6. N. Morimoto and K. Koto, *Am. Mineral.* **55**, 106 (1970); P. B. Barton, *Econ. Geol.* **68**, 455 (1973).
7. J. van Landuyt, G. van Tenderloo, S. Amelinckx, *Phys. Status Solidi* **26**, 359 (1974).
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