purposes of comparison, the inverse of the time required for 50% of the molecules to reach the native configuration ($1/t_{50}$) was used as a general measure of refolding rate.
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21. Mutant BPTI genes were made by site-directed mutagenesis in vitro with oligonucleotide primers on an M13 template [M. Zoller and M. Smith, *Methods Enzymol.* **100**, 468 (1983)]. The sequences (antisense strand) of the primers were: Cys14→Thr, AATTCTGGCCTT*GGT*GGGACCC; Cys38→Thr, TCTCTTAGCTCT*GGT*GCCACCA; Cys14→Ala, AATTCTGGCCTT*GGC*GGGACCC; Cys38→Ala, TCTCTTAGCTCT*GGC*GCCACCA. Mutant BPTIs were expressed in *E. coli* by using the *pho*A secretion vector and purified by affinity chromatography as described (*4*). However, the vector was modified to substitute the heat-stable enterotoxin II signal sequence [C. H. Lee *et al.*, *Infect. Immun.* **42** 264 (1983); R. N. Picken, A. J. Mazaitis, W. K. Maas, M. Rey, H. Heyneker, *ibid.*, p. 269] for the alkaline phosphatase signal sequence. Chymotrypsin-Sepharose was also substituted for trypsin-Sepharose in the affinity chromatography step of the purification.
22. The proteins were fully reduced by incubating them at a concentration of 600 μg/ml in 100 m*M* tris-HCl (*p*H 8.7), 1 m*M* EDTA, 8*M* urea, 10 m*M* dithiothreitol for 60 minutes at 37°C. The reduced proteins were then isolated by gel filtration on Sephadex G-25 in 10 m*M* HCl and used immediately. Refolding reactions were carried out in 100 m*M* tris-HCl (*p*H 8.7), 200 m*M* KCl, 1 m*M* EDTA, 10 m*M* reduced glutathione, 1 m*M* oxidized glutathione, and 30 μ*M* BPTI (*23*). Reactions were started by mixing together warmed solutions of reduced BPTI (in 10 m*M* HCl) and concentrated refolding buffer. Temperatures were maintained in heating blocks in the ranges 24° to 25°C, 37° to 38°C, and 51° to 53°C. At various times 40-μl aliquots were withdrawn, mixed with 10 μl of 0.5*M* iodoacetamide, and incubated at 25°C for 60 minutes in the dark to alkylate protein thiols. Iodoacetamide incubations in the presence of 8*M* urea, which should expose buried thiols (*3*), did not result in further modification of the protein (*8*), indicating that alkylation of all thiols was essentially complete under our conditions.
23. The *p*H of the refolding buffer was adjusted to 8.7 at room temperature before BPTI addition; the actual *p*H values of the refolding reactions were 8.3, 8.0, and 7.6 at 25°C, 37°C, and 52°C, respectively. Essentially the same results were obtained when the *p*H was maintained at 8.7 in all of the reactions (*8*), but the refolding rates were correspondingly faster at the higher *p*H [T. E. Creighton, *J. Mol. Biol.* **144**, 521 (1980)], and the lag time observed for the mutants at 25°C was reduced.
24. We thank B. Bochner and M. Brochier for help in producing the BPTI mutants, A. Kossiakoff for support and encouragement, and R. Drewes for advice on reptile body temperatures. This work was supported by Genentech, Inc. and grants from the NIH Institute of General Medical Sciences and Division of Research Resources.

14 October 1986; accepted 7 January 1987

Superconductivity at 40 K in the Oxygen-Defect Perovskites $La_{2-x}Sr_xCuO_{4-y}$

J. M. TARASCON, L. H. GREENE, W. R. MCKINNON,* G. W. HULL, T. H. GEBALLE†

Structural, magnetic, and electronic properties of compounds in the series $La_{2-x}Sr_xCuO_{4-y}$ for $0.05 \leq x \leq 1.1$, with $\Delta x = 0.025$, were studied. Resistance, susceptibility, Meissner, and shielding measurements have revealed superconductivity among several members of the series. For $x = 0.15$, the transition temperature T_c, measured at the midpoint of the resistive transition, is a maximum at 39.3 K with a width of 2 K. At other compositions the transition is broader and occurs at a lower temperature. Annealing the $x = 0.15$ sample in oxygen at 500°C increases T_c to 40.3 K, while annealing at the same temperature under vacuum suppresses the superconductivity. These changes in oxygen content and T_c are reversible.

OXYGEN-DEFECT PEROVSKITES HAVE been studied for possible applications in electrocatalysis or oxygen sensing because they absorb oxygen. Some are also superconductors: the hexagonal alkali tungsten bronzes, with a critical temperature $T_c = 6$ K (*1*); $SrTiO_3$ doped with niobium, for which $T_c = 1$ K (*2*); and $BaPb_{1-x}Bi_xO_3$, for which $T_c = 13$ K (*3*). In all these metallic perovskites the conduction bands are made up largely of oxygen *p*-orbitals hybridized with metal *s*, *p*, or *d* orbitals (*4*). The nonintegral valence of the metal in these compounds is sometimes called mixed valence, a description that becomes more meaningful when the bands become narrow with respect to correlation or exchange energy.

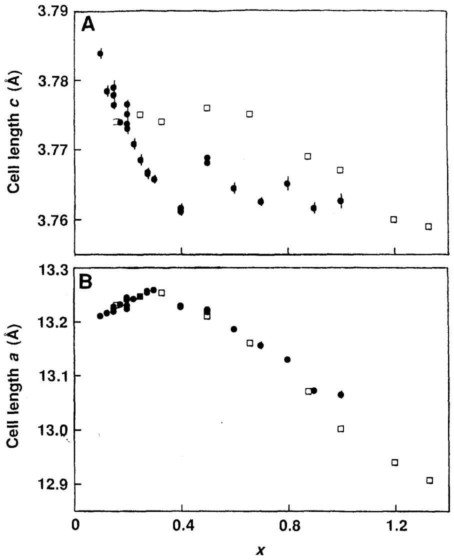

Fig. 1. Lengths *a* and *c* of the tetragonal unit cell as a function of strontium composition, *x*, in $La_{2-x}Sr_xCuO_{4-y}$; circles are our work and squares are from (*16*). Our error bars are twice the standard deviation from a least-squares refinement. For some *x*, more than one diffraction pattern was refined. For both $x = 0.15$ and $x = 0.200$ the highest value of *a* and the lowest value of *c* shown are for samples given different treatments than the rest. For $x = 0.15$ that sample was annealed under vacuum for 24 hours; for $x = 0.2$ that sample was annealed under oxygen and cooled in 10 hours. These different treatments did not change the lattice parameters by more than the scatter between the other points at those compositions.

Recently Bednorz and Müller (*5*) discovered evidence for much higher T_c (33 K) in the barium-lanthanum-copper (Ba-La-Cu) system. Shortly thereafter Bednorz *et al.* (*6*) and Ushida *et al.* (*7, 8*) independently confirmed superconductivity in the oxide $La_{2-x}Ba_xCuO_{4-y}$ with the K_2NiF_4 structure. Chu *et al.* (*9*) later reported an onset temperature for superconductivity of 52.5 K for this material under pressure.

This oxide is one of a large family of copper-oxide perovskites designated La-M-Cu-O, with M = Ba, Sr, or Ca, characterized by the presence of Cu^{+2} and Cu^{+3}. They were first synthesized by Longo and Raccah (*10*), and their structure and transport properties to 77 K were extensively studied by Nguyen *et al.* (*11, 12*). The superconductivity in the barium system prompted us to study the strontium analog $La_{2-x}Sr_xCuO_{4-y}$, which has been reported to be a solid solution for $0 < x < 1.1$ (*11*). [During the course of our work, other groups also observed bulk superconductivity in this system (*13*).] We show that the compound with $x = 0.15$ has $T_c = 39.3$ K and a transition width of 2 K, and we present evidence of sample inhomogeneity or phase segregation that broadens and lowers T_c at other compositions. We also show that T_c can be increased by annealing the compounds under oxygen, suppressed by annealing under vacuum, and that these changes in T_c with oxygen content are reversible. The highest T_c measured to date is on the $x = 0.15$ annealed sample, with a resistive midpoint of 40.3 K.

Bell Communications Research, 331 Newman Springs Road, Red Bank, NJ 07701.

*Permanent address: Division of Chemistry, National Research Council of Canada, Ottawa, Canada K1A OR9.
†Also at the Department of Applied Physics, Stanford University, Stanford, CA 94305.

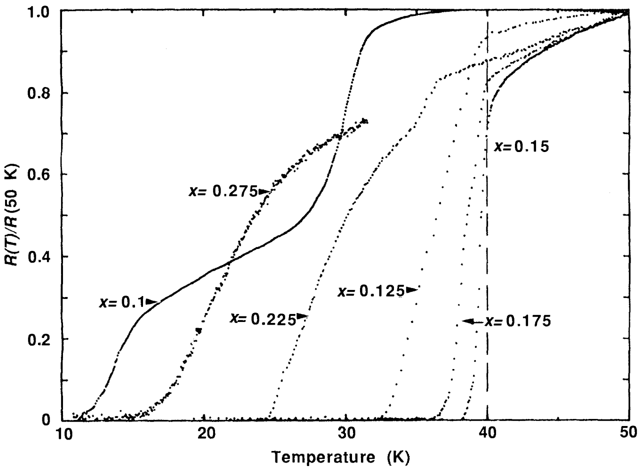

Fig. 2. Resistance versus temperature, normalized to 50 K, showing the superconducting transition for six values of strontium concentration, *x*. As *x* deviates from the optimum value of 0.15, the transition decreases and broadens. Vertical line is drawn at 40 K.

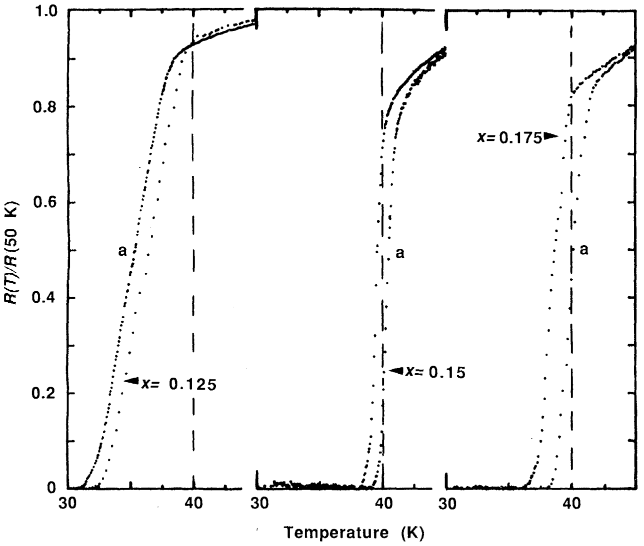

Fig. 3. Resistance versus temperature, normalized to 50 K, is plotted for three strontium concentrations from 30 K to 45 K, for the sample as grown and the same sample annealed to 500°C for 24 hours in 1 atm O_2. The annealed samples are labeled "a". After annealing, the T_c value, taken at the midpoint, decreased by 1.2 K for $x = 0.125$, and increased by 0.8 K and 1.7 K for $x = 0.15$ and 0.175, respectively. Vertical lines are drawn at 40 K.

Table 1. Resistivity, transition temperatures, and lattice parameters for the materials studied. The three samples labeled "A" were annealed at 500°C for 24 hours in 1 atm of oxygen. The onset temperature T_{co} is taken where the resistance noticeably deviates from the extrapolation from high temperature; the midpoint temperature T_{cm} is the temperature where the resistance has fallen to half its extrapolated value. The errors in the lattice parameters are the uncertainty in the last digit, determined from a least-squares refinement of about 20 Bragg peaks. For compositions where more than one refinement was made, the average values are given.

Sample	x	ρ(300 K) (μohm-cm)	ρ(300 K)/ρ(50 K)	T_{co} (K)	T_{cm} (K)	a (Å)	c (Å)	Volume (Å^3)
3S15	0.1	4400	2.4	32.5	26.0	3.7839(8)	13.211(4)	189.16(12)
1S14	0.125	5100	3.4	40.4	36.1	3.7784(8)	13.216(4)	188.68(10)
1S14A				38.7	35.0			
2S14	0.15	2300	4.5	41.2	39.3	3.7771(10)	13.226(3)	188.60(10)
2S14A				42.3	40.3			
3S14	0.175	2200	4.2	40.3	38.2	3.7739(4)	13.232(2)	188.45(6)
3S14A				41.9	40.0			
4S14	0.2	1800	4.3	40.9	35.9	3.7739(8)	13.230(3)	188.54(10)
5S14	0.225	1500	4.8	36.4	29.1	3.7708(8)	13.242(4)	188.30(10)
6S14	0.25	1300	5.2	41.7	31.2	3.7685(8)	13.247(4)	188.12(9)
7S14	0.275	990	5.4	31.7	21.8	3.7666(8)	13.255(3)	188.06(7)
358	0.3	620	4.9	11.5	5.7	3.7657(6)	13.259(4)	188.02(9)
1S11	0.4	4000	0.68	—	—	3.7614(6)	13.228(4)	187.15(8)
	0.5					3.7684(4)	13.220(3)	187.75(7)
	0.6					3.7644(8)	13.185(5)	186.85(10)
	0.7					3.7625(6)	13.156(7)	186.24(10)
	0.8					3.7651(10)	13.129(4)	186.12(10)
	0.9					3.7616(8)	13.071(4)	184.96(8)
	1.0					3.7626(10)	13.064(8)	184.95(13)

The compounds $La_{2-x}Sr_xCuO_{4-y}$ ($x = 0.05$ to $x = 1.1$) were prepared from La_2O_3, CuO, and $SrCO_3$, each 99.999% pure. Amounts appropriate to form 2-g samples were mixed and pressed at 7 kbar into a pellet 1/2 inch in diameter. The pellets were reacted in a platinum boat in a tubular furnace under flowing oxygen. The temperature was increased to 1120°C in 12 hours, held for 36 hours, and cooled to 500°C in 1 hour, after which the sample was removed. Part of the pellet was ground and the powder examined by x-ray diffraction. The samples were single phase for $0.05 < x < 0.3$. For $x \geq 0.4$, however, a trace of a second phase was seen, so these samples were ground, pressed, and reannealed at 1200°C for 24 hours. Rectangular bars 12 by 5 by 1 mm were cut from the pellets and used in the resistance and magnetic measurements.

The thermal stability of the compounds $x = 0.15$ and $x = 0.225$ was investigated by differential thermal analysis (DTA) under oxygen. The samples melted at 1370°C. X-ray diffraction showed two phases in the material that had melted; about 80% of the material was still in the K_2NiF_4 structure, and the second phase is unidentified. Thus the compound probably melts peritectically, a complication for growing crystals.

A second way to change the composition of these compounds, and hence possibly modify the superconductivity, is to change the oxygen content. These compounds have oxygen defects, and the oxygen content y in $La_{2-x}Sr_xCuO_{4-y}$ can be increased or decreased by annealing the samples under oxygen or under vacuum, respectively, near 500°C (*11*). We annealed some of the samples at 500°C under 1 atm of oxygen or under 10^{-3} torr, and then remeasured their properties.

Lattice parameters were determined from x-ray powder diffraction in the Bragg-Brentano geometry with Cu-K_α radiation for $10° < 2\theta < 90°$, where θ is the scattering angle. The lattice parameters and the displacement of the sample off the axis of the diffractometer (*14*) were refined with a least-squares fit to about 20 lines. The errors were calculated from the variance of the fit (*15*). All errors quoted are twice the calculated variances, because lattice parameters for several measurements of the same sample are scattered by this much.

Resistivity versus temperature measurements were made at constant current (~ 0.5 A cm^{-2}) in the standard four-probe configuration. Reducing the current by a factor of 10 had no effect on the T_c value. Measurements were made in helium exchange gas in a tube immersed in liquid helium. The sample was electrically contacted with silver paint and thermally grounded to a copper block that contained a silicon thermometer. We emphasize that we rely entirely (at present) on the manufacturer's calibration (Lakeshore Cryotronics, model DT-500P/GR-M) and quote T_c to ±0.2 K. In some samples the contacts were removed with acetone so the sample could be reannealed and remeasured. The transitions were also measured with a-c mutual inductance. The shielding currents and the Meissner expelled flux were measured with a superconducting quantum interference device (SQUID) magnetometer on powdered samples.

The lattice parameters a and c as a function of x show a change in slope between $x = 0.3$ and 0.4 (Fig. 1 and Table 1). As noted above, this composition is the dividing line between two preparation techniques; those samples with $x > 0.3$ were annealed at a higher temperature. We do not know if this is the cause of this feature at $x = 0.3$. The samples $x = 0.05$ and $x = 0.075$ were orthorhombic, as reported in (*11*). Even after the second anneal, the samples $x = 1.0$ and $x = 1.1$ had a second phase, as yet unidentified. Some of the intermediate compositions showed broadening of some Bragg peaks, but the broadening varied nonsystematically between samples. There are small differences between our lattice parameters and those reported in (*16*).

The superconducting transition temperature, T_c, is highest and the transition is narrowest near $x = 0.15$. This is seen in Fig. 2, where the temperature-dependent resistance, normalized to the value at 50 K, is plotted for six different strontium concentrations. Note how sensitive T_c is to concentration; changing x by ±0.025 decreases the midpoint by about 1 K. The midpoint is defined as the temperature at which the resistance has dropped to half the value extrapolated from high temperatures. Evidence of inhomogeneities (broadening and structure in the transition) increases as x deviates from 0.15.

The value of T_c is changed by annealing in an oxygen atmosphere. Figure 3 shows resistance versus temperature, normalized to 50 K, for three concentrations of strontium both before and after annealing. After annealing, the T_c value, taken at the midpoint, decreased by 1.1 K for $x = 0.125$, and increased by 1.0 K and 1.8 K for $x = 0.15$ and $x = 0.175$, respectively.

In Fig. 4, the resistivity ρ is plotted from below T_c to room temperature for six different strontium concentrations. For each sample, ρ(300 K) is given to about 10% accuracy in Table 1. A roughly linear temperature dependence is observed in all samples at high temperature. Such a linearity is seen in other metal oxides (*17*). As x approaches the optimum value (0.15), the linearity extends closer to T_c. As x increases from 0.125 to 0.3, $d\rho/dT$ decreases. In fact, over this range of x, ρ(300 K) decreases by a factor of 8.2 whereas the resistance ratio ρ(300 K)/ρ(50 K) varies only by a factor of 1.6. For $x = 0.4$, $\rho(T)$ increases monotonically with decreasing T.

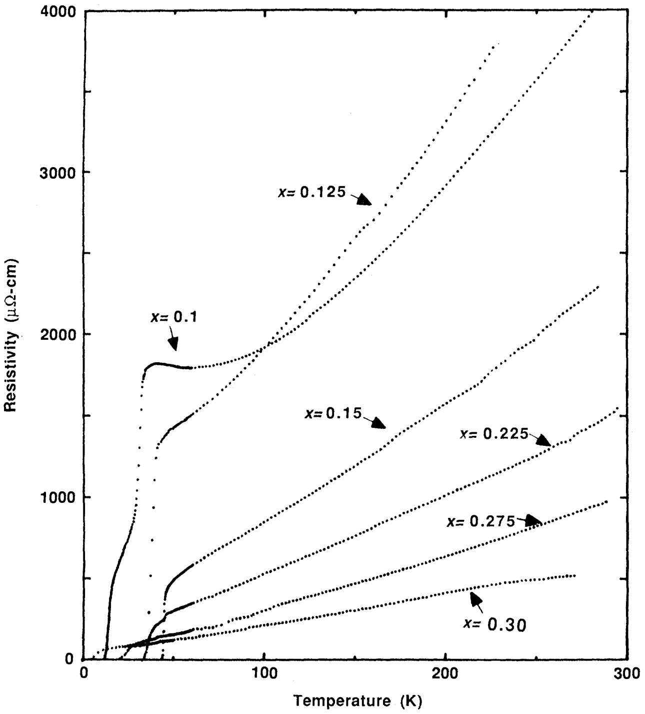

Fig. 4. Resistivity as a function of temperature from below T_c to room temperature, for strontium concentrations $x = 0.1$, 0.125, 0.15, 0.225, 0.275, and 0.30.

Figure 5 shows the a-c susceptibility for $x = 0.15$. The midpoint of the transition is 39 ± 1 K (± value is uncertainty in temperature in this measurement), in agreement with the resistance in Fig. 2. As in the resistance data, the transitions are broader and the midpoints are shifted to lower temperature for neighboring compositions. No superconductivity has been found to 4.2 K for $x = 0.4$ or $x = 0.05$; samples with $x > 0.4$ are still under study. Annealing the material with $x = 0.15$ under vacuum decreases the a-c signal, so that only a broad, partial transition was seen in the sample for $x = 0.15$ after three successive treatments of 10 hours each at 500°C. An amazing result is curve e in Fig. 5, which shows that the superconductivity can be fully restored by simply reannealing under oxygen at 500°C. Nguyen *et al.* (*12*) have shown that annealing under oxygen or vacuum reversibly changes the oxygen composition y in $La_{2-x}Sr_xCuO_{4-y}$. Thus Fig. 5 shows the superconductivity is very sensitive to oxygen concentration.

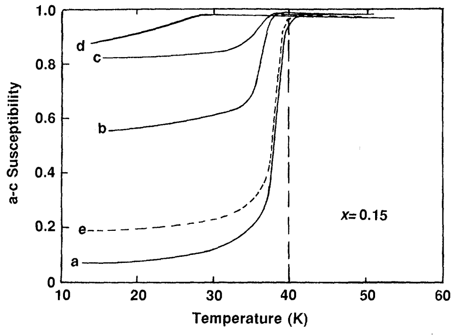

Fig. 5. Susceptibility versus temperature for the sample $La_{1.85}Sr_{0.15}CuO_{4-y}$ as a function of annealing under vacuum of 10^{-3} torr. Curve a is the sample prior to annealing; curves b, c, and d are after successive treatments of 10 hours under vacuum at 500°C. After curve d was obtained, the sample was reannealed under oxygen at 500°C to give curve e (dashed curve). The temperature scale is accurate only to ±1 K.

The experiments described so far indicate superconductivity in part of the sample, but do not prove bulk superconductivity. To prove it, we measured the screening and exclusion of magnetic flux with a SQUID magnetometer. Figure 6 shows the results for $x = 0.15$ of warming the sample in a field of 100 Oe after it had been cooled in

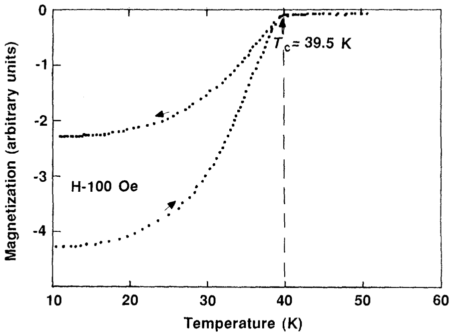

Fig. 6. Temperature-dependent magnetization for unannealed $La_{1.85}Sr_{0.15}CuO_{4-y}$. The upper curve is for cooling in a field of 100 Oe; the lower curve is for warming in 100 Oe after cooling in zero field.

zero field (shielding effect), and of cooling the sample in 100 Oe (Meissner effect). In both of these curves, superconductivity begins at a temperature (39.5 K) that is within ±1 K of that seen in resistance or a-c susceptibility, but the transition is considerably broader. For all the samples measured, the Meissner signal is 50 to 60% of the shielding signal, which is evidence for bulk superconductivity. These measurements were repeated in fields up to 5 T. At this flux density a reduction of T_c along with a broadening of the transition is observed. From our measurements, we estimate $dH_\mathrm{c}/dT = 1.3$ T/K, which extrapolates to a critical field of 40 T at 4.2 K. Preliminary critical field measurements at high fields support this value (*18*).

Superconducting transitions are sensitive to changes in composition, vacancy ordering, and phase segregation. The composition $x = 0.15$ has a sharp transition as measured by d-c resistance, a-c mutual inductance, and Meissner expulsion. These three measurements show this composition to be a bulk superconductor. At other compositions the transitions are broader, and some show structure. It is possible that all our samples have comparable inhomogeneities in the strontium content. A maximum in T_c as a function of x would mean that the minimum in the transition width simply reflects a maximum in T_c versus x near $x = 0.15$. We do not believe the structure in the transition is due to impurity phases, since none are observed by x-ray diffraction to 5% accuracy. It is also possible that the material is a single phase for $x = 0.15$, but not for other compositions, and that the phase separation is not complete for our cooling speed. However, a sample with $x = 0.20$ cooled in 16 hours instead of 1 hour from 1100°C showed features in the superconducting transition similar to those in samples with the same x cooled in 1 hour or quenched. Sharp transitions over a narrow range in composition also occur in $BaPb_{1-x}Bi_xO_3$ (*19*). It has been suggested that inhomogeneities are responsible for the broadening at other compositions (*20*).

The superconducting transition is sensitive to sample composition and preparation, and it is possible that higher T_c will be found. Oxygen vacancies are important, as shown by the shift in T_c with the atmosphere used for annealing. We have also found evidence for $T_\mathrm{c} = 40$ K in these oxides where calcium replaces strontium, but in this case the superconducting transition was more than 10 K wide, and furthermore the Meissner effect indicated that only a small fraction of the sample was superconducting. We are presently studying other compounds in these series.

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21. We thank E. Vogel for the DTA measurements, P. L. Key for use of his equipment, W. L. Feldmann for technical assistance, and J. M. Rowell and J. H. Wernick for helpful discussions.

21 January 1987; accepted 5 February 1987

Ribavirin Antagonizes the Effect of Azidothymidine on HIV Replication

Markus W. Vogt, Kevan L. Hartshorn, Phillip A. Furman, Ting-Chao Chou, James A. Fyfe, Leslie A. Coleman, Clyde Crumpacker, Robert T. Schooley, Martin S. Hirsch*

Azidothymidine and ribavirin both inhibit replication of human immunodeficiency virus in vitro and show promise of clinical utility in patients infected with this virus. In this study, the possible interactions of these drugs were examined in vitro, and a reproducible antagonism between azidothymidine and ribavirin was found to occur under a variety of experimental conditions. The mechanism responsible for this antagonism appeared to be inhibition of azidothymidine phosphorylation by ribavirin. Because similar effects may occur in vivo, clinical trials of these two drugs in combination must be performed only under carefully controlled conditions.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) causes a variety of clinical syndromes including the acquired immune deficiency syndrome (AIDS) and chronic neurological disorders (*1–5*). Several antiviral agents inhibit the replication of HIV in vitro (*6*). One, 3′-azido-3′-deoxythymidine (AZT, N_3dThd) (*7*), reduces morbidity and mortality in patients with AIDS (*8*), and another, ribavirin (*9*), has been reported to delay or prevent development of AIDS in patients with HIV-induced persistent generalized lymphadenopathy (*10*).

Control of HIV infections in patients for prolonged periods may require a combination of antiviral agents. We have shown that AZT and recombinant interferon-α A synergistically inhibit HIV replication in vitro, presumably by acting at different sites of virus replication (*11*). On the basis of these studies, clinical trials of this combination of drugs are planned. Because of the activity of AZT and ribavirin when administered separately, the combination of these drugs is one that deserves further study, particularly since both drugs are bioavailable when administered orally, cross the blood-brain barrier, and have acceptable toxicity (*6, 12, 13*). Furthermore, the mode of antiviral action of each is different: the triphosphate of AZT acts as an inhibitor of HIV DNA synthesis (*14*) and the triphosphate of ribavirin interferes with post-transcriptional processing (*15*). Therefore, we evaluated the effects of various dose combinations of AZT and ribavirin on HIV replication in vitro. To our surprise, the combination proved antagonistic. The mechanism of antagonism appears to be inhibition of AZT phosphorylation by

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M. W. Vogt, K. L. Hartshorn, L. A. Coleman, R. T. Schooley, M. S. Hirsch, Massachusetts General Hospital, Infectious Disease Unit, Harvard Medical School, Boston, MA 02114.
P. A. Furman and J. A. Fyfe, Wellcome Research Laboratories, Research Triangle Park, NC 27709.
T.-C. Chou, Laboratory of Pharmacology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
C. Crumpacker, Beth Israel Hospital, Infectious Disease Unit, Harvard Medical School, Boston, MA 02115.

*To whom requests for reprints should be addressed.