FIGURE S1.—Comparison of three measures of substitution rates in populations with strictly neutral mutations. The dashed, red line tracks the mean origination rate, or the rate at which mutations arise that will fix, in 10,000-generation simulations; the dotted line tracks the rate at which mutations fix in the population. Both rates converge at steady-state, but the origination rate is underestimated near the end of each simulation, and the substitution rate similarly underestimated near the beginning. Note that these transitory periods are proportional to N, as expected from coalescent theory. The error in the origination rate measurement can be fixed by simulating populations for longer than the measurement period; the solid line shows the results of measuring origination rates over 10,000 generations, but running the simulations until a mutation fixes that originated after 10,000 generations. This last method produces an accurate estimate of the substitution rate for the entirety of the observation period.
FIGURE S2.—Deleterious mutations have a negligible effect on the substitution rate of conditionally neutral mutations. For all genotypes, a fraction $p_D = 0.5$ of mutations are unconditionally deleterious with selective coefficient $s_D$. The dashed line shows the mean results from Fig. 3 for comparison. $N = 5000$, $U = 0.004$, $s = 0.1$ for beneficial mutations, and $p_B = 0.001$. 
FIGURE S3.—The substitution rate of conditionally neutral mutations is substantially elevated, even when more evolvable genotypes experience a greater deleterious mutation rate. For all genotypes, a fraction $p_D = 0.5$ of mutations are unconditionally deleterious with selective coefficient $s_D = 0.2$. A separate fraction $\Delta p_D$ of mutations are deleterious in evolvable backgrounds (genotypes for which $p_B = 0.001$) and neutral in unevolvable backgrounds ($p_B = 0$). When $\Delta p_D > 0$ conditionally neutral mutations are shaped by selection against deleterious mutations and do not behave neutrally even under stabilizing selection. However, conditionally neutral sites still substitute much more often than Kimura's expectation when the population is adapting. The dashed line shows the mean results from Fig. 3 for comparison. $N = 5000$, $U = 0.004$, $s = 0.1$ for beneficial mutations, and $p_B = 0.001$. 
FIGURE S4.—Epistatic deleterious mutations reduce but do not eliminate the increase in the substitution rate of conditionally deleterious mutations in adapting populations. For all genotypes, a fraction $p_D = 0.1$ of mutations are unconditionally deleterious with the selective coefficients given in the figure. Conditionally neutral mutations occur at one-tenth this rate; $p_{NE} = 0.01$. Both kinds of epistatic mutations change evolvable genotypes to unevolvable ones and vice versa. The dashed line shows the mean results from Fig. 3 for comparison. $N = 5000$, $U = 0.004$, $s = 0.1$ for beneficial mutations, and $p_B = 0.001$. 