transient CD on the nanosecond time scale (Lewis et al., 1985), making careful use of the optical calculus developed by R. C. Jones. In the latest paper (Shapiro et al., 1995), the optical calculus of Mueller was used to develop the dispersive counterpart of the transient CD, here known as transient ORD, or TRORD. There appear to be several advantages to the new technique. First, it has a much higher S/N ratio than TRCD. Second, the instrumentation appears simpler. Third, one can, as with ORD, detect changes in optical activity far from the optically active absorption bands. Finally, one can, if so desired, use complex Hilbert transforms (Kramers-Krönig relations) to obtain the CD spectrum at a given wavelength from the complete ORD spectrum. In one of the first applications of the new method, photolysis of HbCO was studied as a function of wavelength in the nanosecond to millisecond time regime and SVD analyses used to obtain minimal basis spectra and associated rate constants. Of considerable interest is the finding, when TROD and TRORD data were combined in a restricted global analysis, as shown in Table 2 and described in the paper, of a fifth exponential phase with a time constant of about 1 μs. Perhaps this is related to changes found by the Spiro laboratory by time resolved UVRR spectroscopy. Studies on modified hemoglobins and on solutions where the solvent is varied should further elucidate the nature of this phase. We can expect that the high S/N of the TRORD technique will lead to important results and insights by allowing one to follow protein folding and nucleic acid-protein interactions by photolysis and other techniques.

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A Novel Computational Prediction of Ion Effects in Oligocation-Oligonucleotide Equilibria

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The most exciting and dangerous event for a theoretician is the prediction of an unforeseen physical-chemical phenomenon that can be verified experimentally. Olmsted et al. (in this issue) examine the salt dependence of the association of an octacation with nucleic acids of varying lengths using Grand Canonical Monte Carlo simulations. They use the extraordinarily simple cylindrical model to make the novel prediction that the salt dependence of the association of an octavalent cation with the interior region of nucleic acids of varying length achieves a maximum for a finite length oligonucleotide. This prediction, if experimentally verified, has implications with regard to the stability of oligocation-oligonucleotide complexes and may aid in the evaluation of the accuracy of computational models of nucleic acid solutions.

The salt dependence of the equilibrium association constant (obtained from the slope of a $\log K_{obs}$-$\log[Na^+]$ plot and denoted $-S_a K_{obs}$) as a function of oligonucleotide length demonstrates that end effects may significantly influence the physical chemistry of nucleic acids. For the association of an octavalent cation at low salt concentrations, the predicted values of $-S_a K_{obs}$ range from 2.5 for very short oligonucleotides to 7.3 for long oligomers and pass through a maximum of 10.2 for oligomers of intermediate length (36 bp). Thus, the equilibrium constant is predicted to decrease by three orders of magnitude with a twofold increase in salt concentration for intermediate length oligomers. These predicted changes in the sensitivity of the equilibrium association constant to salt con-

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centration for different length oligomers are sufficiently large that experimental verification should be forthcoming.

The existence of a maximum in the predicted length dependence of $-S_aK_{obs}$ is, at first glance, a puzzling result. The maximum, if verified, illustrates the influence of end effects on the thermodynamic properties of oligonucleotide solutions. In the absence of oligocation complexation, Olmsted et al. showed previously that model double-stranded oligonucleotides of N charges (N-mers) behave as polyelectrolytes when $N >$ 48, whereas shorter oligomers behave more like simple electrolytes (Olmsted et al. 1991). Recently, Allison computed the electrostatic potential near cylindrical model oligonucleotides of various lengths using the Poisson-Boltzmann equation to determine how far into the interior region of the oligomer end effects modulate the electrostatic potential (Allison, 1994). At low salt concentrations, a reduction in the potential below the polymeric limit occurred at the surface of the oligomer and extended approximately 5–10 bp from the ends of the oligomer. At distances farther from the oligonucleotide surface, the reduction of the potential persisted more than 20 bp into the interior region of the oligomer. In this issue, Olmsted et al. predict that there is a range of N values over which the double-stranded polynucleotide is converted into a simple electrolyte upon oligocation association. The net result of this conversion is the concomitant release of counterions in excess of the polymeric limit upon association. This highly unusual result is a direct consequence of the creation and persistence of end effects upon binding that extends substantially beyond the binding site.

Computational models of nucleic acid solutions fall roughly into two categories: those that include some molecular details of the nucleic acid and surrounding solution and those that use the highly idealized, cylindrical model. Electrostatic nonideality in nucleic acid solutions, which accounts for the extraordinary sensitivity of the physical-chemical properties of nucleic acids to salt, is a consequence of the steep ion gradients in the vicinity of the nucleic acid. However, computer simulations that incorporate various degrees of complexity into the model of the nucleic acid and surrounding solution, predict considerably different ion distributions (Mills et al., 1992; Pack et al., 1993; Allison, 1994).

The test of the accuracy of any model lies in its ability to predict experimental observables. The widespread use of oligonucleotides in biophysical studies affords a computationally accessible means to simulate electrostatic nonideality in nucleic acid solutions. Olmsted et al. were the first to predict accurately the salt dependence of oligonucleotide denaturation using the primitive model (Olmsted et al., 1991). With a detailed, three-dimensional representation of the nucleic acid and surrounding solution, Misra et al. (1994) were able to reproduce the salt dependence of the complexation of divalent antibiotics to oligonucleotides. Surprisingly, Misra et al. showed that the idealized cylindrical model predicted the identical, experimentally observed salt dependence, although the interpretations of the molecular origins of the salt effects differ depending upon the model chosen. The predicted maximum of $-S_aK_{obs}$ on length reported by Olmsted et al. in this issue offers another opportunity to examine the ability of various molecular models to predict accurately the thermodynamic consequences of electrostatic nonideality in nucleic acid solutions. If both the simple cylindrical model and models that include greater molecular detail make the same thermodynamic prediction, then two questions must be asked: what is the necessary and accurate molecular model for the three-dimensional ionic structure near nucleic acids?; and are the thermodynamic coefficients actually sensitive to the three-dimensional details of these ion distributions?

It is interesting to speculate that the thermodynamic consequences of the ion distributions are essentially independent of the detailed ionic structure near nucleic acids, even though the ion distributions themselves appear to be sensitive to the choice of the model of the nucleic acid and surrounding solution. This suggests either that the structural parameters responsible for electrostatic nonideality in highly charged poly- and oligoelectrolyte solutions are primarily due to the axial charge density and the length of the nucleic acid or that compensations exist that allow the primitive model to accurately represent electrostatic nonideality in nucleic acid solutions despite the lack of physical detail. The key to delineating the accuracy of and necessity for detailed molecular models of nucleic acid solutions clearly lies in the further comparison of experimental observables with predictions from computational models.

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