Title:	Molecular Origin of Internal Friction in Intrinsically Disordered Proteins
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Abstract:	Protein folding and dynamics are controlled by an interplay of thermal and viscosity effects. The effect of viscous drag through the solvent molecules is described by the classic Kramers theory in the high friction limit, which considers the dampening of the reactant molecules in the solution and quantifies the dependence of the reaction rate on the frictional drag. In addition to the external energy dissipation originating from the surrounding solvent molecules, there is an additional mode of internal energy dissipative force operative within the polypeptide chain reflecting the internal resistance of the chain to its conformational alterations. This dry, solvent-independent intrinsic frictional drag is termed internal friction. In the case of natively folded proteins, the physical origin of internal friction is primarily attributed to the intrachain interactions or other nonnative interactions in their compact states. However, the molecular origin of internal friction in intrinsically disordered proteins (IDPs) remains elusive. In this Account, we address this fundamental issue: what are the principal drivers of viscosity-independent (dry) friction in highly solvated, expanded, conformationally flexible, rapidly fluctuating IDPs that do not possess persistent intrachain interactions? IDPs exhibit diffusive conformational dynamics that is predominantly dominated by the segmental motion of the backbone arising due to the dihedral rotations in the Ramachandran Φ–Ψ space. The physical origin of friction in a complex biopolymeric system such as IDPs can be described by classic polymer models, namely, Rouse/Zimm models with internal friction. These one-dimensional models do not invoke torsional fluctuation components. Kuhn's classic description includes the connection between internal friction and microscopic dihedral hopping. Based on our time-resolved fluorescence anisotropy results, we describe that the sequence-dependent, collective, short-range backbone dihedral rotations govern localized internal friction in an archetypal IDP, namely, α-synuclein. The highly sensitive, residue-specific fluorescence depolarization kinetics offers a potent methodology to characterize and quantify the directional decorrelation engendered due to the short-range dihedral relaxation of the polypeptide backbone in the dihedral space. We utilized this characteristic relaxation time scale as our dynamic readout to quantify the site-specific frictional component. Our linear viscosity-dependent model of torsional relaxation time scale furnished a finite nonzero time constant at the zero solvent viscosity representing the solvent-independent internal friction. These results unveil the effect of the degree of dihedral restraining parameter on the internal friction component by showing that a restrained proline residue imparts higher torsional stiffness in the chain segments and, therefore, exhibits higher internal friction. This Account sheds light on the molecular underpinning of the sequence-specific internal friction in IDPs and will be of interest to unmask the role of internal friction in a diverse range of biomolecular processes involving binding-induced folding, allosteric interaction, protein misfolding and aggregation, and biomolecular condensation via phase separation.
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