Title:	N-Terminal Extensions Appear to Frustrate HU Heterodimer Formation by Strengthening Intersubunit Contacts and Blocking the Formation of a Heterotetrameric Intermediate
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Abstract:	HU is a bacterial nucleoid-associated protein. Two homologues, known as HU-A, and HU-B, are found in Escherichia coli within which the early, late, and stationary phases of growth are dominated by HU-AA, HU-BB, and HU-AB dimers, respectively. Here, using genetic manipulation, mass spectrometry, spectroscopy, chromatography, and electrophoretic examination of glutaraldehyde-mediated cross-linking of subunits, in combination with experiments involving mixing, co-expression, unfolding, and refolding of HU chains, we show that the spontaneous formation of HU-AB heterodimers that is reported to occur upon mixing of wild-type HU-AA and HU-BB homodimers does not occur if chains possess N-terminal extensions. We show that N-terminal extensions interfere with the conversion of homodimers into heterodimers. We also show that heterodimers are readily formed at anticipated levels by chains possessing N-terminal extensions in vivo, when direct chain–chain interactions are facilitated through production of HU-A and HU-B chains from proximal genes located upon the same plasmid. From the data, two explanations emerge regarding the mechanism by which N-terminal extensions happen to adversely affect the conversion of homodimers into heterodimers. (1) The disappearance of the α-amino group at HU's N-terminus impacts the intersubunit stacking of β-sheets at HU's dimeric interface, reducing the ease with which subunits dissociate from each other. Simultaneously, (2) the presence of an N-terminal extension appears to sterically prevent the association of HU-AA and HU-BB homodimers into a critically required, heterotetrameric intermediate (within which homodimers could otherwise exchange subunits without releasing monomers into solution, by remaining physically associated with each other).
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