

Publication**The price of flexibility - a case study on septanoses as pyranose mimetics****JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)****ID** 4029939**Author(s)** Sager, Christoph P.; Fiege, Brigitte; Zihlmann, Pascal; Vannam, Raghu; Rabbani, Said; Jakob, Roman P.; Preston, Roland C.; Zalewski, Adam; Maier, Timm; Peczu, Mark W.; Ernst, Beat**Author(s) at UniBasel** [Maier, Timm](#) ; [Jakob, Roman Peter](#) ; [Zalewski, Adam](#) ; [Ernst, Beat](#) ; [Sager, Christoph](#) ; [Fiege, Brigitte](#) ; [Zihlmann, Pascal](#) ; [Rabbani, Said](#) ; [Preston, Roland](#) ;**Year** 2018**Title** The price of flexibility - a case study on septanoses as pyranose mimetics**Journal** Chemical Science**Volume** 9**Number** 3**Pages / Article-Number** 646-654

Seven-membered ring mimetics of mannose were studied as ligands for the mannose-specific bacterial lectin FimH, which plays an essential role in the first step of urinary tract infections (UTI). A competitive binding assay and isothermal titration calorimetry (ITC) experiments indicated an approximately ten-fold lower affinity for the seven-membered ring mannose mimetic 2-O-n-heptyl-1,6-anhydro-D-glycero-D-galactitol (7) compared to n-heptyl α -D-mannopyranoside (2), resulting exclusively from a loss of conformational entropy. Investigations by solution NMR, X-ray crystallography, and molecular modeling revealed that 7 establishes a superimposable H-bond network compared to mannoside 2, but at the price of a high entropic penalty due to the loss of its pronounced conformational flexibility. These results underscore the importance of having access to the complete thermodynamic profile of a molecular interaction to "rescue" ligands from entropic penalties with an otherwise perfect fit to the protein binding site.

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