

Abstract

The conformational preorganization and anion-induced conformational changes of indole-based receptors have been studied by a combination of heteronuclear NMR spectroscopy and quantum mechanical calculations. In the first group of receptors, a single indole scaffold has been functionalized with an amide group at C2 and a variety of amide, urea and thiourea moieties at C7. NOE enhancements showed that *anti-anti* conformation across C2–C2 α and C7–N7 α bonds is preferred in an acetone- d_6 solution in the absence of anions. Upon anion binding to receptors, *syn-syn* conformation becomes predominant. Anion–receptor interactions were evaluated through ^1H and ^{15}N chemical shift changes. In 2,7-bis-carboxamido functionalized indoles, the interaction with chloride and bromide anions primarily occurs at the indole H1 proton. The introduction of urea and thiourea moieties increases the number of hydrogen bond donor sites, which manifests itself in a distribution of halide–receptor interactions among the H1, H7 α and H7 γ protons. Acetate anions also interact strongly with all four available donor groups, whereas nitrate anions interact solely with H7 α and H7 γ urea/thiourea protons. The second group of receptors exhibited an extra indole group, which resulted in diindolyl(thio)ureas. NOE experiments showed that the *anti-anti* conformer along the C7–N7 α bonds was favored in DMSO- d_6 solution in the absence of anions. Anion-induced ^1H and ^{15}N chemical shift changes suggested weak binding of chloride anions and negligible conformational changes. Strong deshielding of the ureido protons and moderate deshielding of the indole NH has been observed upon the addition of acetate, benzoate, bicarbonate and dihydrogen phosphate, which indicates that the predominant hydrogen bond interactions occurred at urea donor groups. Binding of oxoanions caused conformational changes along the C7–N7 α bonds and the *syn-syn* conformer was preferred for anion–receptor complexes. The conformational changes in functionalized indoles and diindolyl(thio)ureas upon anion binding are in good agreement with the energy preferences established by *ab initio* calculations. NMR data proved to be an excellent sensor for hydrogen-bonding interactions between anions and their receptors. The ability to observe characteristic redistributions of electron density and conformational preorganization of anion receptors enabled us to evaluate their different propensity and selectivity for interactions with anions. Moreover, NOE enhancements reflected receptors' aptitude for conformational reorganization upon binding of anions. An understanding of the conformational preferences of the studied anion receptors and their complexes with anions in solution provides new insights and thus gives fresh ideas for the design of anion specific receptors.

Keywords: anion recognition; conformation analysis; host–guest systems; indole; NMR spectroscopy

Povzetek

S pomočjo heteronuklearne NMR spektroskopije in kvantno mehanskih izračunov smo študirali konformacijsko predorganizacijo anionskih receptorjev na osnovi indolnega obroča in njihove konformacijske spremembe po dodatku anionov. V prvi skupini teh spojin je indolni skelet funkcionaliziran z amidno skupino na mestu C2 in kombinacijo amidne, sečninske oziroma tiosečninske na mestu C7. NOE eksperimenti so pokazali, da v raztopini acetona- d_6 ob odsotnosti anionov prevladuje konformacija *anti-anti* vzdolž C2–C2 α in C7–N7 α vezi. Po vezavi anionov na receptor v raztopini prevladuje konformacija *sin-sin*. Interakcije med anioni in receptorji smo primerjali na podlagi ^1H in ^{15}N kemijskih premikov. V 2,7-bis-karboksamido funkcionaliziranem indolu interakcija s kloridnimi in bromidnimi anioni primarno poteka na indolnem H1 protonu. Umestitev sečninske oziroma tiosečninske skupine poveča število donorjev vodikove vezi, kar se je pokazalo na porazdelitvi interakcije halid–receptor med H1, H7 α in H7 γ protone. V primeru acetatnih anionov interakcija poteka z vsemi štirimi NH donorskimi skupinami, medtem ko se nitratni anioni preferenčno vežejo le na sečninske oziroma tiosečninske NH protone. Druga skupina receptorjev vsebuje dodatni indolni obroč, kar nam da diindolil(tio)sečnine. Na podlagi NOE ojačitev sklepamo, da v raztopini DMSO- d_6 v odsotnosti anionov vzdolž C7–N7 α vezi prevladuje konformacija *anti-anti*. Spremembe kemijskih premikov, ki jih povzroči dodatek kloridnih anionov, kažejo na šibko vezavo le-teh in zanemarljive konformacijske spremembe. Ob dodatku acetatnih, benzoatnih, bikarbonatnih in dihidrogenfosfatnih anionov smo opazili močno odsenčenje sečninskih in zmerno odsenčenje indolnih protonov, kar kaže na to, da se anioni preferenčno vežejo na sečninske NH skupine. Ob vezavi oksoanionov je posledično prišlo do konformacijskih sprememb vzdolž C7–N7 α vezi, tako da v primeru kompleksov anion–receptor prevladuje konformacija *sin-sin*. Konformacijske spremembe funkcionaliziranih indolov in diindolil(tio)sečnin ob vezavi anionov se dobro ujemajo z izračunanimi *ab initio* energetskimi preferencami. NMR podatki so odličen senzor za interakcije med anioni in njihovimi receptorji. Sposobnost spremljanja prerazporeditve elektronske gostote in konformacijske predorganiziranosti anionskih receptorjev nam je omogočila primerjavo njihove težnje za vezavo in selektivnosti do anionov; razlike med NOE ojačitvami pa so bile osnova za določitev konformacijskih ravnotežij po vezavi anionov. Ugotovitve o konformacijskih preferencah anionskih receptorjev in njihovih kompleksov z različnimi anioni v raztopini bodo prispevale k boljšemu razumevanju interakcij anion–receptor in dale nove spodbude za sintezo specifičnih anionskih receptorjev.

Ključne besede: indol; konformacijska analiza; NMR spektroskopija; prepoznavanje anionov; sistemi anion–receptor