ＲＳＣＡＮ並びにＰＢＥ関数を用いた密度汎関数理論ＣＡＳＴＥＰ核磁気共鳴によるアミノ酸並びにそれらの塩の異方性特性の知見

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Understanding anisotropic properties of amino acids and their salts by DFT CASTEP NMR using functionals RSCAN versus PBE

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The combination of experimental solid-state NMR and computational techniques in NMR crystallography have the potential to help understand the stability of the overall pharmaceutical formulation. The aim of the presented research is to evaluate whether the RSCAN meta-GGA functional can be used in place of the more common PBE GGA functional when carrying out GIPAW calculations of ^{13}C chemical shift anisotropy. We are developing an analytical tool using solid-state NMR to assess the protonation state of the carboxyl group in salts between amino acids and small molecule pharmaceuticals containing weakly acidic groups, such as phosphate prodrugs or phenol groups, where there may be some uncertainty as to which acid group is deprotonated.

GIPAW[1] calculations were performed using CASTEP[2] on a series of amino acids and their hydrochloride salts for which crystal structures were available in the Cambridge Structural Database, using the PBE[3] GGA functional or the RSCAN[4] meta-GGA functional. The results of the calculations were compared to experimental solid state NMR data obtained from literature[5]. This was evaluated by determining the root mean squared deviation between the calculated values and the experimental values reported in literature.

The calculations were carried out on the high-performance cluster, Avon, at the University of Warwick SCRTP, with each compute node having two Intel Xeon Platinum 8268 2.9 GHz CPUs and 192 GB DDR4-2933 RAM. Each calculation was set to use 12 tasks across four CPUs per task per node, with four nodes being used, giving a total of 192 CPUs, with the calculation distributed 48 ways. Each calculation had the maximum number of iterations for the geometry optimisation step set to 500 with an energy cut-off of 600 eV.

The calculated and experimental chemical shielding tensor values for the carboxyl carbon of the considered amino acids and their hydrochloride salts are presented in Table 1. The first CSA tensor element, δ_{11} is indicative of the protonation state of the carboxyl group, with an experimental value below 250 ppm indicating that it is deprotonated, and a value above 250 ppm indicating that it is protonated.[5] Both sets of calculations reproduce the effect of a higher δ_{11} for the hydrochloride salt samples. There is better agreement with the experimental data for PBE as compared to RSCAN, with the difference between the first and last tensor elements being larger for PBE than in the experimental data from literature, whereas it is smaller for RSCAN. Using a single point for σ_{ref}, the root mean squared deviation was 3.62 ppm using PBE, and 3.68 ppm using

RSCAN. Table 2 shows the spans of these tensor values, and shows that the descrepancy in the calculated span is less for PBE than for RSCAN when compared to the experimental data from literature.

The root mean squared deviation δ_{11} results obtained thus far suggest that PBE is only slightly more accurate than RSCAN, however it was observed that results obtained with PBE were often above the expected values, whereas those obtained using RSCAN were below than the values in literature.

Table 1. Comparison of GIPAW calculated and experimental ^{13}C CSA tensors of amino acids and HCl salts obtained from literature.

Compound	PBE Calculated Tensors (ppm)	RSCAN Calculated Tensors (ppm)	Experimental Tensors (ppm)[5]
L-glutamine	247, 167, 104	237, 169, 113	241, 172, 106
L-alanine	246, 178, 107	238, 178, 115	240, 184, 110
L-aspartic acid	243, 158, 106	238, 177, 113	242, 179, 106
L-cystine	244, 170, 107	237, 173, 115	243, 174, 108
L-glutamic acid	243, 153, 110	238, 183, 112	243, 185, 107
L-threonine	243, 142, 110	238, 161, 115	243, 168, 107
L-asparagine	247, 168, 106	238, 169, 113	243, 170, 108
L-alanine HCl	259, 164, 106	253, 163, 114	254, 163, 111
Glycine HCl	257, 152, 104	254, 156, 113	254, 155, 111
L-aspartic acid HCl	256, 155, 107	254, 161, 114	253, 149, 106

Referenced using $\sigma_{ref(PBE)}$=169 ppm and $\sigma_{ref(RSCAN)}$=188 ppm, as determined such that δ_{iso}(L-glutamine)=173 ppm

Table 2. Comparison of GIPAW calculated and experimental ^{13}C CSA tensor spans of amino acids and HCl salts obtained from literature.

Compound	PBE Calculated Tensors Span (ppm)	RSCAN Calculated Tensors Span (ppm)	Experimental Tensors Span (ppm)[5]
L-glutamine	143	124	135
L-alanine	139	123	130
L-aspartic acid	137	125	136
L-cystine	137	122	135
L-glutamic acid	133	126	136
L-threonine	133	123	136
L-asparagine	141	125	135
L-alanine HCl	153	139	143
Glycine HCl	153	141	143
L-aspartic acid HCl	149	140	147

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