Ab initio calculation of A-beta (PrP$_{109\text{-}122}$) fragments

The specific IR peaks in a biological system are mainly in three types (cf., fig. 1): amide I bands (80% C=O stretch, near 1650cm^{-1}), the amide bands II (60% N–H bend and 40% C–N stretch, near 1550cm^{-1}), and the amide bands III (40% C–N stretch, 30% N–H bend, near 1300 cm^{-1}). Here we would like to focus on the Amide I bands, especially on the coupling among those C=O stretch in the system with several beta strains.

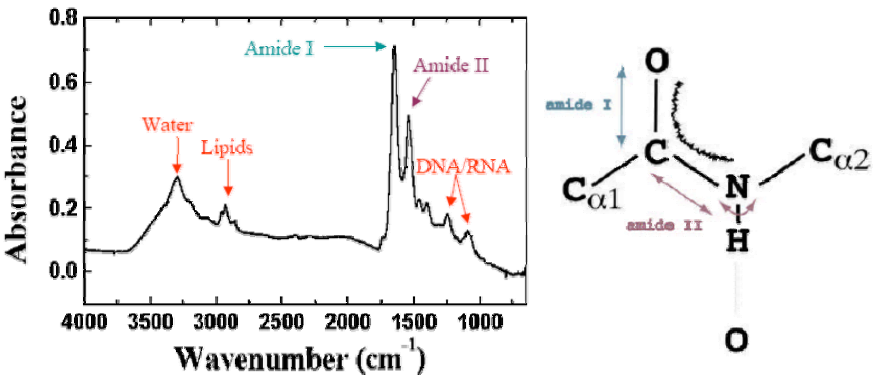


Figure 1 Typical IR absorptions of Amide Bonding

The direction of x-axis of the IR spectrum (Fig. 2) is made for the convenience of comparison to the calculation outputs. Why we want to check the system by an alternative approach is that the IR observation of this A-beta fragment peak is shifted by 10 cm^{-1}. We want to see whether the C=O stretching frequency is affected by the coupling of the carbon 13 labeling carbonyl C=O stretching or not. In Vicky's system, an anti-parallel system with residues 117-to-117 h-bonding formation, both of them have ^{13}C=O group. And the result IR peak locates with 10 cm^{-1} difference in compared with other labeled schemes.

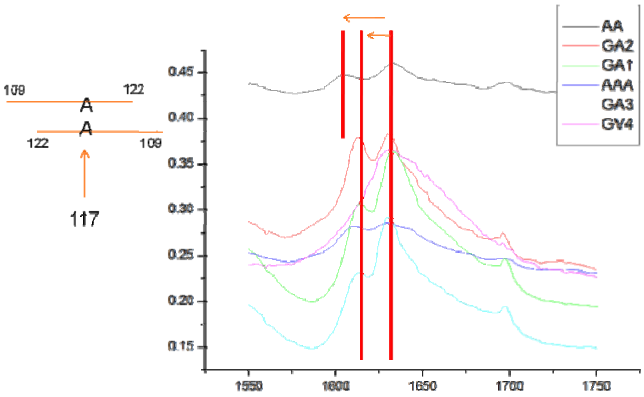


Figure 2 IR shift on Amide I in a carbonyl isotope labeling A-beta

The carbonyl stretching of carbonyl groups in a fibrilizing system at least contain a dimer hyperstructure seems to be affected by the formation of H-bonding. If there is not only a multi-mer system but also a layer-layer stacking situation. Whether the C=O stretching frequency shift is due to an intra-layer coupling or by an inter-layer vibration coupling between carbonyl groups would be the aim of calculation.

In the steps so far, I chose Ac-(G)$_n$-NHCH$_3$, a polyglycine fragment with number of glycine equals to 3, 5, and 7. The modifications on both two termini, acetylation and aminomethylation groups are used to cap the central residues so that the most configuration strains are the same as a long beta-sheet. The structure is based on the 2ONA protein crystal structure. After modification on the termini and change all the side chain to hydrogen, i.e. polyglycine, two energy minimizations are performed by Gaussian 03. In the first optimization, all the heavy atoms on the backbone except the modification groups are fixed on their positions. Only hydrogens and the terminal capping groups are optimized in order to reduce the energy penalty from abnormal bond lengths, bond angles, and torsion angles. The second step in whole optimization process is an all-atom energy minimization of the result conformation in the first optimization. These two energy minimization is using density functional theory (DFT) with B3LYP methods and 6-311++G as the basis set.

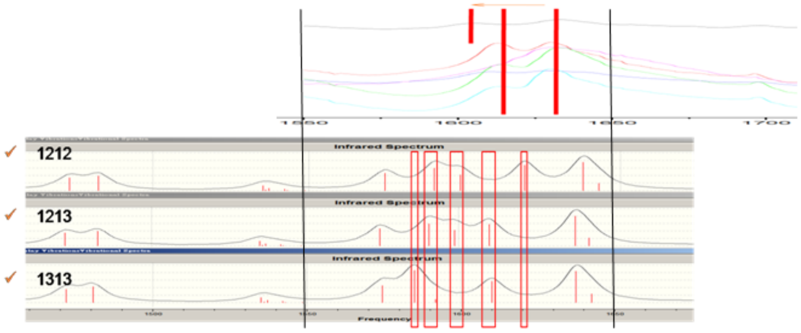


Figure 3 Comparison between experimental and calculated data

The experimental data show that when two ^{13}C=O stretching couple to each other, the IR stretching would be of a 10 cm^{-1} smaller than systems with “12-13” isotope configuration. 12-13 mean the isotope of carbon number 11 and 36, respectively. My calculation results are performed in the following procedure: **(1) Geom. Opt. (frozen all the heavy atoms, using DFT (b3lyp) method with 3-21g basis set); (2) Frequency calculation (DFT (b3lyp) method with 6-311++g basis set).** We got the initial backbone structure from 2ONA pdb file. There are also amidations and acetylations on the C-termini and N-termini of each beta strain, respectively. In the theoretical calculation results, we can only see the right TREND (red shift from 13-13 to 12-13) and the difference is only 4 cm^{-1}. Also, we found the group of peaks shifts in the way just like right trend of the frequency-to-reduced mass relation (i.e., $\nu \propto$ (1/ μ)^0.5). Therefore, the result shows a continuous red shift from 12-12, 12-13, to

13-13. The above figure shows the comparison among different configurations and between two approaches.

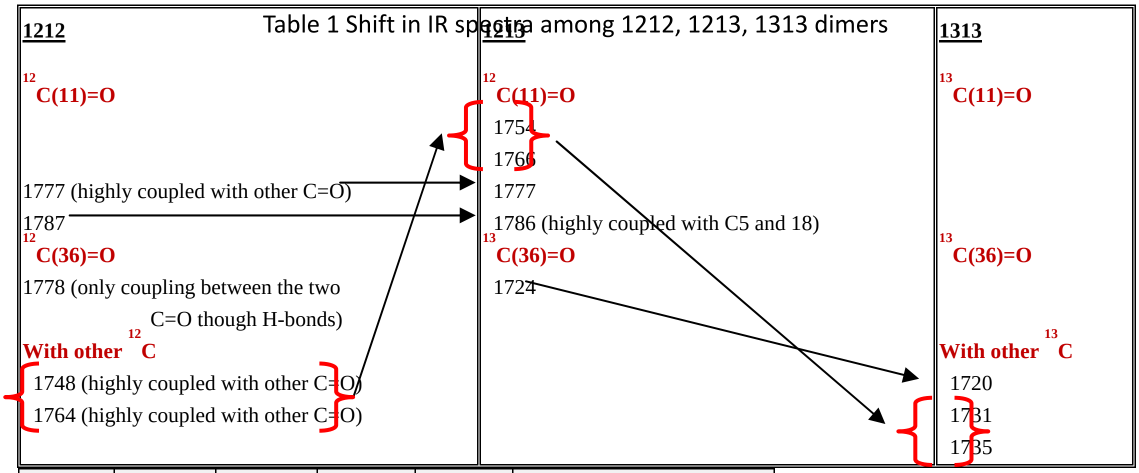


Table 1 Shift in IR spectra among 1212, 1213, 1313 dimers

1212

^{12}C(11)=O

1777 (highly coupled with other C=O)

1787

^{12}C(36)=O

1778 (only coupling between the two C=O though H-bonds)

With other ^{12}C

1748 (highly coupled with other C=O)

1764 (highly coupled with other C=O)

1213

^{12}C(11)=O

1754

1766

1777

1786 (highly coupled with C5 and 18)

^{13}C(36)=O

1724

1313

^{13}C(11)=O

^{13}C(36)=O

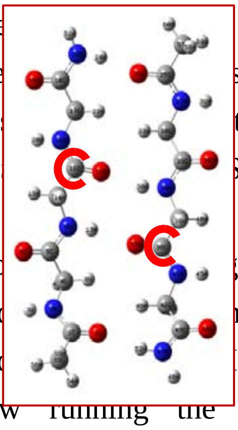
With other ^{13}C

1720

1731

1735

system	freq	Int.	C_{11}=O	C_{36}=O	coupled C=O Carbons
1212	1749.65	899.753	oo	ooo	C5, C25, C29
	1767.79	71.2707	oooo	ooo	C5, C25, C29, C43
	1779.34	646.194	oo	o	C5, C18, C25, C29
	1780.74	111.896	oooo	ooooo	C18, C25, C29, C43



After checking the ace that the some mi t *ab ini* Some of be mo group an the en am now running the new calculation with the same basis set in both of geometry optimization and frequency calculation. Besides, because of the erroneous result from those new calculations, I would execute them separately. Also, to restart a failed calculation with checkpoint file would be used. Arranged results so far are list in the following table.

	1788.6	176.025	oooo	ooo	C1, C5, C18, C25, C29, C43
	1800.02	455.343	-	o	C1, C43
	1807.87	170.872	ooo	-	C1, C5, C18, C25, C29, C43
	1825.86	332.693	-	o	C1, C43
system	**freq**	**Int.**	**C_{11}=O**	**$^{13}C_{36}$=O**	**coupled C=O Carbons**
1213	1724.23	539.1	o	ooooo	C5, C29, C43
	1752.87	312.961	o	ooo	C18, C25, C29, C43
	1770.58	40.7339	oooo	o	C5, C18, C25, C29
	1778.48	908.971	ooo	-	C5, C18, C25, C29
	1788.1	331.597	oo	o	C1, C5, C18, C43
	1790.1	92.048	oooo	-	C5, C18, C43
	1805.94	112.617	oooo	-	C1, C5, C18, C25, C29
	1823.8	355.444	o	o	C1, C5, C43
system	**freq**	**Int.**	**$^{13}C_{11}$=O**	**$^{13}C_{36}$=O**	**coupled C=O Carbons**
1313	1722.58	751.916	ooo	ooooo	C5, C29
	1736.28	119.166	ooooo	ooooo	C5, C18
	1753.93	181.225	o	ooo	C25, C29
	1776.13	525.224	o	o	C18, C25, C29
	1786.11	290.008	o	o	C1, C5, C18, C43
	1788.59	270.118	-	-	C1, C5, C43
	1802.14	173.813	o	-	C5, C18, C25
	1823.65	332.557	-	-	C1, C5, C43

Figure 4 dimer structure

Table 2 Shift calculation on the appropriate modifications on termini

Where the third and the forth columns are the relative “vibration-strength” of the specific carbonyl carbon, i.e. C12 and C36, represented by number of the “o”. “-“ means a neglectable vibrational motion, which couples with others very little. The other carbons (carbonyl carbon, mostly) participate a specific mode are listed in the last column. Peaks in the blue dash box are those assigned to the C=O bonds. The left are the spectra of three dimers with the same optimized structure (using 12-12 labeled, anti-parallel crystal structure as the initial structure). Compared with the former result (without acetylation), peaks seem to be a blue shift. The reason why the acetyl and amide modified, closer to the real-case system, deviate the IR experiments is going to be studied. There are several calculations including three strain length, two hyperstructures (dimer, layer by two dimers), and also the modification on the ends that would be checked.

Fig.5 is the result of formylated, amidated, three-residue dimer system IR spectra are listed as this wavenumber region. Cross and the region outside the blue dash box indicate the carbonyl free normal modes (for example, N-H stretching) or the vibration mode that C11 and C36 do NOT participate.

Peaks left would be compared between 1212, 1213 or between 1212 and 1313 systems. From 1212 to 1213, we can use the former mentioned conditions to find the shift on peaks. It is very clear that the isotope effect on the vibration frequencies by the other strain is performed. The shifts seem to be the same between corresponding modes. However, from 1212 to 1213, it would be less siginificant shifts presented, many modes disappear in the 1313 system, the paired carbon 13s couple so much and hence like a isolated portion in the dimer. If we check the type of vibration, I think this peaks is from this peak.

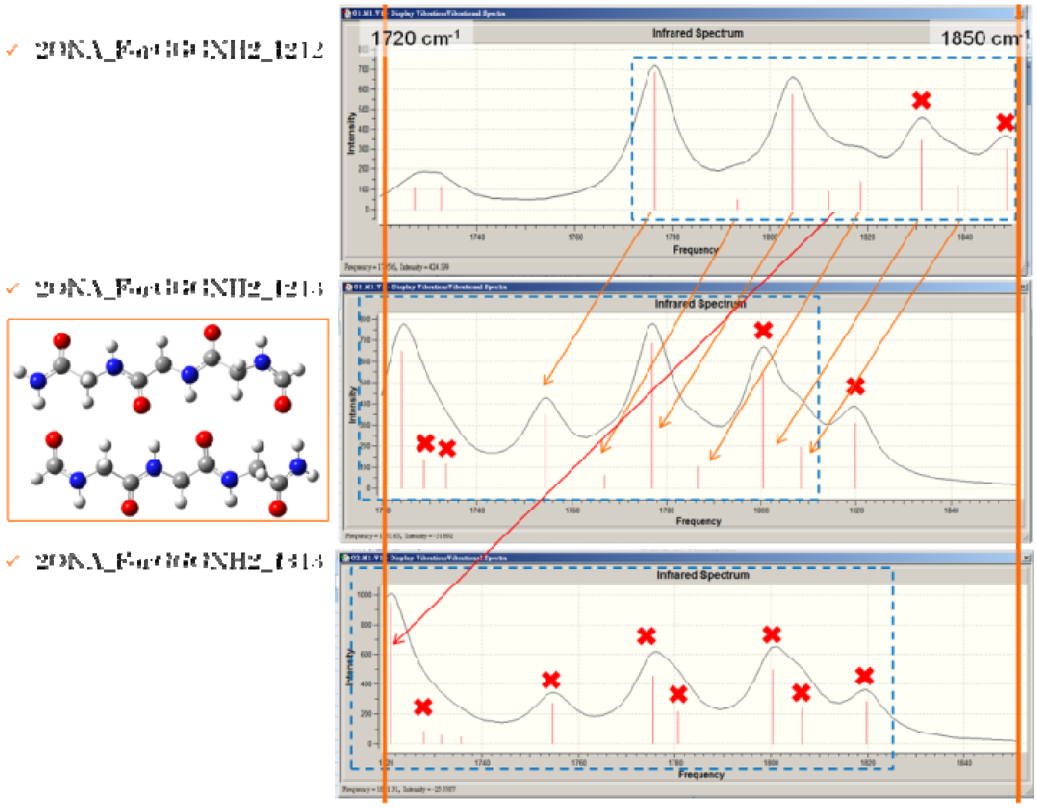
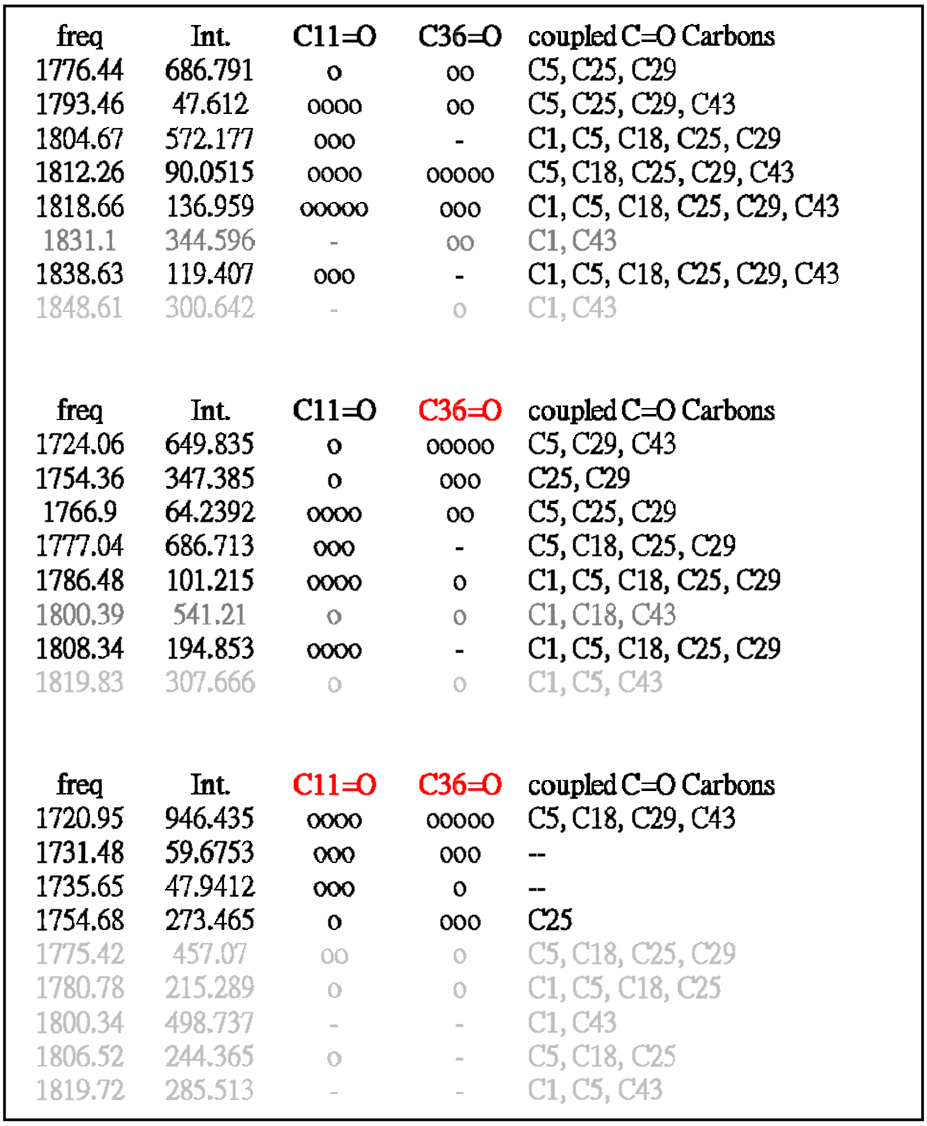


Figure 5 Calculation results of dimer system with For- and -NH2 modifications



freq	Int.	C11=O	C36=O	coupled C=O Carbons
1776.44	686.791	o	oo	C5, C25, C29
1793.46	47.612	oooo	oo	C5, C25, C29, C43
1804.67	572.177	ooo	-	C1, C5, C18, C25, C29
1812.26	90.0515	oooo	ooooo	C5, C18, C25, C29, C43
1818.66	136.959	ooooo	ooo	C1, C5, C18, C25, C29, C43
1831.1	344.596	-	oo	C1, C43
1838.63	119.407	ooo	-	C1, C5, C18, C25, C29, C43
1848.61	300.642	-	o	C1, C43

freq	Int.	C11=O	C36=O	coupled C=O Carbons
1724.06	649.835	o	ooooo	C5, C29, C43
1754.36	347.385	o	ooo	C25, C29
1766.9	64.2392	oooo	oo	C5, C25, C29
1777.04	686.713	ooo	-	C5, C18, C25, C29
1786.48	101.215	oooo	o	C1, C5, C18, C25, C29
1800.39	541.21	o	o	C1, C18, C43
1808.34	194.853	oooo	-	C1, C5, C18, C25, C29
1819.83	307.666	o	o	C1, C5, C43

freq	Int.	C11=O	C36=O	coupled C=O Carbons
1720.95	946.435	oooo	ooooo	C5, C18, C29, C43
1731.48	59.6753	ooo	ooo	--
1735.65	47.9412	ooo	o	--
1754.68	273.465	o	ooo	C25
1775.42	457.07	oo	o	C5, C18, C25, C29
1780.78	215.289	o	o	C1, C5, C18, C25
1800.34	498.737	-	-	C1, C43
1806.52	244.365	o	-	C5, C18, C25
1819.72	285.513	-	-	C1, C5, C43

Table 3 Calculation results of dimer with for- and -NH2 modifications

An alternative presentation is the table here (table 3), the intensity, the displacements of labeled carbons, and the other coupled carbons are listed after frequencies as well. The Grey lines mean these normal modes mainly belong to vibrations on other carbons. However ,the mode includes mainly C11 and C36 with relative small displacements would still be thought as the characteristic one, for example, the second line in the 1213 dimer system. “-” means that the displacement, or the vibration on specific carbon is neglectable. Hence we can now find shifts between two isotope-labeled system on the basis of intensity, displacements and coupled status. That is, those carbons participate the vibration mode. Besides, I also checked the dipole derivative unit vector for another certification. It could be present through a cartoon with possible shift arrows (start from the original peak and end to the final peak). In acetyl modification cases, spectra are illustrated in the same notation. But the shifts are not so clear to assigned. However, I can still assign some of them but not the carbonyl vibration modes. For example, this is the stretching of the carbonyl group which contributed almost all by the terminal one. The shift on this mode is not observed. These peaks are around 1823 cm-1. Besides coupling between C11 and C36 is still observed in here, but in the 1212 system, even the coupling exists, it is a minor contribution. In the 1213 and 1313 system, characteristic coupling frequency shift to about 1720 cm^{-1}.

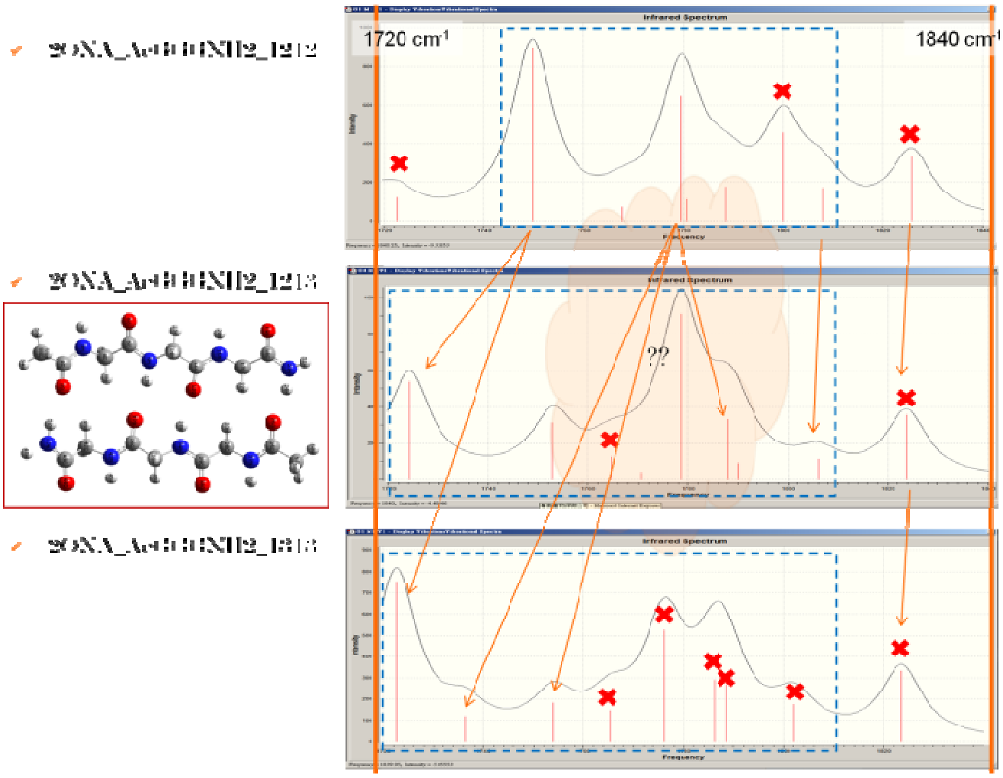
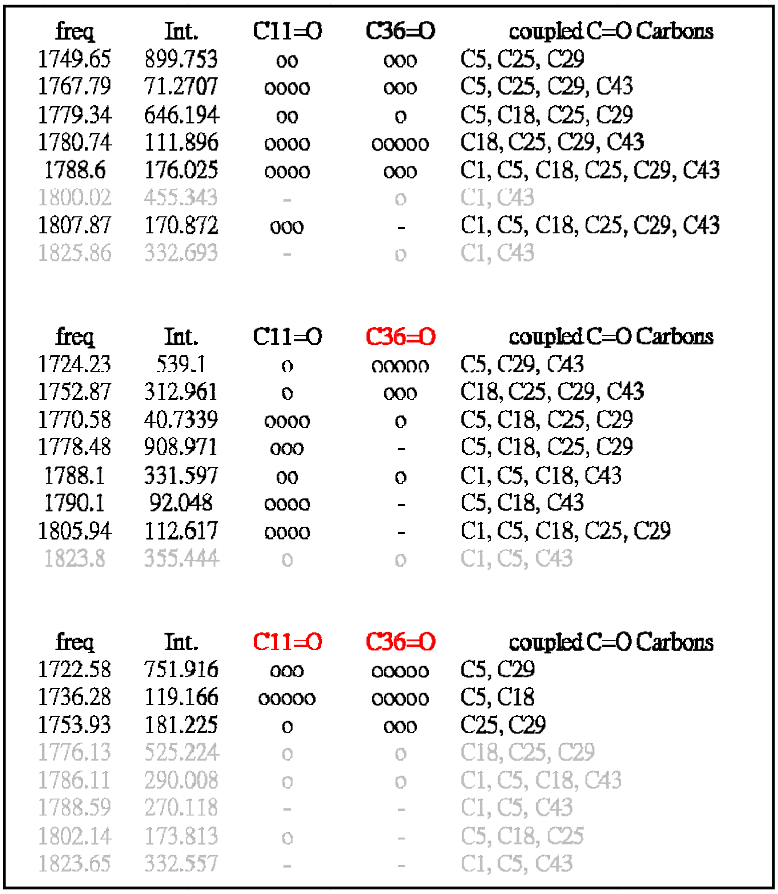


Figure 6 Dimer calculation results with Ac- and -NH2 modifications



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1788.59	270.118	-	-	C1, C5, C43
1802.14	173.813	o	-	C5, C18, C25
1823.65	332.557	-	-	C1, C5, C43

Table 4 Dimer calculation results with Ac- and -NH2 modifications

Because the longer fragments with G more than 5 never converge in the energy minimizations, I change the method and the basis set level to perform the minimizations. The calculations are running.