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*ORIGINAL ARTICLE*

# Calculation of the magnetic resonance isotropy tensors of the nucleus of POPC phospholipid bilayers in a cell membrane

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Importance of membrane phospholipids and their various applications in various sciences and industries including chemistry and biochemistry, chemical sensors and treatment of diseases and effective delivery of drugs and materials through cellular membrane is clear. Investigation of the NMR parameters including isotropy of the isotropic value ($\sigma_{iso}$), anisotropy chemical shift ($\sigma_{aniso}$), reduced anisotropy (δ), asymmetric parameter (η) of the anisotropy parameter (Δσ) and skew parameter (Ƙ) enables the recognition of target active centers. Phospholipid structure was optimized using calculation of molecular mechanics and quantum mechanics. Then, using ab initio calculations, factors of NMR chemical isotropy tensor were calculated for membrane phospholipids. According to results, it was found out that carbon no. 2 bonded to nitrogen and after that, no. 32 carbon atom bonded to the oxygen have most contribution to the dynamics movements of phospholipid in membrane. It can be concluded that high electronegativity of the nitrogen and oxygen plays an important role in sensitivity of the phospholipid carbons. Increased number of electronegative agents in the phospholipid results in better control of the dynamic role of the membrane. Evaluation of the NMR parameters of phospholipid structure led to recognition of the active centers and owing to the mutual effect of these centers, transfer and exchange in these active sites and if agents similar to the human's genetic structure are taken into account for transfer and exchange, they can be very useful and rapid transmitters for delivery of drugs to the target cells.
**Key words:** Theoretical chemistry; phospholipids; nucleus magnetic resonance; chemical isotropy tensors

## Introduction

One of the biological processes of organisms and enzymatic reactions is the reaction of membrane phospholipids (Young, 2001). Computational chemistry enables us to study the chemical reactions and complexes using computerized calculations rather than laboratory. In reality, computational chemistry can simulate molecules and their reactions and yields results faster (Jensen, 2001; Anishkin, *et al.*, 2006). In summary, quantum chemistry is the application of quantum mechanics in chemical issues and drawing upon the quantum mechanics, it intends to answer chemical problems (Elsagh *et al.*, 2015). Quantum chemistry includes ab initio studies, semi-empirical studies, molecular mechanics studies, and simulation studies (Amara and Field, 2003). Molecular interactions calculations are done using molecular mechanics, quantum mechanics, or a combination of both (Senn and Thiel, 2009; Elsagh *et al.*, 2016; Gao and Truhlar, 2002; Klahn, *et al.*, 2005; Friesner and Guallar, 2005).

Cellular membrane is a structure having 7-10 nm thickness which determines the borders of the cells and controls the materials exchange between cell and surrounding environment as a selection barrier. Membrane is composed of a continuous lipid layer in which protein particles are dispersed. Phospholipids are molecules composed of a head-like part and a tail connected to it. Most of the membrane molecules are phospholipid molecules. Each phospholipid molecule has two parts: a hydrophilic head and a lipophilic tail.

Phospholipid is a type of lipid composed of a glycerol molecule and a phosphate molecule. This material is available in cellular membrane of all living organisms. Cellular shell or plasma membrane refers to one- or two-layer phospholipid shell around the cells. Cellular shell is also a border surrounding intercellular organelles. In fact, cellular shell is a wall, which protects the cell (Looish *et al.*, 2007). Phospholipids are the most important polar lipids which constitute the main part of the cellular shell in all organisms. Phospholipids form a two-layer membrane to act as a protective and selective barrier and adjust the survival of the cell. Two phospholipid layers are arranged so that their polar heads are toward the outside of the layers and nonpolar heads are toward each other (Elsagh *et al.*, 2015).

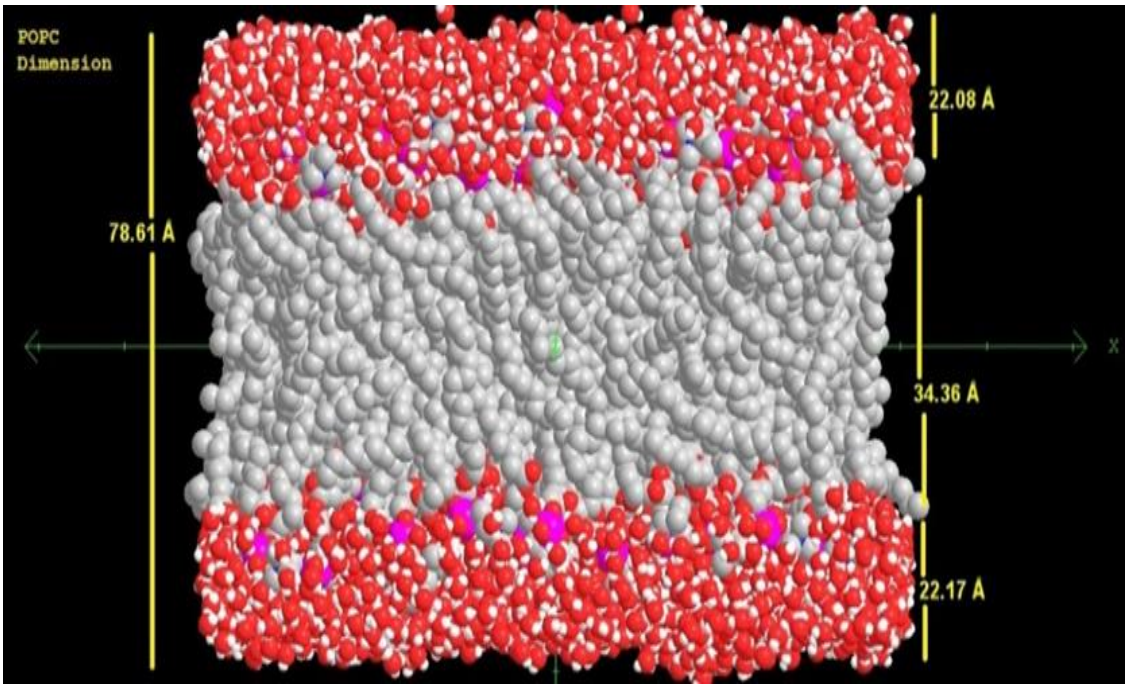


**Fig. 1.** Phospholipids of two-layer membrane (from Elsagh et al., 2016)

Nuclear resonance spectrometry (NMR) engages with the intranuclear interactions and magnetic fields and is a strong technique for evaluation of the structural and dynamic properties of the molecules in different physical conditions (Alam, 1970; Hou *et al.*, 2013). Structures used in calculations quantum must be well optimized. Following instructions are used for calculation of the magnetic resonance (Elsagh *et al.*, 2014).

**Table 1.** Instructions used for NMR calculations

| Command | Method | Basic sets |
|---|---|---|
| NMR | # HF | sto-3g |
| | | 3-21g |
| | | 6-31g |
| | | 6-31g* |
| | # $B_3$LYP | 6-31g |
| | | 6-31g* |
| | # M062X | 6-31g |

In this study, using quantum mechanics computations, the NMR parameters of phospholipid structures are computed which enables the recognition of Phospholipid active centers having high electronegativity. These centers can impart significant effects on the transfer and exchange of targeted smart drugs. Hence, the mutual effects of the active centers and drug agents can be investigated. This can open up very useful and interesting areas of research in different sciences and industries, such as medicinal chemistry and pharmacology.

## Method

The Hartree-Fock method is a general method used for the isotropy computations (Alam, 1998; Gendron and Autschbach, 2016). This approximation which represents the electron wave function as a single-electron form, introduces the effect of other electrons as an effect of static field (Brown, 1996). Chemical displacement reaction is expressed usually in the form of $H_{cs}$ term.

$$\hat{H}_{cs} = \gamma \hbar \Gamma.\sigma.B_0 \quad (1)$$

Where, γ is the gyromagnetic ratio, Γ is the operator of spin angular momentum vector, $B_0$ is the magnetic field and h is the Planck coefficient divided by 2π. Since the chemical displacement occurs as a result of environmental electrons, it can provide unique information about chemical environment of the nucleus (Alam and Jenkins, 2012). When a sample is outside of the magnetic field, electronic cloud around the nuclei tend to become aligned in rotation so that they can establish a field in the opposite direction of the external field. Such rotation is called diamagnetic rotation. Overall field in atom nucleus is expressed as follows:

$$B_{effective} = B_{external} - B_{induced} \quad (2)$$

Since the induced field is directly proportional to the external field, it can be said that:

$$B_{induced} = \sigma B_{external} \quad (3)$$

Where, σ is proportionality factor. Then, we have:

$$B_{effective} = B_z (1 - \sigma) \quad (4)$$

The electromagnetic diamagnetic rotation has the effect of shielding an external field on a nucleus in which the amount of coverage for a particular atom is constant, but changes with the electron density around the atom in a molecule. So we can write the above equation as follows:

$B_i=B_Z (1- \sigma_i)$ (5)

Where, $B_i$ is the field received by nucleus i having isotropy constant $\sigma_i$. For example, since oxygen is more receptive of the electron compared to carbon and has more electronegativity, density of the electron around hydrogen in C-H bonds is considerably higher than that of H-O bonds. Therefore, it is expected that $\sigma_{CH}<\sigma_{OH}$ and we have:

$B_{CH}= B_Z (1- \sigma_{CH}) < B_{OH}=B_Z (1- \sigma_{OH})$ (6)

Hence, it can be said that chemical isotropy implies to those phenomena which are dependent upon secondary magnetic field resulted from electrons' movement around the nucleus and are under an external magnetic field. Energy of a magnetic moment under magnetic field B is:

$E= - \mu (1- \sigma B)$ (7)

Where, σ is the isotropy constant and the differential displacement as a result of electrons movement. It is given by a 3×3 matrix. Relationship between magnetic field having induced magnetic field and external magnetic field will be a 3×3 isotropy tensor as follows.

$$\begin{bmatrix} B_1 \\ B_2 \\ B_3 \end{bmatrix}_{ind} = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{21} & \sigma_{22} & \sigma_{23} \\ \sigma_{31} & \sigma_{32} & \sigma_{33} \end{bmatrix} \begin{bmatrix} B_1 \\ B_2 \\ B_3 \end{bmatrix}_0$$

In the principal axis system (PAS), symmetric part of the isotropy tensor is defined as follows and σ is defined using diagonal elements.

$$\sigma = \begin{bmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{bmatrix} \longrightarrow \sigma_{PAS} = \begin{bmatrix} \sigma_{11} & 0 & 0 \\ 0 & \sigma_{22} & 0 \\ 0 & 0 & \sigma_{33} \end{bmatrix}$$

Three main elements, $\sigma_{11}$, $\sigma_{22}$ and $\sigma_{33}$ represents the chemical isotropy interactions in three dimensions.

Chemical isotropy tensor implies normally to the anisotropy chemical displacement tensor. Measuring the diagonal components in PAS (Principle Axis System) enables the complete description of CSA (chemical shift anisotropy) (Hazime and Isao, 2010).

The Isotropic value ($\sigma_{iso}$) is obtained as follows.

$\sigma_{iso} = (\sigma_{11} + \sigma_{22} + \sigma_{33}) / 3$ (8)

Furthermore, skew parameter (Ƙ) is given as follows.

$Ƙ = 3 * (\sigma_{iso} - \sigma_{22}) / (\sigma_{33} - \sigma_{11})$ (9)

Using above formula, anisotropy chemical shift ($\sigma_{aniso}$), reduced anisotropy (δ), asymmetric parameter (η) and anisotropy parameter (Δσ) of the isotropy tensor will be calculated.

a) If $[\sigma_{11}- \sigma_{iso}] \geq [\sigma_{33}- \sigma_{iso}]$, we have:

$\delta = \sigma_{11} - \sigma_{iso}$ (10)

$\eta = (\sigma_{22} - \sigma_{33)} / \delta$ (11)

$\Delta\sigma = \sigma_{11} - (\sigma_{22} + \sigma_{33)} / 2$ (12)

b) If $[\sigma_{11}- \sigma_{iso}] \leq [\sigma_{33}- \sigma_{iso}]$, we have:

$\delta = \sigma_{33} - \sigma_{iso}$ (13)

$\eta = (\sigma_{22} - \sigma_{11)} / \delta$ (14)

$\Delta\sigma = \sigma_{33} - (\sigma_{22} + \sigma_{11)} / 2$ (15)

Ƙ is the skew parameter and varies from -1 to 1. η is the asymmetric parameter and varies from 0 to 1 (Hazime and Isao, 2010; ShakibayiFar *et al.,* 2015; Pandey *et al.,* 2016).

All of the measurements of magnetic isotropy were performed using GIAO method. Hence, structure of phospholipid was optimized using 6-31G series in HF level and Gaussian input was prepared after sketching by Chem3D. In this work, effect of inter intermolecular interactions on chemical isotropy of the phospholipid nuclei was evaluated and calculations are presented below. This study has been performed based on recent works by famous researchers (Widdifield and Schurko, 2009; Alam *et al.,* 2016).

## Results and Discussion

Fig. 2 represents the single phospholipid molecule in membrane with respect to spatial coordinates through quantum mechanical-molecular mechanical (QM-MM) and using Monte Carlo simulation method. For calculations, we need output of the molecular optimization and upon typing corresponding command, software starts calculations.

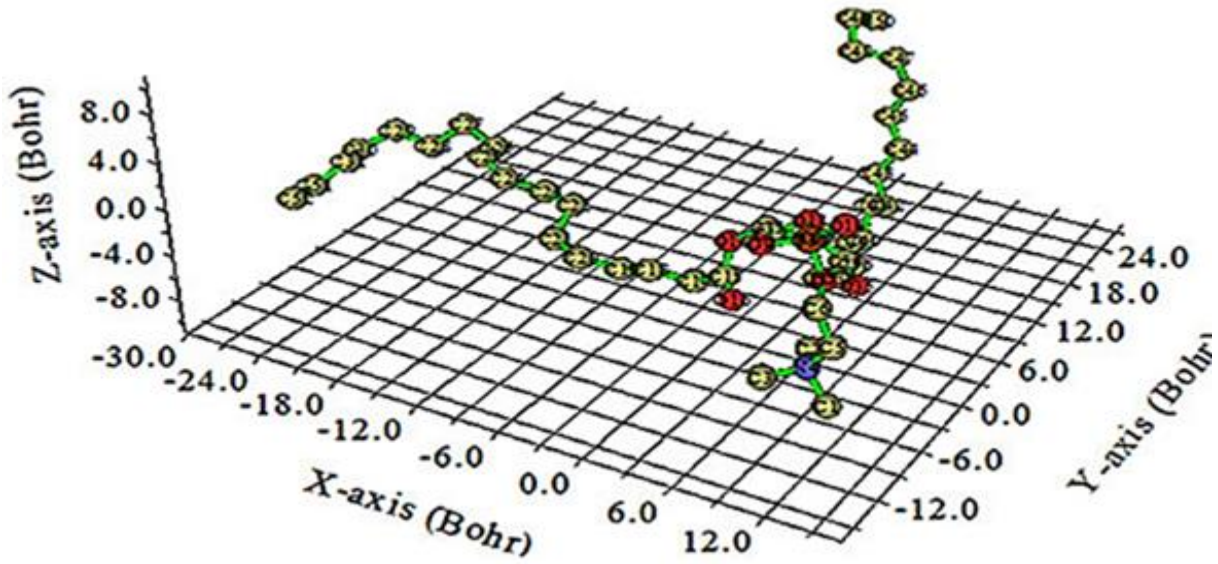


**Fig. 2.** Simulated and optimized phospholipid molecule (from Elsagh et al., 2016)

In resulting output file, SCRF (Self-consistent reaction field) and GIAO (gauge including atomic orbital) Magnetic Shielding Tensor data are important. Values and numbers of isotropy, anisotropy, xx, yy and zz are noted and using calculations, NMR factors including isotropic value ($\sigma_{iso}$), anisotropy chemical shift ($\sigma_{aniso}$), reduced anisotropy (δ), asymmetric parameter (η), parameter anisotropy (Δσ) and skew parameter (Ƙ) are calculated for membrane phospholipids.
In fig. 3, arrangement of phospholipid molecules is presented. Atom 4 is nitrogen in blue, atom 8 is phosphor in orange, atoms 7, 9, 10, 11, 14, 16, 33 and 35 are oxygen in red and all other gray atoms are carbon.

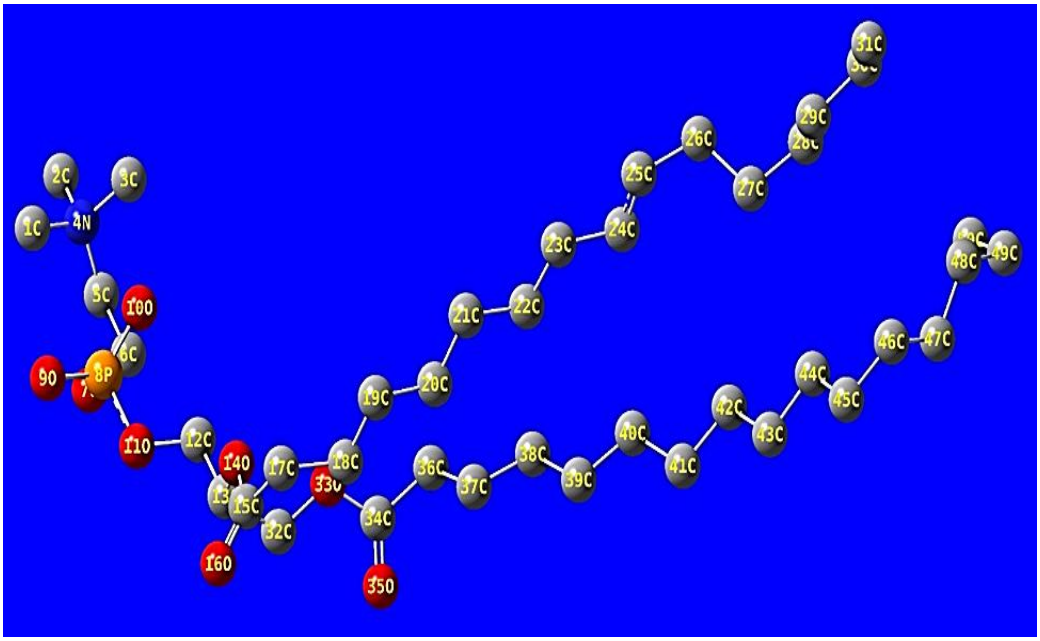


**Fig. 3.** Arrangement of atoms in phospholipid, NMR

Below we presented the results of NMR calculations for phospholipid molecules over magnetic resonance isotropy tensor of nuclei involving in the aforesaid structure (Tables 2-3, Figs 4-9).
By comparison of the $\sigma_{iso}$, $\sigma_{aniso}$, δ, η, Δσ and Ƙ reveals that highest value of reduced anisotropy (δ) is that of 2C atom which can be attributed to the C-N bond and high electronegativity of nitrogen leading to the intensified field. Regarding anisotropy parameter (Δσ), same is true. Least isotropic value ($\sigma_{iso}$), isotropy is for 32C atom while maximum value is for 2C bonded to nitrogen. Importantly, this trend can be observed in anisotropy of anisotropy chemical shift ($\sigma_{aniso}$). Minimum asymmetric parameter (η), of the isotropy tensor is for 32C as well. Usually, carbons have highest and oxygens have lowest values. Moreover, maximum value of skew parameter (Ƙ) refers to no. 2 carbon and minimum value is for no. 32 carbon atom.

**Table 2.** $\sigma_{iso}$ and $\sigma_{aniso}$ for atom number in phospholipid

| Atoms | $\sigma_{11}$ | $\sigma_{22}$ | $\sigma_{33}$ | $\sigma_{iso}$ | $\sigma_{aniso}$ |
|---|---|---|---|---|---|
| 1 C | -1882.7644 | -335.7212 | 2879.5645 | 220.3596333 | 3988.807 |
| 2 C | -427.8979 | 294.1625 | 10382.7655 | 3416.343367 | 10449.63 |
| 3 C | -409.7171 | 1517.5564 | 4319.8307 | 1809.223333 | 3765.911 |
| 4 N | -576.9714 | 438.9246 | 881.732 | 247.8950667 | 950.7554 |
| 5 C | -2020.4701 | -142.8077 | 658.0186 | -501.7530667 | 1739.658 |
| 6 C | -1414.6743 | 22.7533 | 192.4987 | -399.8074333 | 888.4591 |
| 7 O | -351.89 | 79.4902 | 319.0267 | 15.5423 | 455.2266 |
| 8 P | 306.4769 | 377.4227 | 613.719 | 432.5395333 | 271.7691 |
| 9 O | 163.7777 | 225.9251 | 254.0657 | 214.5895 | 59.2143 |
| 10 O | 158.048 | 223.2238 | 261.7767 | 214.3495 | 71.1408 |
| 11 O | -766.9731 | -109.1587 | 210.2496 | -221.9607333 | 648.3155 |
| 12 C | -562.0234 | -44.2992 | -8.1094 | -204.8106667 | 295.0518 |
| 13 C | -399.6897 | -28.7373 | 124.8405 | -101.1955 | 339.054 |
| 14 O | -218.5579 | 80.5799 | 244.7619 | 35.59463333 | 313.7509 |
| 15 C | -70.345 | 75.7058 | 115.7109 | 40.35723333 | 113.0305 |
| 16 O | -637.5526 | -197.0989 | 270.664 | -187.9958333 | 687.9897 |
| 17 C | -1114.3382 | -130.8726 | 129.2197 | -371.9970333 | 751.8251 |
| 18 C | -340.5527 | -108.5392 | 833.781 | 128.2297 | 1058.327 |
| 19 C | -635.4755 | -159.0393 | -52.6479 | -282.3875667 | 344.6096 |
| 20 C | -281.0157 | -105.7139 | 507.9354 | 40.40193333 | 701.3002 |
| 21 C | -381.303 | -164.7386 | -118.7603 | -221.6006333 | 154.2605 |
| 22 C | -207.4236 | -94.3906 | -26.9380 | -109.5840667 | 123.9691 |
| 23 C | -307.6108 | -108.7427 | 57.2438 | -119.7032333 | 265.4205 |
| 24 C | -505.4349 | -273.1289 | 131.9279 | -215.5453 | 521.2098 |
| 25 C | -516.9936 | -12.7449 | 551.6906 | 7.317366667 | 816.5598 |
| 26 C | -1392.8101 | 15.3257 | 1225.4353 | -50.68303333 | 1914.178 |
| 27 C | -1559.281 | -262.684 | 1079.1418 | -247.6077333 | 1990.124 |
| 28 C | -1441.7666 | -77.924 | 513.4920 | -335.3995333 | 1273.337 |
| 29 C | -686.4697 | -305.0012 | 856.1331 | -45.1126 | 1351.869 |
| 30 C | -1324.5057 | -217.2408 | -6.7068 | -516.1511 | 764.1664 |
| 31 C | -1951.6369 | -460.7551 | -285.7949 | -899.3956333 | 920.4011 |
| 32 C | -2999.1727 | -20.5477 | 111.9816 | -969.2462667 | 1621.842 |
| 33 O | -1291.7999 | -26.1616 | 178.6126 | -379.7829667 | 837.5933 |
| 34 C | -101.4155 | 88.7277 | 102.5315 | 29.9479 | 108.8754 |
| 35 O | -900.2234 | -207.9584 | 302.7163 | -268.4885 | 856.8072 |
| 36 C | -1570.8802 | -95.4996 | 153.5392 | -504.2802 | 986.7291 |
| 37 C | -701.7934 | -203.1773 | 1692.1678 | 262.3990333 | 2144.653 |
| 38 C | -428.016 | -205.9908 | 88.3373 | -181.8898333 | 405.3407 |
| 39 C | -895.4739 | -227.7463 | 231.9034 | -297.1056 | 793.5135 |
| 40 C | -363.6715 | -269.575 | 391.721 | -80.5085 | 708.3442 |
| 41 C | -1366.1111 | -254.9263 | 53.1696 | -522.6226 | 863.6883 |
| 42 C | -409.9734 | -164.0482 | 1425.0058 | 283.6614 | 1712.017 |
| 43 C | -1292.1202 | -260.3443 | 8.6987 | -514.5886 | 784.9309 |
| 44 C | -376.5119 | -63.7841 | 1376.1947 | 311.9662333 | 1596.343 |
| 45 C | -1095.4117 | -284.8178 | -144.524 | -508.2511667 | 545.5908 |
| 46 C | -1344.2799 | -114.3012 | 178.2566 | -426.7748333 | 907.5471 |
| 47 C | -413.9978 | 357.4879 | 2538.7394 | 827.4098333 | 2566.994 |
| 48 C | -1826.2077 | -410.5146 | 112.4363 | -708.0953333 | 1230.797 |
| 49 C | -919.7707 | -300.4216 | 805.4422 | -138.2500333 | 1415.538 |
| 50 C | -2384.2914 | -437.3046 | 87.6772 | -911.3062667 | 1498.475 |

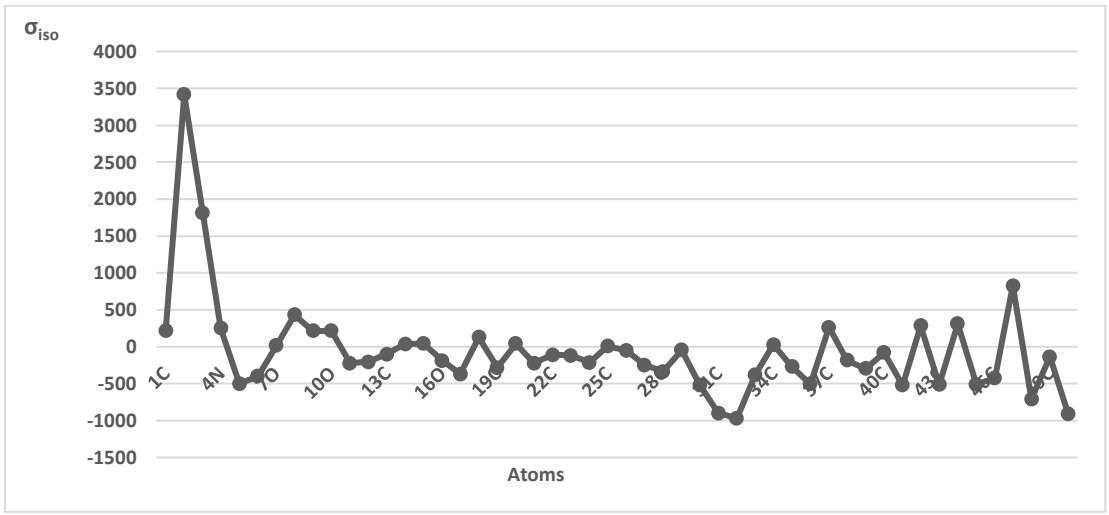


**Fig. 4.** $Q_{iso}$ versus atom number for phospholipid

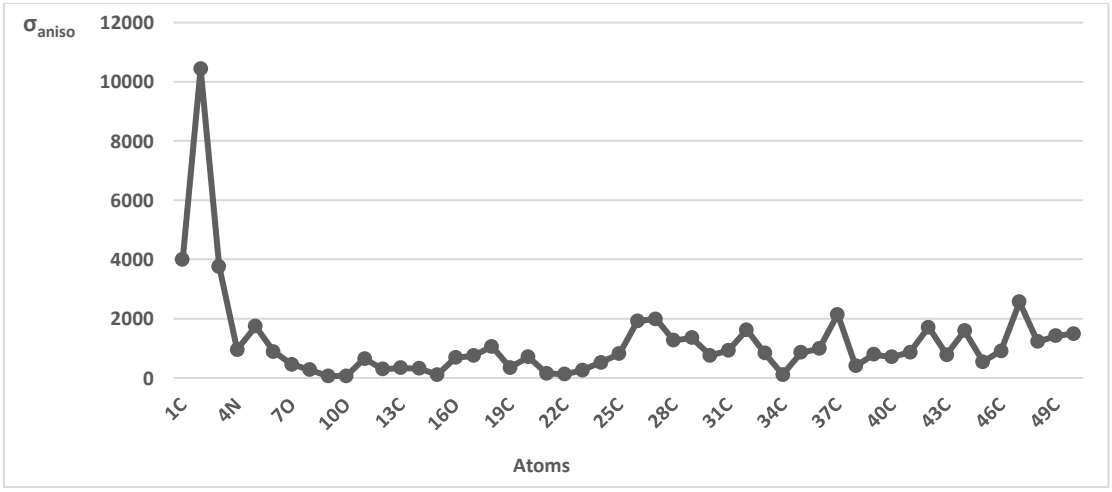


**Fig. 5.** $Q_{aniso}$ versus atom number for phospholipid

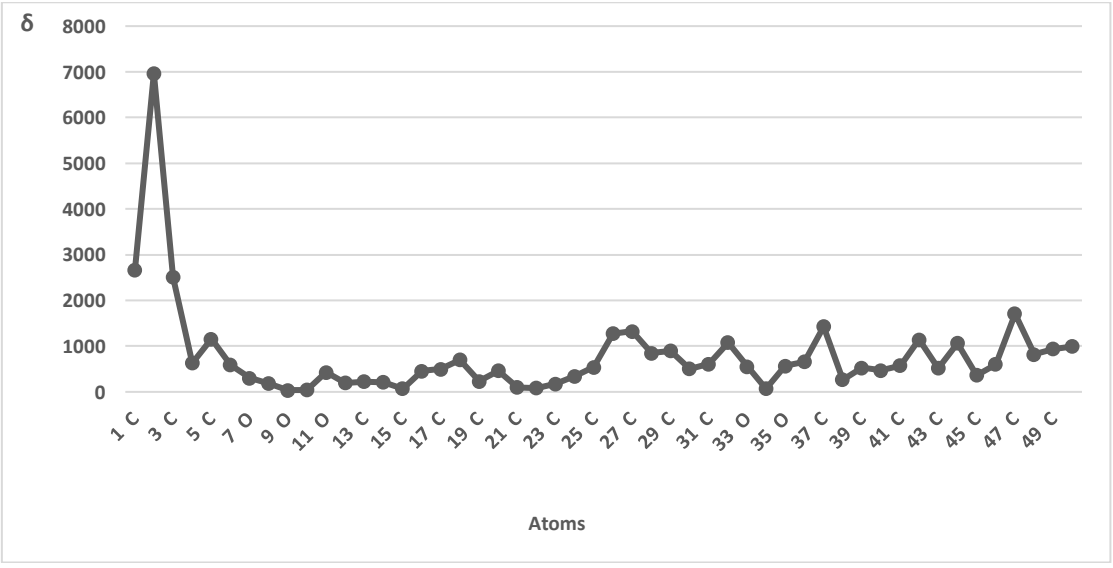


**Fig. 6.** δ versus atom number for phospholipid

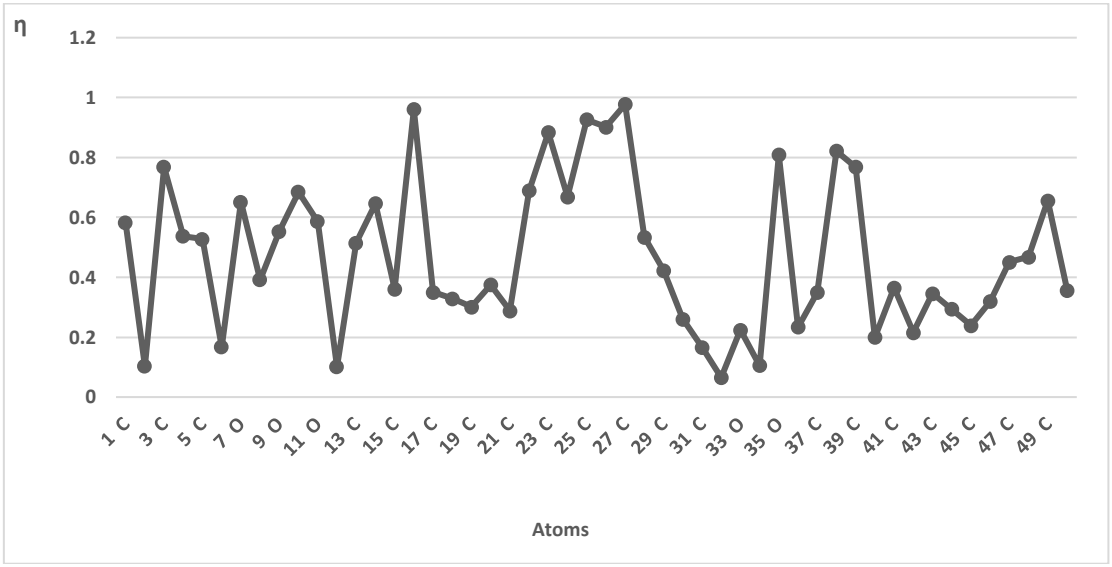


**Fig. 7.** η versus atom number for phospholipid

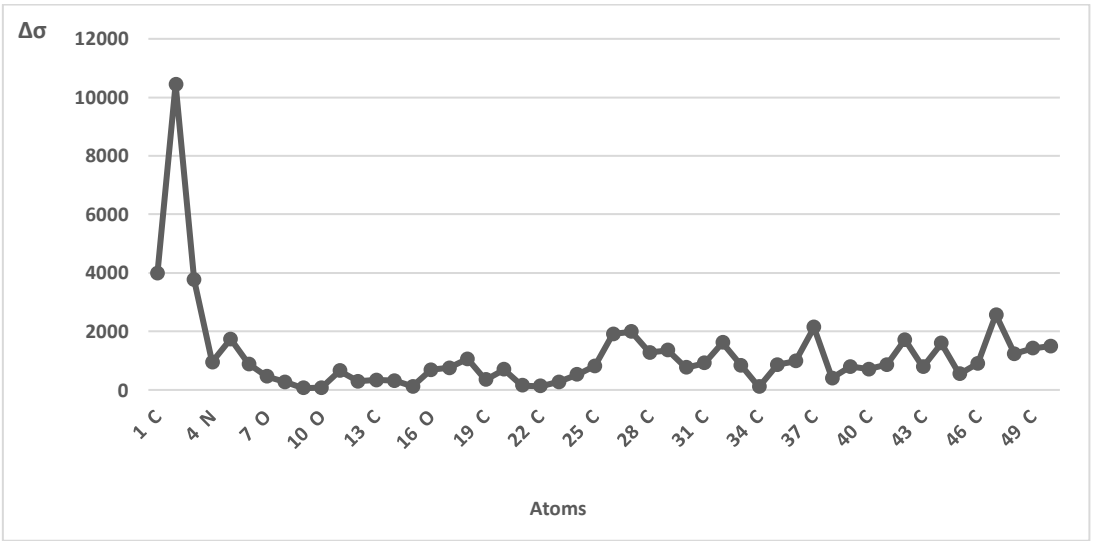


**Fig. 8.** Δσ versus atom number for phospholipid

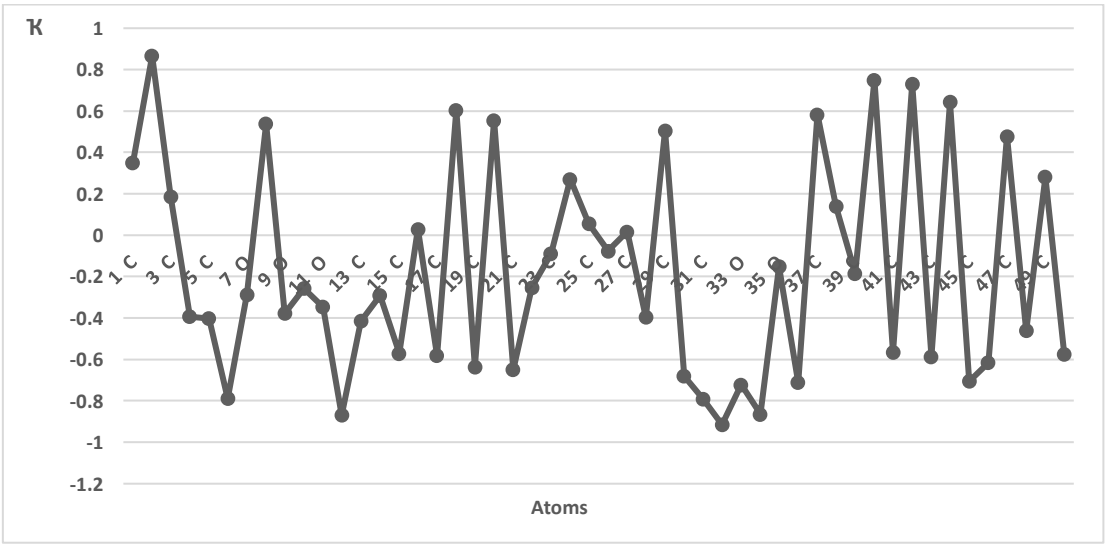


**Fig. 9.** Ϗ versus atom number for phospholipid

**Table 3.** Calculation of δ, η, Δσ and Ƙ for atom number in phospholipid

| Atoms | δ | η | Δσ | Ƙ |
|---|---|---|---|---|
| 1 C | 2659.204867 | 0.581769 | 3988.8073 | 0.350299724 |
| 2 C | 6966.422133 | 0.103649 | 10449.6332 | 0.866417005 |
| 3 C | 2510.607367 | 0.767652 | 3765.91105 | 0.185007285 |
| 4 N | 633.8369333 | 0.536823 | 950.7554 | -0.392875344 |
| 5 C | 1159.771667 | 0.527304 | 1739.6575 | -0.402031228 |
| 6 C | 592.3061333 | 0.167259 | 888.4592 | -0.788765242 |
| 7 O | 303.4844 | 0.65192 | 455.2266 | -0.285942651 |
| 8 P | 181.1794667 | 0.391577 | 271.7692 | 0.538176572 |
| 9 O | 39.4762 | 0.55382 | 59.2143 | -0.37664806 |
| 10 O | 47.4272 | 0.684758 | 71.1408 | -0.256658957 |
| 11 O | 432.2103333 | 0.586057 | 648.3155 | -0.346293736 |
| 12 C | 196.7012667 | 0.101312 | 295.0519 | -0.869330618 |
| 13 C | 226.036 | 0.514508 | 339.054 | -0.414417702 |
| 14 O | 209.1672667 | 0.645998 | 313.7509 | -0.291280019 |
| 15 C | 75.35366667 | 0.361376 | 113.0305 | -0.569966876 |
| 16 O | 458.6598333 | 0.960306 | 687.98975 | 0.030069039 |
| 17 C | 501.2167333 | 0.350368 | 751.8251 | -0.581696518 |
| 18 C | 705.5513 | 0.32884 | 1058.32695 | 0.604859334 |
| 19 C | 229.7396667 | 0.301317 | 344.6095 | -0.634912966 |
| 20 C | 467.5334667 | 0.37495 | 701.3002 | 0.555607946 |
| 21 C | 102.8403333 | 0.2879 | 154.2605 | -0.649746117 |
| 22 C | 82.64606667 | 0.689421 | 123.9691 | -0.252543139 |
| 23 C | 176.9470333 | 0.883341 | 265.42055 | -0.090122476 |
| 24 C | 347.4732 | 0.668558 | 521.2098 | 0.271039979 |
| 25 C | 544.3732333 | 0.926292 | 816.55985 | 0.056318602 |
| 26 C | 1276.118333 | 0.901636 | 1914.1775 | -0.07563317 |
| 27 C | 1326.749533 | 0.977273 | 1990.1243 | 0.017142362 |
| 28 C | 848.8915333 | 0.534557 | 1273.3373 | -0.395050864 |
| 29 C | 901.2457 | 0.423268 | 1351.86855 | 0.505422264 |
| 30 C | 509.4443 | 0.260448 | 764.16645 | -0.680476285 |
| 31 C | 613.6007333 | 0.166274 | 920.4011 | -0.789943824 |
| 32 C | 1081.227867 | 0.065288 | 1621.8418 | -0.914803776 |
| 33 O | 558.3955667 | 0.224529 | 837.59335 | -0.721473804 |
| 34 C | 72.5836 | 0.105081 | 108.8754 | -0.864633459 |
| 35 O | 571.2048 | 0.808369 | 856.8072 | -0.150955447 |
| 36 C | 657.8194 | 0.233488 | 986.7291 | -0.711162145 |
| 37 C | 1429.768767 | 0.348739 | 2144.65315 | 0.583438445 |
| 38 C | 270.2271333 | 0.821624 | 405.3407 | 0.140026025 |
| 39 C | 529.009 | 0.768172 | 793.5135 | -0.184568112 |
| 40 C | 472.2295 | 0.19926 | 708.34425 | 0.750867264 |
| 41 C | 575.7922 | 0.365264 | 863.6883 | -0.56584219 |
| 42 C | 1141.3444 | 0.21547 | 1712.0166 | 0.731958597 |
| 43 C | 523.2873 | 0.346022 | 784.93095 | -0.586348261 |
| 44 C | 1064.228467 | 0.293854 | 1596.3427 | 0.643148716 |
| 45 C | 363.7271667 | 0.238936 | 545.59075 | -0.70492036 |
| 46 C | 605.0314333 | 0.318862 | 907.54715 | -0.615696832 |
| 47 C | 1711.329567 | 0.450811 | 2566.99435 | 0.477443709 |
| 48 C | 820.5316333 | 0.467709 | 1230.79745 | -0.460498266 |
| 49 C | 943.6922333 | 0.656304 | 1415.53835 | 0.282002702 |
| 50 C | 998.9834667 | 0.356407 | 1498.4752 | -0.575252048 |

## Conclusion

Based on the results of NMR calculations for phospholipid, we find out that no. 2 carbon connected to the nitrogen has the most contribution to the dynamic movements of phospholipid in membrane and after that, no. 32 carbon atom which is bonded to the oxygen. Therefore, it can be inferred that high electronegativity of nitrogen and oxygen play an important role in sensitivity of carbon atoms of phospholipid. Therefore, more electronegative agents in phospholipid lead to better control of the membrane dynamic role. Investigation of the NMR parameters in phospholipid structure results in finding charge active

centers and owing to the mutual effect of these centers with pharmaceutical agents, issue of exchange in these active sites will be addressed. If agents with a structure similar to that of human genetic are taken into account, they can act as useful and rapid exchangers for delivery of drugs for the target cells so that at last, they can be removed from body with no side effects. Therefore, mutual effect of these centers and pharmaceutical agents can be evaluated. It can be a new and attractive research topic for all branches of chemistry including pharmaceutical chemistry and organic chemistry.

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