



Solvent Effects on N-Phthaloyl Chitosan Polymer: Prediction of Solubility in Different Solvents Using Theoretical Calculations

AMMAR A. IBRAHIM* and ROSIYAH YAHYA

Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia

*Corresponding author: E-mail: dr.ammar_1974@yahoo.com

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The theoretical calculations for different solvents in the gas phase have been evaluated by semi-empirical using (PM3) method and *ab initio* calculations using both HF/3-21G and DFT/B3LYP/3-21G methods. The physical properties of these solvents were compared between them to choose the best solvent to dissolve the [phthalic anhydride-chitosan] monomer, (I). These solvents are: dimethylsulfoxide, N,N-dimethyl formamide, tetrahydrofuran, 1,2-ethylene diamine, ethylene-carbonic acid and propylene-carbonic acid. The calculations show that (dimethylsulfoxide, N,N-dimethyl formamide and 1,2-ethylene diamine) are the good solvents to dissolve the [phthalic anhydride-chitosan] monomer, (I). The physical properties of the formation of [phthalic anhydride-chitosan] monomer, (I), were also calculated, using the parameters: dipole moment, HOMO, LUMO, hardness (η), electronic chemical potential (μ) and global electrophilicity index (ω). The results show that the computed geometrical parameters using the (PM3), (HF/3-21G) and (DFT/B3LYP/3-21G) are in good agreement with the experimental and the parameters play an important role to choose the best solvent. The synthesized N-phthaloyl chitosan polymer was also dissolved in many solvents in order to study the effect of solvent experimentally, but only three organic solvents (dimethylsulfoxide, N,N-dimethyl formamide and 1,2-ethylene diamine) were found to be able to dissolve it. These results are in agreement with the theoretical calculations. Finally, these calculations are useful for choosing the best solvent to dissolve the polymer of [phthalic anhydride-chitosan] monomer, (I).

Key Words: Chitosan, Solvent effect, QSAR, Physical properties, DFT.

INTRODUCTION

Chitosan is a natural and abundant polysaccharide obtained by N-deacetylation of chitin. Chitin is extracted from crustaceans and insect shells, algae and certain fungi. The physico-chemical and biological properties of chitosan such as biodegradability, biocompatibility, non-toxicity, mucosal adhesion, absorption enhancement and pH-dependent swelling are of great interest in the biomedical and pharmaceutical fields^{1,2}. Several modification techniques have been carried out for imparting hydrophobicity to the chitosan structure, such as phthaloylation, alkylation and acylation reactions. Acylated chitosan has been found to be an interesting chitosan derivative suitable for biomedical applications³⁻⁶. Chitosan, being one of the most abundant biopolymers, has recently become an interesting subject in many fields of science, as well as in industry because of its extensive applications in wastewater treatment, cosmetics, biomedicine and biology among other areas^{7,8}.

Chitosan, being a cationic polysaccharide in neutral or basic pH conditions, contains free amino groups and hence, it is insoluble in water. In acidic pH, the amino groups can

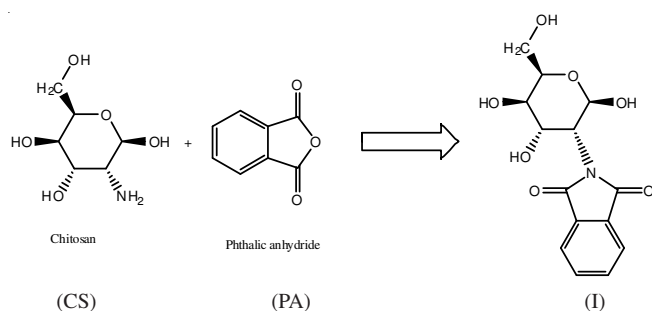
undergo protonation thus, making it soluble in water. It breaks down slowly to harmless products (amino sugars), which are completely absorbed by the human body⁹. Low molecular weight chitosan can function as drug release enhancers for poorly water-soluble drugs due to an improvement in wettability resulting from the solubility of low molecular weight chitosan in water¹⁰.

The solid systems for several drugs using chitosan have been reported with solid dispersions, co-ground mixture and solid complexes, physical mixture and co-ground products and spray dried products at different ratios^{11,12}. Chitin and chitosan have similar polymeric structures, differing in the amount of acetylated units, as represented by the degree of deacetylation, which is a useful parameter related to this property¹³. To our best of knowledge this is first study on [phthalic anhydride-chitosan] monomer using theoretical calculations. So, the aim of this study is to evaluate the physical properties of the monomer and also to study the physical parameters of the solvents and later to compare to the experimental values. Beside that, the choice of best solvent to dissolve the polymer will also depend on the theoretical calculations.

EXPERIMENTAL

Synthesis of N-phthaloyl chitosan: N-Phthaloyl chitosan polymer is synthesized by reacting chitosan with phthalic anhydride in DMF. 1 g of chitosan (Aldrich, > 75 % of deacetylation, viscosity: 800-2000 cps) and 4.39 g phthalic anhydride (Aldrich) in DMF (Aldrich) was reacted in a temperature range of 100-120 °C under nitrogen atmosphere for 6 h. The temperature was reduced to 60 °C and the mixture was left overnight. The clear yellowish solution was poured into ice water to precipitate out the product. The precipitate was collected and washed with hot ethanol in a Soxhlet extractor. The product was dried in vacuum at 60 °C.

Solubility: 0.05 g of chitosan and N-phthaloyl chitosan polymers were put into the test tubes separately and tested with various solvents (5 mL) for (a) 1 h stirring at room temperature, (b) 1 h stirring and left overnight at room temperature (c) heating in water bath for 1 h at 60 °C. The experimental values of the solvents are given in Table-1



Scheme-I: Formation of [phthalic anhydride-chitosan] monomer (I) from a chitosan monomer (CS) and phthalic anhydride (PA)

Theoretical calculations: All the calculations have been performed using the GAMBESS package. The GAMBESS program was employed for the calculation of different descriptors including dipole moment, HOMO, LUMO, hardness (h), electronic chemical potential (m) and global electrophilicity index (w). Table-1 lists the experimental dielectric constants (e) and dipole moment (m) values for the solvents¹⁴.

TABLE-1
EXPERIMENTAL VALUES OF THE SOLVENTS

Solvent	Formula	Dielectric constant (ε)	Dipole moment (Debye)
DMF	C ₃ H ₇ NO	38.25	3.82
DMSO	C ₂ H ₆ OS	47.24	3.96
ECA	C ₃ H ₄ O ₃	89.78	4.90
PCA	C ₄ H ₆ O ₃	66.14	4.90
THF	C ₄ H ₈ O	7.52	1.75
EDA	C ₂ H ₈ N ₂	13.82	1.99

DMF = N,N-Dimethyl formamide; DMSO = Dimethylsulfoxide; ECA = Ethylene-carbonic acid; PCA = Propylene-carbonic acid; THF = Tetrahydrofuran; EDA = 1,2-Ethylene diamine.

RESULTS AND DISCUSSION

Solubility: Table-2 shows the experimental solubility of the N-phthaloyl chitosan polymer whereby only DMF, DMSO and EDA are the best solvents to dissolve the polymer.

TABLE-2
SOLUBILITY OF N-PHTHALOYL CHITOSAN
IN VARIOUS SOLVENTS

Solvents	Heat in water bath for 1 h at 60 °C
DMF	Completely dissolved
EDA	Completely dissolved
DMSO	Completely dissolved
THF	Not dissolved
PCA	Not dissolved
ECA	Not dissolved

Theoretical calculations: Table-3 shows the physical properties of the solvents calculated using different methods (PM3), (HF/3-21G) and (DFT/B3LYP/3-21G).

TABLE-3
THEORETICAL DIPOLE MOMENT
VALUES FOR THE SOLVENTS

Solvent	Dipole moment			
	PM3	HF/3-21G	DFT/B3LYP/3-21G	Experimental
DMF	3.062	4.149	3.765	3.82
DMSO	4.492	4.914	–	3.96
ECA	4.616	6.313	5.416	4.90
PCA	4.810	6.387	5.493	4.90
THF	1.665	2.134	1.802	1.75
EDA	2.157	0.001	0.002	1.99

The correlation coefficient between the theoretical observed parameters with the experimental values are show below.

$$Y_{(\text{Theor./dipole/PM3})} = 0.136 (\pm 0.57) + 0.938 (\pm 0.15)_{(\text{Expt./dipole})} \quad [R = 0.950]$$

$$Y_{(\text{Theor./dipole/HF})} = -2.097 (\pm 1.12) + 1.711 (\pm 0.29)_{(\text{Expt./dipole})} \quad [R = 0.944]$$

$$Y_{(\text{Theor./dipole/DFT})} = -1.816 (\pm 1.07) + 1.472 (\pm 0.28)_{(\text{Expt./dipole})} \quad [R = 0.947]$$

The results show that PM3 method is the best method to predict the experimental dipole moment. It is clearly observed that the theoretical values are nearest to the experimental.

These results also correlate the experimental values dielectric constant with the theoretical calculated (dipole moment) which further show that the PM3 is a better method.

$$\text{Dipole}_{(\text{Theor./PM3})} = 1.730 (\pm 0.47) + 0.039 (\pm 0.009)_{(\text{Expt./dielect.})} \quad [R = 0.908]$$

$$\text{Dipole}_{(\text{Theor./HF})} = 0.840 (\pm 0.93) + 0.071 (\pm 0.018)_{(\text{Expt./dielect.})} \quad [R = 0.894]$$

$$\text{Dipole}_{(\text{Theor./DFT})} = 0.661 (\pm 0.93) + 0.061 (\pm 0.018)_{(\text{Expt./dielect.})} \quad [R = 0.896]$$

Table-4 shows the parameters (HOMO and LUMO energies) for the solvent used for the theoretical calculation.

TABLE-4
HOMO AND LUMO ENERGIES FOR THE SOLVENTS

Solvent	PM3		HF/3-21G		DFT/B3LYP/3-21G	
	HOMO [eV]	LUMO [eV]	HOMO [eV]	LUMO [eV]	HOMO [eV]	LUMO [eV]
DMF	-9.559	1.038	-9.829	5.801	-6.204	1.124
DMSO	-9.353	0.255	-9.587	5.151	–	–
ECA	-11.777	1.176	-12.457	6.003	-7.796	1.018
PCA	-11.689	1.235	-12.324	6.055	-7.706	1.078
THF	-10.267	3.284	-11.007	6.819	-6.270	2.795
EDA	-9.490	2.717	-9.753	7.366	-5.412	2.993

The calculated hardness (η), electronic chemical potential (μ) and global electrophilicity index (ω) for the solvents are shown in Table-5.

Solvent	PM3	HF/3-21G	DFT/B3LYP/3-21G
η [eV]			
DMF	5.3414	5.4764	3.6639
DMSO	4.6765	4.7935	–
ECA	6.3974	6.7374	4.4069
PCA	6.3833	6.7008	4.3918
THF	6.5308	6.9008	4.5323
EDA	6.2416	6.3731	4.2026
μ [eV]			
DMF	-4.2176	-4.3526	-2.5401
DMSO	-4.6765	-4.7935	–
ECA	-5.3796	-5.7196	-3.3891
PCA	-5.3057	-5.6232	-3.3142
THF	-3.7362	-4.1062	-1.7377
EDA	-3.2484	-3.3799	-1.2094
ω [eV]			
DMF	1.6651	1.7297	0.8805
DMSO	2.3383	2.3968	–
ECA	2.2619	2.4278	1.3032
PCA	2.2050	2.3595	1.2505
THF	1.0687	1.2217	0.3331
EDA	0.8453	0.8962	0.1740

Application of multiple linear regression model: Multiple linear regression (MLR) analysis was used to investigate the correlation between two or more independent variables (physico-chemical properties) with dependent variable (experimental values) by fitting a linear equation to the observed data.

The aim of using this model was to explore the effects of the theoretical calculation of the solvents on the experimental measurements. The calculated parameters for the solvents will thus be compared with the experimental values.

The multiple linear regressions for the experimental dipole moment values with all calculated parameters are shown in Table-6.

Table-7 shows the multiple linear regressions for the experimental dielectric constant values with all calculated parameters.

Following the above results, stepwise method is then used to show the direct effect of the theoretical calculated (independent) to the experimental measurement (dependent) for both the dipole moment and the dielectric constant.

Dipole moment:

$$\text{Dipole}_{(\text{Expert.})} = 0.213 (\pm 0.58) + 0.964 (\pm 0.15)_{(\text{Theor./dipole/PM3})} \quad [R = 0.950]$$

$$\text{Dipole}_{(\text{Expert.})} = 1.477 (\pm 0.41) + 0.521 (\pm 0.09)_{(\text{Theor./dipole/HF})} \quad [R = 0.944]$$

$$\text{Dipole}_{(\text{Expert.})} = 1.176 (\pm 0.26) + 2.912 (\pm 0.28)_{(\text{Theor./}\omega/\text{DFT})} \quad [R = 0.986]$$

Dielectric constant:

$$\text{Dielect.}_{(\text{Expert.})} = -108.77 (\pm 27.18) - 34.46 (\pm 6.04)_{(\text{Theor./}\mu/\text{PM3})} \quad [R = 0.944]$$

$$\text{Dielect.}_{(\text{Expert.})} = -104.74 (\pm 30.94) - 31.85 (\pm 6.53)_{(\text{Theor./}\mu/\text{HF})} \quad [R = 0.925]$$

$$\text{Dielect.}_{(\text{Expert.})} = -7.21 (\pm 11.27) + 63.83 (\pm 12.33)_{(\text{Theor./}\omega/\text{DFT})} \quad [R = 0.948]$$

From these results, it is noticed that the experimental dipole moment may be calculated theoretically (depending or effecting) based on values of dipole moment using (PM3) and (HF/3-21G) and depending or effecting on global electrophilicity index (ω) using (DFT/B3LYP/3-21G) method.

PM3	Expert	Dipole	HOMO	LUMO	η	μ	ω
Expert	1.000	–	–	–	–	–	–
Dipole	0.950	1.000	–	–	–	–	–
HOMO	-0.598	-0.529	1.000	–	–	–	–
LUMO	-0.829	-0.851	0.064	1.000	–	–	–
η	-0.193	-0.273	-0.641	0.705	1.000	–	–
μ	-0.948	-0.927	0.741	0.701	0.040	1.000	–
ω	0.928	0.961	-0.459	-0.887	-0.385	-0.934	1.000
HF/3-21G	Expert	Dipole	HOMO	LUMO	η	μ	ω
Expert	1.000	–	–	–	–	–	–
Dipole	0.944	1.000	–	–	–	–	–
HOMO	-0.528	-0.609	1.000	–	–	–	–
LUMO	-0.727	-0.779	-0.004	1.000	–	–	–
η	-0.155	-0.091	-0.728	0.673	1.000	–	–
μ	-0.909	-0.967	0.771	0.621	-0.125	1.000	–
ω	0.931	0.963	-0.471	-0.851	-0.258	-0.923	1.000
DFT/B3LYP	Expert	Dipole	HOMO	LUMO	η	μ	ω
Expert	1.000	–	–	–	–	–	–
Dipole	0.947	1.000	–	–	–	–	–
HOMO	-0.863	-0.931	1.000	–	–	–	–
LUMO	-0.958	-0.943	0.774	1.000	–	–	–
η	-0.092	0.032	-0.383	0.288	1.000	–	–
μ	-0.966	-0.995	0.944	0.940	-0.056	1.000	–
ω	0.986	0.986	-0.918	-0.958	-0.010	-0.995	1.000

TABLE-7
CORRELATION COEFFICIENT BETWEEN THE EXPERIMENTAL DIELECTRIC
CONSTANT VALUES WITH ALL CALCULATED PARAMETERS

PM3	Expert	Dipole	HOMO	LUMO	η	μ	ω
Expert	1.000	–	–	–	–	–	–
Dipole	0.908	1.000	–	–	–	–	–
HOMO	-0.721	-0.529	1.000	–	–	–	–
LUMO	-0.694	-0.851	0.064	1.000	–	–	–
η	-0.005	-0.273	-0.641	0.705	1.000	–	–
μ	-0.944	-0.927	0.741	0.701	0.040	1.000	–
ω	0.870	0.961	-0.459	-0.887	-0.385	-0.934	1.000
HF/3-21G	Expert	Dipole	HOMO	LUMO	η	μ	ω
Expert	1.000	–	–	–	–	–	–
Dipole	0.894	1.000	–	–	–	–	–
HOMO	-0.661	-0.609	1.000	–	–	–	–
LUMO	-0.582	-0.779	-0.004	1.000	–	–	–
η	0.034	-0.091	-0.728	0.673	1.000	–	–
μ	-0.925	-0.967	0.771	0.621	-0.125	1.000	–
ω	0.886	0.963	-0.471	-0.851	-0.258	-0.923	1.000
DFT/B3LYP	Expert	Dipole	HOMO	LUMO	η	μ	ω
Expert	1.000	–	–	–	–	–	–
Dipole	0.896	1.000	–	–	–	–	–
HOMO	-0.898	-0.931	1.000	–	–	–	–
LUMO	-0.862	-0.943	0.774	1.000	–	–	–
η	0.100	0.032	-0.383	0.288	1.000	–	–
μ	-0.935	-0.995	0.944	0.940	-0.056	1.000	–
ω	0.948	0.986	-0.918	-0.958	-0.010	-0.995	1.000

On the other hand, dielectric constant can be predicted theoretically based on electronic chemical potential (μ) using (PM3) and (HF) and on global electrophilicity index (ω) using (DFT/B3LYP/3-21G) method.

As for the physical properties of a chitosan monomer, phthalic anhydride and [phthalic anhydride-chitosan] monomer calculated using HF/3-21G, the [phthalic anhydride-chitosan] monomer was minimized by (HF/3-21G) after being minimized by (MM2) method. Table-8 shows the physical properties which were calculated.

Based on all these calculations, the 3D dimension for the [phthalic anhydride-chitosan] monomer can be viewed as shown in Fig. 1.

Conclusion

This theoretical study is the first study on chitosan monomer, phthalic anhydride and [phthalic anhydride-chitosan] monomer using (HF/3-21G) method. The physical properties of many solvents including DMSO, DMF, THF, EDA, ECA and PCA using different methods of calculations PM3, HF/3-21G and DFT/B3LYP/3-21G, were compared with the experimental measurements. The theoretical calculations show that the dipole moment plays a major effect on the solvation. When the solvent is less polar like EDA, DMF and DMSO,

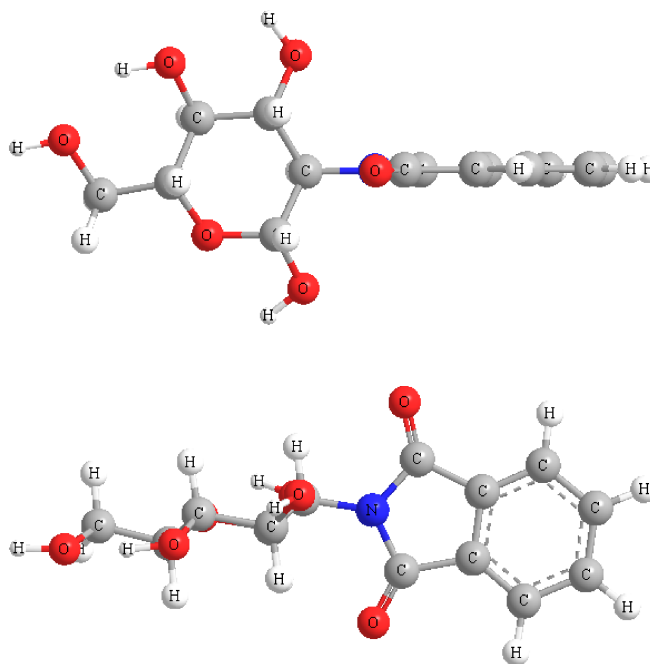


Fig. 1. 3D-dimension viewer for the [phthalic anhydride-chitosan] monomer

TABLE-8
PHYSICAL PROPERTIES OF CHITOSAN MONOMER, PHTHALIC ANHYDRIDE AND
[PHTHALIC ANHYDRIDE-CHITOSAN] MONOMER AS SHOWN IN SCHEME-I

HF/3-21G	Dipole (debye)	HOMO [eV]	LUMO [eV]	Total energy (kcal/mol)	Total potential energy (kcal/mol)
Chitosan	3.749	-10.223	6.327	-414037.59	-827188.10
Phthalic anhydride	6.725	-10.661	1.050	-330651.72	-660548.40
Chitosan-phthalic anhydride monomer	3.243	-9.908	1.736	-697291.57	-1393109.62

it can dissolve the polymer. Although less polar, THF shows contrary result due to the steric effect similar to that of ECA and PCA. Experimentally, the N-phthaloyl chitosan polymer dissolved in three solvents namely EDA, DMF and DMSO and this is in agreement with the theoretical calculations.

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