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Elucidating the Structure–Spectrum Relationship of Choline and Citicoline: Approaches From Experimental FT-IR and Theoretical DFT/HF Methods

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In this study, the structural and vibrational properties of choline and citicoline at the molecular level were investigated comprehensively through the integration of experimental and theoretical methods. The main purpose of the study is to provide an accurate interpretation of FT-IR spectra of these molecules and to contribute to molecular identification processes. Experimentally, spectral data obtained from pure citicoline powder using ATR/FT-IR spectroscopy were compared theoretically with Hartree–Fock (HF) and density functional theory (DFT) approaches; in this context, B3LYP functional and 6–311++G(d,p) basis set were taken as basis. Thanks to this method, supported by theoretical calculations, full vibrational (IR and Raman) spectra and structural parameters of choline and citicoline were modeled in detail, and systematic assignments were made to vibrational modes. The obtained findings show that experimental and theoretical data are in high agreement; this situation emphasizes the complementarity and reliability of both approaches, especially in terms of functional group analysis of citicoline molecule. In addition, this holistic analysis method provides a strong basis for predicting the potential interactions, chemical stabilities, and possible side effects of choline and citicoline molecules in biological systems at the molecular level. The obtained results contribute to the development of a deeper understanding of the roles of such compounds in biochemical processes, as well as providing guidance for structural optimization and targeted design studies in future pharmaceutical and biotechnological applications.

1. Introduction

Citicoline is a molecule with a very specific structure in terms of crossing the blood–brain barrier, reaching the central nervous system, and interacting with the phospholipid structures of cells. The fact that it has a structure that plays a role in the synthesis of phospholipids in the structure of neuronal membranes has the potential for the prognosis of neurodegenerative diseases. The emergence of nerve cells that do not have the ability to regenerate as a result of cumulative total damage at an advanced age is an extremely limiting factor in terms of prognosis. Citicoline also increases brain metabolism and positively stimulates its development by acting on the levels of different neurotransmitters. It also appears to increase the levels of neuroepinephrine and dopamine in the central nervous system. Along with all these, its positive effects in terms of reducing the effect of lesions that develop after ischemic problems encountered, especially in the hemodynamic system, have also been pointed out in the literature. It restored ATPase and membrane Na+/K + ATPase activity in the mitochondrial mechanism, especially in energy gain and biotransformation, which is another vital metabolic function. It has been reported to inhibit the activation of phospholipases.[1]

In addition, with the demonstration that it accelerates the reabsorption of cerebral edema in the study designs, its potential pharmaceutical effect is thought to be an alternative solution situation other than stem cell applications for damage conditions in the highly sensitive nervous system mechanisms that are not capable of regeneration.[1,2]

Citicoline has been reported in the literature to have the potential not only to repair neurodegenerative damage but also to ensure the preservation of all healthy components, such as cells, tissues, and molecular metabolites in the existing healthy nervous system. In fact, by stimulating the expression of enzymes such as glutathione, which is among the detoxification system phase 2 enzymes, inhibition of structures that may cause cytotoxic stress and damage in the cell is also reported.[3]

Based on all these properties of citicoline, the positive results reported in experimental designs and clinical applications suggest that it is a solution for neurodegenerative diseases, especially for the treatment and improvement of memory loss symptoms in diseases such as dementia and Alzheimer's.[4]

Citicoline's effects on the apoptotic pathway in tumor formation, especially in brain tissue, and even pre-invasive angiogenesis and tendency toward metastatic status have been reported, and its effects have also been investigated and observed under the title of cancer biology.[5]

However, when the studies in the literature are examined, it is seen that most of them consist of clinical applications and their reviews, and especially when the chemical structure of citicoline is considered, it is seen that studies that are biochemical link demonstrations related to proteins or other molecular structures, with which the cell interactions are limited.[6–8]

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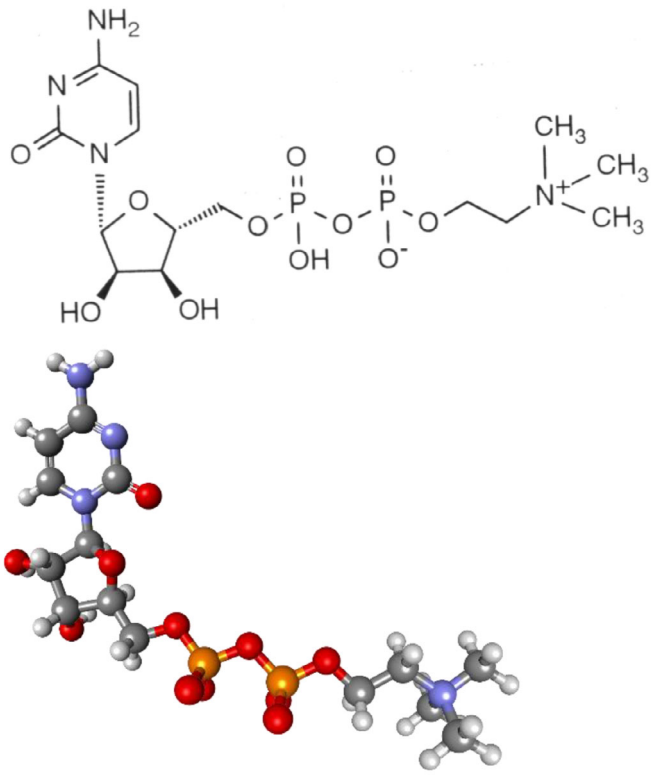

Figure 1. Molecular structure of citicoline, showing cytidine on the left and diphospho-choline (trimethyl-ethanol-ammonium) on the right.

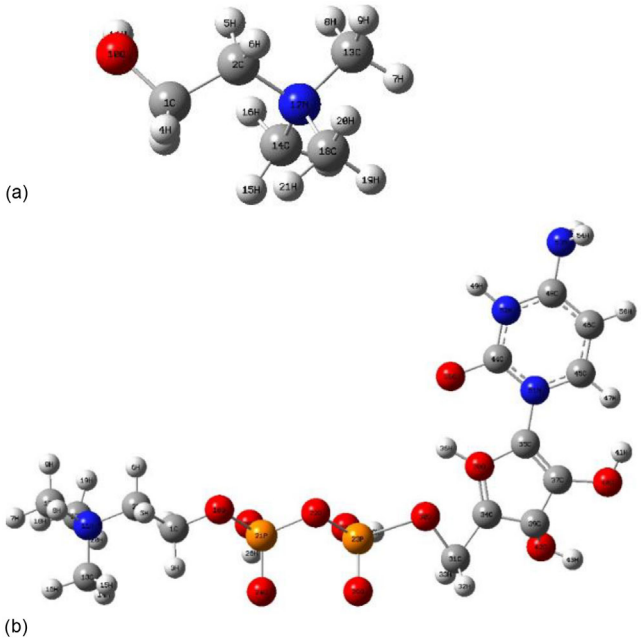

Figure 2. Calculated optimized structures of a) choline (CH)– and b) citicoline.

Choline (2-hydroxy-N,N,N-trimethylethan-1-aminium) is known as Vitamin B4, which is an essential nutrient for human beings.[9] Some researchers are working on Raman spectroscopy, distribution functional theory (DFT) programming, X-ray and Potential structures (EPSR) by combining oxygen bonds in aqueous choline chloride solutions.[10]

Citicoline ($C_{14}H_{26}N_4O_{11}P_2$), also known as cytidine-5′-diphosphocholine (CDP-choline) or Cytidinediphosphate-choline is an intermediate in the generation of phosphatidylcholine from choline, a common biochemical process in cell membranes. Citicoline is an endogenous compound that occurs naturally in the cells of human and animal tissue, especially organs.[11]

Citicoline consists of two basic molecules that are structural phospholipids of cell membranes: cytidine and choline (Figure 1). Phospholipids are essential components of cells and have a high turnover rate, requiring their continuous synthesis. They are compounds that ensure adequate function of cell membranes. It appears that an important component of citicoline's neuroprotective capacity is its ability to improve phosphatidylcholine synthesis in the injured brain.[12,13] Additionally, a study was conducted on the oxidative stress ameliorating effect of choline and citicoline on acute kidney injury in rats.[14] There are many experimental studies on the protective structure of citicoline.[15–19]

In this study, we report experimental FT-IR spectra of citicoline, and we wish to report the assignments of the complete vibration IR spectrum and vibrational parameters of choline and citicoline supported by the Hartree–Fock (HF) and density functional theory (DFT) methods. Our study was designed to support the importance of potential solution proposals and designs based on molecular pathways and biochemical connection situations in terms of revealing possible risks and side effects, and to support the recognition of citicoline at the molecular level.

2. Experimental Details and Computational Methods

Citicoline monosodium was purified by HAVER Pharma using the HPLC (High Performance Liquid Chromatography) method and was provided for use in the study as pure citicoline. ATR/FT-IR spectroscopy (Perkin Elmer, Spectrum 100 model) was used for the functional group analysis of the purified citicoline powder sample. The IR spectra were analyzed in the range of 650–4000 cm^{-1}.

The vibrational frequencies of choline and citicoline were calculated using the HF and B3LYP methods with the 6–311++G(d,p) basis set. This basis set incorporates polarization functions, including five d-type functions for non-hydrogen atoms and three p-type functions for hydrogen atoms. Additionally, it includes one s-type diffuse function for all atoms and one p-type diffuse function for non-hydrogen atoms. All calculations were conducted using the Gaussian 03 program package (with Linda),[20] and the normal vibrational modes were visualized using the Gausview software.[21] Scaling factors of 0.9131 and 0.9774 were applied to the HF and B3LYP vibrationalfrequencies, respectively.[22]

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Table 1. Experimental and calculated scaled vibrational frequencies of choline and citicoline.

Sym.	Assignments	Exp.	Calculated Frequencies (cm^{-1}) 6–311++G (d, p)											
		Freq. (cm^{-1})	Choline						Citicoline					
		IR(exp.)	HF	IR inten. (km/mol)	R activity (Å^4/amu)	DFT	IR inten. (km/mol)	R activity (Å^4/amu)	HF	IR inten. (km/mol)	R activity (Å^4/amu)	DFT	IR inten. (km/mol)	R activity (Å^4/amu)
A′	ν(OH)	3344	3491	404	147.65	3470	11.26	394.9	3438	14.91	236.46	3468	12.39	359.4
A′	ν(CH)	–	3161	14.37	69.18	3169	11.34	68.49	3135	19.8	164.39	3167	19.9	194.8
A′	ν(CH)	–	3155	1.70	2.55	3158	6.38	90.33	3115	17.5	125.96	3144	12.0	10.2
A′	ν(CH)	–	3151	7.86	14.55	3143	8.85	129.97	3111	4.32	39.27	3141	1.19	60.1
A′	ν(CH)	–	3148	8.16	0.59	3140	7.86	23.89	3107	1.69	32.06	3135	4.94	39.5
A′	ν(CH)	–	3144	0.59	9.11	3100	11.34	68.49	3035	19.88	164.39	3067	17.96	134.8
A′	ν(CH)	–	3113	12.63	6.30	3090	6.58	90.33	3110	17.51	125.96	3044	12.09	160.2
A′	ν(CH)	–	3110	6.40	1.80	3078	8.85	129.97	3099	4.32	39.27	3041	1.19	6.17
A′	ν(CH)	3056	3070	44.71	193.31	3069	11.34	68.49	3035	19.88	164.39	3067	17.96	134.8
A′	ν(CH)	3033	3062	23.88	115.24	3058	6.58	90.33	3015	17.51	125.96	3044	12.09	160.2
A′	ν(CH)	3001	3053	25.93	106.69	3043	8.85	129.97	3011	4.32	39.27	3041	1.19	6.17
A′	ν(CH)	2951	3040	44.95	15.64	3040	0.86	23.44	3007	1.69	32.06	3035	4.24	69.5
A′	ν(CH)	2906	3031	80.48	113.22	3019	20.26	149.52	2996	21.69	111.90	3016	21.09	151.3
A′	ν(CH)	2840	2966	169.77	56.95	2888	34.15	63.75	2788	120.21	126.13	2730	151.22	181.4
A′	ν(C = O)+ δ(CH)	1712, 1664	1631	31.06	88.53	1786	279.95	124.45	1603	383.13	98.27	1716	278.77	117.4
A′	δ(CH)	–	1516	15.32	1.81	1685	19.78	11.85	1441	56.32	1.76	1586	19.03	5.84
A′	ν(CN)+ δ(CH)	–	1512	24.06	23.54	1595	31.04	60.65	1388	9.20	21.72	1560	1.59	15.9
A′	ν(CC) + ν(CN) + δ(CH)	1585	1584	7.90	14.50	1569	7.92	1.94	1418	7.84	2.01	1543	13.27	8.59
A′	ν(CC) + δ(CH)	1526	1500	18.05	141.17	1541	114.37	151.19	1500	78.76	139.94	1537	72.26	129.3
A′	ν(CC) + δ(CH_3)	1485	1495	0.77	12.32	1474	26.71	9.08	1480	42.68	25.22	1472	29.68	23.2
A′	δ(CH)	1449	1493	1.49	1.59	1438	3.76	9.20	1469	2.53	0.89	1430	7.64	5.77
A′	δ(CH)	–	1479	0.53	75.56	1402	14.06	89.50	1433	13.48	40.61	1390	5.57	58.9
A′	δ(CH_3)+ δ(COH)	1367	1470	39.89	21.54	1375	11.04	40.65	1413	6.20	21.12	1365	1.29	5.93
A′	δ(CH_3)+δ(CH)	1345	1456	13.14	15.93	1335	4.18	5.88	1380	1.56	33.90	1322	1.32	42.5
A′	ν(CN) + ν(CC) + δ(CH_3)	–	1449	9.15	306.9	1324	1.49	155.04	1320	0.83	266.38	1317	1.00	129.8
A′	ν(C = C)+ν(C = N)+δ(CH)	1284	1443	12.04	15.51	1296	11.22	8.50	1286	5.74	25.17	1290	8.86	26.4
A′	δ(CCC)+ ν(C-O)	1237	1438	14.68	1.77	1220	27.94	2.41	1243	3.44	2.26	1215	6.95	1.21
A′	ν(CC)+ δ(CH)	–	1391	1.80	14.25	1214	32.13	21.06	1222	20.75	17.40	1202	29.11	14.9
A′	δ(CH)	1199	1356	2.70	5.79	1188	7.07	7.18	1171	4.58	6.39	1176	4.54	3.44
A′	ν(CN)+ δ(CH)	1123	1298	0.18	4.56	1142	7.97	0.56	1150	28.49	1.39	1131	16.61	3.25
A′	ν(CO)+ δ(CH)	1082	1291	7.09	5.19	1113	7.94	6.49	1148	16.06	6.59	1109	8.93	4.65
A′	ρ_r(CH)	1063	1265	1.50	16.12	1056	1.55	24.57	1099	5.18	25.84	1043	6.92	17.6
A′	δ(CH)	1033	1222	9.48	5.41	1012	7.58	5.44	1040	28.27	5.58	1008	33.28	18.5
A′	δ(CH)	991	1157	1.32	4.11	999	0.73	2.90	1027	0.00	5.62	990	2.16	8.57
A′	γ(CH)	–	1143	8.33	1.19	997	6.20	9.33	1008	0.78	1.24	982	0.29	3.68
A′	γ(CH)	–	1090	55.21	1.38	965	1.20	0.23	996	0.36	1.18	960	1.15	0.28
A′	ρ_r(CH_3)	–	1084	0.61	0.22	954	0.06	0.41	983	0.00	0.51	951	0.02	0.11
A′	γ(CH)	961	1071	35.22	3.13	933	0.00	0.06	974	10.04	2.22	931	0.01	0.11
A′	ν(CC) + ν(CN)	938	1033	2.58	1.34	914	0.08	0.33	945	0.76	1.70	901	0.07	0.93
A′	δ(CN)+ w(CH)	902	980	25.26	9.03	899	29.45	7.58	872	28.75	11.08	864	25.58	9.17
A″	w(CN)	870	946	19.55	0.45	811	36.81	0.22	834	42.96	0.44	809	29.03	0.11
A″	w(CN)	843	882	39.78	6.43	794	1.04	8.16	798	1.08	0.16	787	0.12	0.29
A″	w(CN)	817	805	10.05	0.32	774	56.17	0.13	796	67.24	0.32	769	64.18	0.10
A″	δ(CCO)	779	774	10.74	0.68	748	24.79	28.26	769	7.17	0.98	740	2.91	0.31
A′	ρ_r(OH)	715	718	78.72	26.74	743	1.21	0.12	688	17.51	14.64	682	12.55	21.8
A′	δ(CCO)	–	675	0.49	3.95	630	14.97	3.61	629	38.74	7.14	629	28.54	5.04

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Table 1. (Continued)

Sym.	Assignments	Exp. Freq. (cm^{-1}) IR(exp.)	Calculated Frequencies (cm^{-1}) 6–311++G (d, p) Choline HF	IR inten. (km/mol)	R activity (Å^4/amu)	DFT	IR inten. (km/mol)	R activity (Å^4/amu)	Citicoline HF	IR inten. (km/mol)	R activity (Å^4/amu)	DFT	IR inten. (km/mol)	R activity (Å^4/amu)
A′	ρ_r(CCO)	–	664	0.39	0.22	611	0.03	0.10	618	0.06	0.50	607	0.13	0.31
A″	γ(CH)	–	544	4.47	9.29	532	2.98	11.00	540	6.38	13.40	521	4.30	17.5
A″	γ(CH_3)	–	531	0.24	0.12	508	1.54	0.14	480	3.14	0.47	499	1.80	0.67
A′	ρ_r(CHO)	–	497	5.96	7.56	494	6.47	11.57	372	7.37	11.43	485	4.38	15.9
A″	γ(CH)	–	470	3.27	0.09	457	0.47	0.09	336	0.01	0.11	445	0.00	0.07
A′	ρ_r(CH_3)	–	426	1.33	3.98	429	8.68	6.41	327	2.69	0.65	411	2.37	1.64
A″	*w*(CH) + γ(CH) in the CH_3	–	411	0.35	1.98	400	0.15	1.04	307	0.06	2.55	396	0.00	1.75
A′	t_r(CH_3)	–	363	0.96	3.97	341	6.95	5.94	271	2.15	2.13	336	1.48	2.46
A″	*w*(CH) + γ(CH) in the CH_3	–	252	2.91	1.07	225	6.25	1.07	230	6.30	0.26	219	4.46	0.17
A′	*Breathing*	–	185	30.95	0.86	188	1.90	1.35	183	6.82	2.08	173	5.13	2.42
A″	*w*(N-CH_3)	–	178	12.69	0.19	175	9.40	0.27	124	2.11	0.13	167	1.50	0.19
A″	*w*(CH_2)+ *w*(CCO)	–	136	9.59	1.40	133	5.99	1.09	113	10.54	0.31	131	7.82	0.29
A″	*w*(CH_3)	–	91	1.96	0.53	82	1.89	0.88	87	4.84	1.69	79	2.48	2.39
A″	*w*(N-CH_3)	–	38	9.04	4.77	34	8.18	5.18	32	34.9	3.66	29	4.55	13.9

ν: stretching; δ: bending; γ out of plane bending: ρ_r rocking; w: wagging, torsion.

3. Results and Discussion

The molecular structures of the target compounds, optimized through ab initio methods, are shown in Figure 2. Table 1 presents the computed vibrational frequencies, IR intensities, Raman activities, and proposed assignments for the optimized geometries. The frequencies were scaled using factors of 0.9050 and 0.9614 for HF and B3LYP methods with the 6–311++G basis set, respectively.[23] Additionally, experimental data are included for comparison. It is evident that the theoretical and experimental vibrational values align closely. Figure 3 illustrates the correlation graphs between these data, with correlation coefficients for choline and citicoline being 0.9930 and 0.9696 (HF) and 0.9626 and 0.9670 (DFT), respectively, demonstrating strong agreement. Furthermore, it can be inferred that the B3LYP method provides better correlation than HF. The vibrational modes are identified in the first column of Table 1. In this table, the calculated frequencies for the choline moiety of the citicoline molecule are compared with those of the isolated choline molecule. Scaled theoretical IR spectra and normalized IR band intensities are depicted in Figure 4.

The characteristic peaks reflecting the vibrations of the functional groups in the chemical structure of the purified citicoline monosodium molecule are given by FT-IR (Fourier Transform Infrared) analysis, as shown in Figure 5. The FTIR spectrum of the purified citicoline monosodium molecule reveals key insights into its molecular structure, highlighted by prominent absorption bands. The characteristic peaks at 1664 and 1712 cm^{-1} correspond to the stretching vibration of the carbonyl (C═O) groups, indicating the presence of ester or amide functionalities within the pyrimidine ring. These peaks, observed around 1650–1750 cm^{-1} and corresponding to the C═O stretching bands of the ester or carbonyl group, are consistent with carbonyl stretching frequencies typically found in conjugated systems, suggesting that citicoline's biochemical activity may be significantly influenced by these functional groups.[24,25] Additionally, the broad band at 3344 cm^{-1} can be attributed to O–H stretching, likely due to hydroxyl groups, further supporting the molecule's involvement in hydrogen bonding.[26] The peak observed at 779 cm^{-1} in Figure 5a may indicate C—H bending vibrations or bending modes of the P—O bond due to the presence of heteroatoms, particularly phosphorus. This suggests the presence of specific functional groups within the citicoline structure.[27] In the literature, C—H stretching bands belonging to methyl (CH^{-3}) and methylene (CH^{-2}) groups were generally observed in the range of 3100–2800 cm^{-1}, but in this study, C—H stretching bands belonging to methyl (CH^{-3}) and methylene (CH^{-2}) groups were observed at 3001, 3033, and 3056 cm^{-1}.[28]The FTIR spectrum of pure citicoline sodium exhibited characteristic peaks at 1237 cm^{-1} (RCOR' in the pyrimidine ring), 1082 cm^{-1} (C—O in tetrahydrofuran), and 1123 cm^{-1} (C—N in the tertiary amine).[29]

4. Conclusion

In this study, theoretical and experimental vibrational spectral properties of choline and citicoline compounds were investigated in detail. Theoretical IR and Raman data obtained in line with molecular structures optimized by ab initio methods were compared with experimental FT-IR results, and it was found that they showed high correlation. Especially, the results obtained with the B3LYP method showed higher correlation coefficients (0.9626 for choline; 0.9670 for citicoline) compared to the HF

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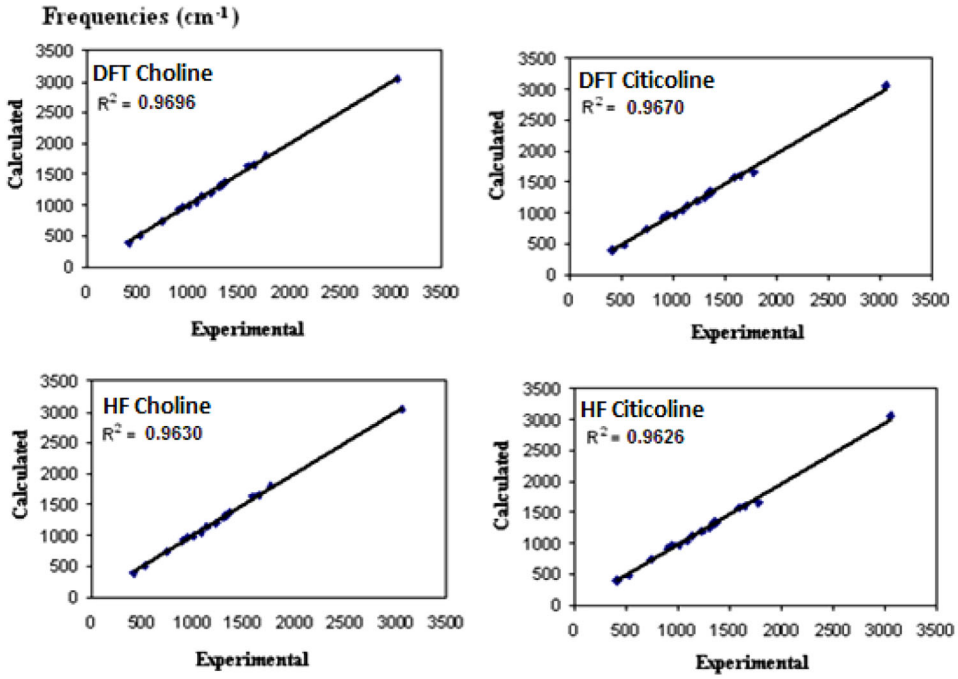

Figure 3. Correlation graphics between experimental and calculated scaled vibration frequencies of choline and citicoline.

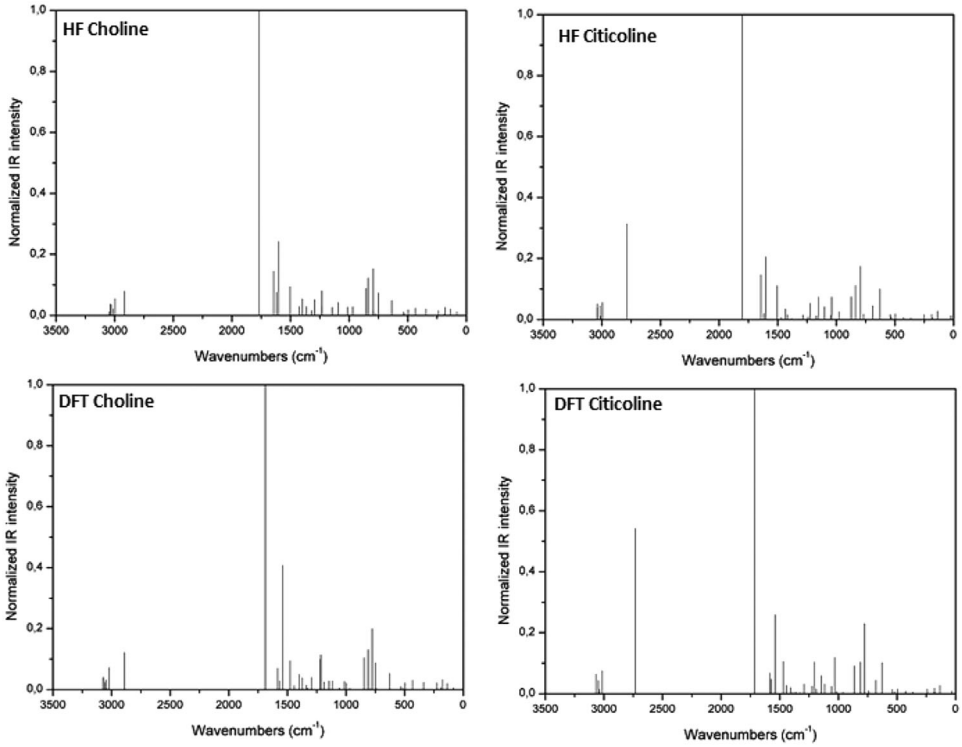

Figure 4. Comparison of calculated scaled frequencies in cm^{-1} and normalized IR intensities of choline and citicoline.

method, showing that this method is more reliable in predicting vibrational frequencies.

The characteristic bands observed in vibrational analyses confirmed the presence of functional groups in the chemical structure of the citicoline molecule. The C═O stretching vibrations at 1664 and 1712 cm^{-1} suggest that there are ester or amide functionalities in the molecule and that these groups may contribute to biochemical activity. In addition, the broad band observed at 3344 cm^{-1} indicates the O—H stretching due to hydroxyl groups and shows that the molecule

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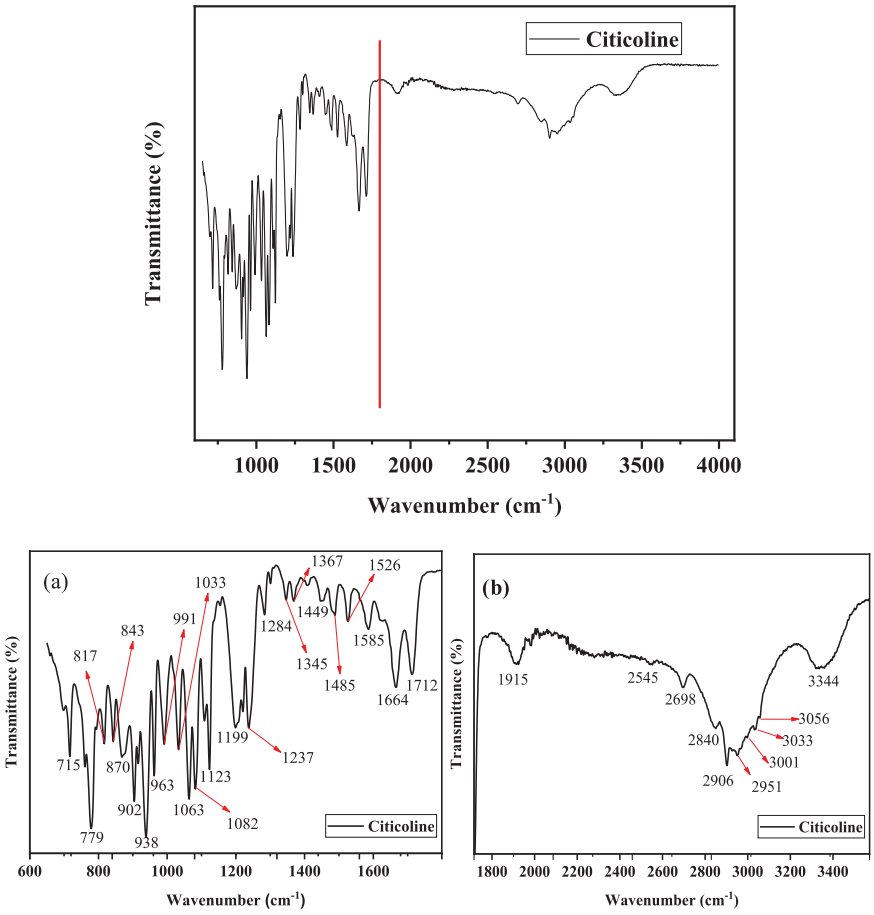

Figure 5. ATR/FT-IR spectrum of purified citicoline monosodium a) in the range of approximately 650–1800 cm^{-1} and b) 1800–4000 cm^{-1} wavenumbers.

may play an important role in interactions through hydrogen bonds.

In spectral analyses, the bending vibrations of the P—O bond observed at 779 cm^{-1} supported the presence of phosphorus-containing groups in the molecule, while the C—H stretching bands observed at wavelengths such as 3001, 3033, and 3056 cm^{-1} represented the characteristic vibrations of the methyl and methylene groups. These bands provided information about the aliphatic building blocks of the molecule and contributed to the analysis of structural integrity.

In addition, the bands at 1237 cm^{-1} (RCOR'), 1082 cm^{-1} (C—O), and 1123 cm^{-1} (C—N) revealed the characteristic traces of the pyrimidine ring, tetrahydrofuran-derived oxygenated structures, and tertiary amine functionalities in the citicoline molecule. These findings have elucidated the chemical properties of citicoline monosodium at the molecular level in detail, allowing us to better understand the potential of this compound for pharmacological and biochemical applications.

In conclusion, the high level of agreement between theoretical modeling and experimental data demonstrates the accuracy and reliability of the calculation methods used. This comprehensive analysis of the vibrational spectra of citicoline and choline molecules provides in-depth information on the structural properties of these compounds and paves the way for further detailed investigation of structure–activity relationships related to their biological activities in future studies.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Choline · Citicoline · DFT · HF · IR spectrum

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