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A Theoretical Study on Inclusion Complexes of Various Noscapines with Different Cyclodextrin

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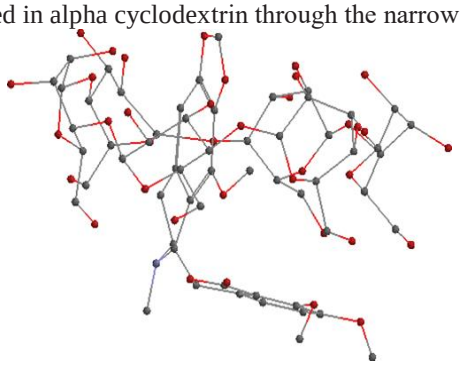
Abstract: Literature reported the synthesis of inclusion complexes between cyclodextrin and noscapine but it provides partial information due to its limitations in understanding the supramolecular interaction between the noscapine and cyclodextrin. Authors reported the inclusion complexation between the few noscapines and α-cyclodextrin and the present work is focussed to study the non-covalent interaction between noscapines and different cyclodextrin (alpha, beta or gamma). Supramolecular interaction between the noscapines (guest) and the various cyclodextrin (host) were studies considering that the isoquinoline ring (partly to completely) is able to included into the host cavity (alpha, beta or gamma) through alcoholic rims. The investigation was mainly emphasized on the most stable conformation of the inclusion complex and predicted to be energy driven process in gaseous phase i.e. negative binding energies. It revealed that the most stable complex is formed when the noscapines were partly included in alpha cyclodextrin through the narrow hydroxyl's rim.



Keywords: Cyclodextrin, noscapine, inclusion complex.

1 Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.[1-5] The burden of cancer is increasing in economically developing countries as a result of population aging and growth. Noscapine is a major phthalideisoquinoline alkaloid, a structural subclass of the large and diverse benzylisoquinoline alkaloid group of plant-specialized metabolites.

It has long been used as a cough suppressant and also known for its mitotic poisoning effect. Noscapines display anticancer properties by binding tubulin and arresting tumor cell mitosis. Noscapine binds to the tubulin subunits, alters tubulin assembly, arrests a variety of mammalian cells in mitosis and causes apoptosis in cycling cells .This may also be true for other agents known to cause mitotic arrest.[1,6-10]

Cyclodextrins (CDs) are cyclic oligosaccharides with central hydrophobic cavities and hydrophilic exterior edges. Cyclodextrins are composed of 6–12 α-(1-4)-linked D (+) glucopyranose units linked in macrocyclic ring.11-14 Researchers reported the inclusion complexes with β -CD mainly. The ability of CD mainly β–CD to form inclusion complexes with different products is well known. This cavity possesses a relatively low polarity that can accommodate

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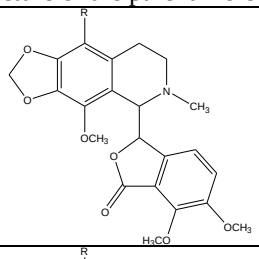
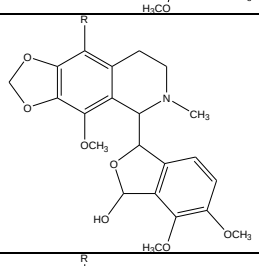
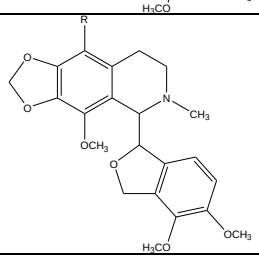
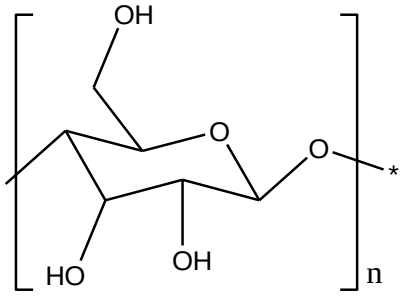
guest organic molecules inside. The formation of inclusion complexes of organic molecules with cyclodextrins is important for their pharmaceutical and technological applications.[15,16] In the last decade, quantum chemical computations have become an

Table 1 Structure of the noscapines (1a-1k, 2s-2k, 3a-3k) and different cyclodextrins (4-6).

Structure of the parent molecule	Compound no.	R
	1	-H (1a); -NH_2 (1b); -Br (1c), -CHO (1d); -COCl (1e); -COOH (1f); Cl (1g); -CH_2Cl (1h); -F (1i); -CH_2OH (1j), -NO_2 (1k)
	2	-H (2a); -NH_2 (2b); -Br (2c), -CHO (2d); -COCl (2e); -COOH (2f); Cl (2g); -CH_2Cl (2h); -F (2i); -CH_2OH (2j), -NO_2 (2k)
	3	-H (3a); -NH_2 (3b); -Br (3c), -CHO (3d); -COCl (3e); -COOH (3f); Cl (3g); -CH_2Cl (3h); -F (3i); -CH_2OH (3j), -NO_2 (3k)
	Cyclic structure of the natural cyclodextrins, n = 6, 7 and 8 for α, β and γ CDs, where the monomers are α-D-glucoses	**Table 2:** Different CDs were used and their energies

Cyclodextrin	Energy		
	Spartan	AM1	PM3
alpha- (4)	-4904.77	-4904.77	-4726.3
beta- (5)	2931.872	-14311.9	-14144.4
gamma- (6)	15946.72	-13820.1	-13838.9

Table 3 Energies of various noscapines (1a-1k, 2s-2k, 3a-3k) as in Table 1.

Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3
1a	599.9123	-5639.13	-5657.07	2a	520.464	-5762.14	-5774.2	3a	659.7029	-5655.88	-5669.38
1b	617.9349	-5798.51	-5812.82	2b	535.6525	-5923.64	-5929.98	3b	677.8886	-5814.36	-5824.28
1c	624.5008	-5601.5	-5619.01	2c	539.4054	-5731.29	-5736.36	3c	681.8656	-5612.85	-5630.54
1d	651.8385	-5897.85	-5916.71	2d	572.8328	-6022.9	-6033.8	3d	705.1005	-5914.16	-5928.66
1e	691.1816	-5871.71	-5898.04	2e	610.8387	-5999.13	-6015.57	3e	740.3842	-5893.23	-6038.72
1f	601.0815	-6003.31	-6025.35	2f	520.9225	-6128.6	-6142.37	3f	652.7386	-6025.31	-5911.13
1g	623.005	-	-	2g	542.580	-	-	3g	680.261	-	-

	8	5617.37	5638.21		5	5744.99	5754.79		7	5636.35	5649.71
1h	632.7697	-5901.24	-5918.68	2h	548.867	-6027.68	-6034.91	3h	691.2867	-5919.51	-5929.89
1i	608.8753	-5646.26	-5663.66	2i	526.9975	-5771.89	-5781.38	3i	669.4191	-5662.99	-5675.95
1j	615.6129	-6018.81	-6035.28	2j	533.1388	-6145.84	-6152.99	3j	675.1949	-6036.96	-6046.24
1k	717.2906	-5756.95	-5803	2k	637.2432	-5880.69	-5919.03	3k	763.5719	-5774.87	-5816.67

Table 4 Energies of inclusion complexes of noscapines (1a-1k) with α-cyclodextrin (4-6).

	Inclusion complex with α-CD			Inclusion complex with β-CD			Inclusion complex with γ-CD		
Compound	Spartan	AM1	PM3	Spartan	AM1	PM3	Spartan	AM1	PM3
1a	3075.257	-17258.6	-17186.6	7090.125	-14343	-14613.1	20690.28	2161338	2144565
1b	3056.14	1481361	1628924	3442.533	-14358.8	-14563.3	21518.26	213310.4	2190187
1c	3112.844	1691970	1631450	7111.514	1941236	-10183.4	20593.76	2182452	2093762
1d	3150.113	5396.016	4920.525	3416.673	-14358.6	-14566.6	20627.76	23614.08	2097402
1e	3124.567	1634220	1598501	3511.689	-11697.1	-12154	26341.54	229880.3	2146021
1f	3052.101	1531904	1509250	7094.416	-19663	-19625.6	32003.24	2169122	2744792
1g	3089.192	1456740	1562345	7067.289	-13149.9	-13490.9	21463.26	2214548	2157583
1h	3050.088	1678573	1596103	7076.949	-13839.3	-13839.3	26942.71	2131166	2029944
1i	3096.514	1621699	1463839	7136.778	-14373.4	-14649.4	20593.16	2111498	2143664
1j	3109.903	1510933	1505131	7043.35	-12533.2	-12596.4	26912.44	2201695	2209972
1k	3157.458	1662809	1526356	7186.893	-13494.2	-13924.5	20870.26	2216001	2108358

Table 5 Energies of inclusion complexes of noscapines (2s-2k) with β-cyclodextrin (4-6).

	Inclusion complex with α-CD			Inclusion complex with β-CD			Inclusion complex with γ–CD		
Compound	Spartan	AM1	PM3	Spartan	AM1	PM3	Spartan	AM1	PM3
2a	2963.457	1621830	1646665	3299.383	-9430.73	-10196.3	24167.23	2120965	20277952
2b	7849.019	1609058	1414933	3434.698	-14668.7	-14476.4	31612.54	2154772	2090848
2c	7881.307	1592365	1594047	3414.322	-15177.5	-14863.6	29076.98	2018873	2043012
2d	3006.248	7043.836	1639331	3394.913	-14360.6	-14574.8	24184.77	2188175	2222968
2e	3106.289	5051.809	1689941	7116.641	-12033.4	-12460.7	25153.28	21905150	2146777
2f	2992.556	8359.038	1653057	3336.521	-14360.6	-14574.8	31274.56	2187631	2256563
2g	7859.724	1644891	1613145	3412.798	-13589.3	-13848.8	26989.43	2176698	2120300
2h	2939.303	6950.242	1664541	6995.789	-13589.3	-13848.8	31352.62	2214723	2104743
2i	7832.602	1629563	1614534	3404.24	-15338.2	-15096.4	29355.34	2025076	21032124
2j	2950.734	1740112	1545353	7004.281	-12725.3	-12794.2	26993.15	2165442	2183361
2k	7945.745	1609787	1627373	3355.479	-14998.6	-14806.1	27025.02	2208300	1994100

Table 6 Energies of inclusion complexes of noscapines (3a-3k) with γ-cyclodextrin (4-6) using various methods.

	Inclusion complex with α-CD			Inclusion complex with β-CD			Inclusion complex with γ-CD		
Compound	Spartan	AM1	PM3	Spartan	AM1	PM3	Spartan	AM1	PM3
3a	7949.32	-17291.3	-17213.9	3465.656	-14994.5	-14739.4	28988	2095471	2026530
3b	7970.068	1599565	1517291	3612.507	-14753.4	-14629	26821.71	2179788	2106317
3c	7930.961	1308815	1538899	3532.598	-14799.7	-14633.8	29123.09	2075987	18638.63
3d	8053.127	1636325	1553939	3552.438	-14358.6	-14566.6	28838.7	2129678	20262125
3e	8035.851	1564060	1534097	3590.685	-14803.5	-14654	25718.58	2176078	2058261
3f	7955.95	1556327	1594202	3402.406	-14909.3	-14741	31582.43	2209052	2095203
3g	8015.238	1477407	1551243	3482.161	-14816.2	-14529.2	29043.56	2138294	1785435
3h	8003.2	1661359	1040767	3546.878	-14670.8	-14621.7	31696.83	2154015	1924656
3i	7970.395	1577345	1581904	3473.181	-14940.1	-14754.1	29317.22	2119874	2101049
3j	7915.401	1631378	1290057	3522.789	-15230.3	-15172.8	31697.34	2141883	2009560
3k	8057.352	1630160	1722364	3541.199	-15081.6	-15155	29360.75	2093195	19651012

Table 7 Change in energies (ΔE) for the formation of inclusion complexes via reaction between noscapines (1a-1k) with α-cyclodextrin (4) using various methods.

ΔE for the Inclusion complexes with α-CD											
Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3
1a	-12.0669	-6714.741	-6803.22	2a	-44.4184	1632496.8	1657166	3a	4802.206	-6730.645	-6818.19
1b	-49.2063	1492064.5	1639463	2b	4825.956	1619886	1425590	3b	4804.768	1610284.4	1527842
1c	0.9316	1702476.7	1641795	2c	4854.49	1603000.7	1604510	3c	4761.684	1319333.1	1549255
1d	10.8632	16198.641	15563.53	2d	-53.9966	17971.504	1650091	3d	4860.615	1647144.3	1564594
1e	-54.0263	1644996.9	1609126	2e	8.0394	15955.709	1700683	3e	4808.055	1574879.3	1544862
1f	-36.3917	1542812.5	1520002	2f	-15.7776	19392.409	1663926	3f	4815.801	1567257.4	1604839
1g	-21.2247	1467262.1	1572710	2g	4829.733	1655540.7	1623626	3g	4847.565	1487947.9	1561619
1h	-70.0928	1689378.5	1606748	2h	-96.9753	17882.698	1675302	3h	4824.502	1672182.9	1051143
1i	0.2274	1632250.4	1474229	2i	4818.194	1640239.4	1625041	3i	4813.564	1587912.5	1592306
1j	6.8784	1521856.3	1515892	2j	-69.8159	1751162.2	1556232	3j	4752.795	1642319.3	1300830
1k	-47.2444	1673470.3	1536885	2k	4821.091	1620572.8	1638018	3k	4806.369	1640840.1	1732907

Table 8 Change in energies (ΔE) for the formation of inclusion complexes via reaction between noscapines (1a-1k) with β cyclodextrin (5) using various methods.

ΔE for the Inclusion complexes with β-CD											
Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3
1a	3558.341	5608.02	5188.403	2a	-152.953	10643.26	3948.167	3a	-125.919	4973.2589	5074.401
1b	-107.275	5751.553	5393.985	2b	-32.8269	5566.806	5598.001	3b	2.7456	5372.7641	5339.689
1c	3555.141	1961149.8	9580.069	2c	-56.9556	4865.6364	5017.164	3c	-81.1401	5124.973	5141.214
1d	-167.038	5851.0843	5494.522	2d	-109.793	5974.119	5603.424	3d	-84.5347	5867.403	5506.474
1e	-111.366	8486.4309	7888.438	2e	3573.93	8277.5602	7699.323	3e	-81.5715	5401.577	5529.13
1f	3561.462	652.138	544.158	2f	-116.274	6079.822	5711.995	3f	-182.205	5427.841	5442.201
1g	3512.411	6779.369	6291.771	2g	-61.6548	6467.503	6050.466	3g	-129.973	5131.971	5264.993
1h	3512.307	6373.813	6223.843	2h	3515.05	6750.195	6330.584	3h	-76.2813	5560.604	5452.632
1i	3596.031	5584.6904	5158.658	2i	-54.6295	4745.584	4829.39	3i	-128.11	5034.7239	5066.299
1j	3495.865	7797.484	7583.347	2j	3539.27	7732.438	7503.22	3j	-84.2788	5118.51	5017.839
1k	3537.73	6574.6362	6022.894	2k	-213.636	5193.9876	5257.401	3k	-154.245	5005.1464	4806.134

Table 9 Change in energies (ΔE) for the formation of inclusion complexes via reaction between noscapines (1a-1k) with γ-cyclodextrin (6) using various methods.

γ-CD											
Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3	Compound	Spartan	AM1	PM3
1a	4143.653	2180797.1	2164060	2a	7700.045	2140547.6	20297565	3a	12381.58	2114947	2046038
1b	4953.611	232929.01	2209839	2b	15130.16	2174515.7	2110617	3b	10197.1	2199422.7	2125980
1c	4022.539	2201873.6	2113220	2c	12590.86	2038424.8	2062588	3c	12494.5	2095419.7	38108.06
1d	4029.205	43332.034	2117158	2d	7665.219	2208018.1	2242840	3d	9066.758	2149412.6	20281893
1e	9703.637	249572.14	2165758	2e	8595.718	21924969	2166632	3e	9031.474	2195791.6	2078139
1f	15455.44	2188945.1	2764656	2f	14806.92	2207579.5	2276544	3f	14982.97	2228897.7	2114953
1g	4893.531	2233985.2	2177060	2g	10493.84	2196262.8	2139894	3g	12416.58	2157750.6	1804923
1h	10387.12	2150886.9	2049702	2h	14857.03	2234570.8	2124337	3h	15058.82	2173754.9	1944425
1i	4037.563	2130964.4	2163167	2i	12881.62	2044668.1	21051744	3i	12701.08	2139357	2120564
1j	10350.1	2221533.5	2229846	2j	10513.29	2185408	2203353	3j	15075.42	2161740.5	2029445
1k	4206.253	2235577.8	2128000	2k	10441.06	2228001	2013858	3k	12650.46	2112790.4	19670668

established method for the prediction of novel structures and properties and are now being used widely to support experimental work. As such, they could provide a powerful tool for the rotational design of supramolecular systems and inclusion phenomena. Computational chemistry has been applied to a variety of host-guest complexes involving cyclodextrins (CDs).[17]

In this study, the complexation and deformation energies of both noscapines and β-CD during the formation of inclusion complexes were studied. We will also determine the driving intermolecular interactions during the formation of such complexes. A method to systematically manipulate the relative position and orientation between the interacting molecules is proposed.

2 Experimental

2.1 Software used

Chem-draw 2002- Structure of CDs, noscapines were drawn on chemdraw as in Table 1. They were optimized using MM2 calculations and energies are represented in Table 2-3.

Spartan- Inclusion complexes of α-, β- and γ-cyclodextrins with noscapines by appending them and energy was calculated as in Table 4-6.

Hyperchem 8.0- Inclusion complexes of α-, β- and γ-cyclodextrins with noscapines by appending them and energy was calculated using AM1 And PM3 model as in Table 4-6.

3 Result and Discussion

On the basis of Table 2-6, we have calculated changes in

energy (ΔE) for the formation of inclusion complexes via reaction between noscapines (1a-1k) with α-cyclodextrin (4) using various methods as in Table 7. Compound 1a showed the best formation of inclusion complex with α-CD.

On the basis of Table 2-6, we have calculated changes in energy (ΔE) for the formation of inclusion complexes via reaction between noscapines (1a-1k) with α-cyclodextrin (4) using various methods as in Table 8. Compound 3k showed the best formation of inclusion complex with β-CD.

On the basis of Table 2-6, we have calculated changes in energy (ΔE) for the formation of inclusion complexes via reaction between noscapines (1a-1k) with α-cyclodextrin (4) using various methods as in Table 9. Compound 3b showed the best formation of inclusion complex with γ-CD.

Out of the α-, β- and γ- CDs, α-CD showed best binding with all noscapines for the formation of inclusion complexes as the change in energy is less.

4 Conclusion

The complexation and deformation energies of both noscapines and CD during the formation of inclusion complexes were studied and it was found that α-CD showed effective binding with noscapines in comparison of others. This methodology will be beneficial to make inclusion complex of noscapine with alpha-CD although literature reported that researchers have focussed on beta-CD.

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