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Conformational study of arbutin by quantum chemical calculations and multivariate analysis

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ABSTRACT

A conformational study of the molecule of arbutin (4-hydroxyphenyl-β-D-glucopyranoside) has been undertaken. The molecule is composed by a glucopyranoside moiety bound to a phenol ring. It has eight conformationally relevant dihedral angles, five of them related with the orientation of the hydroxyl groups and the remaining three taking part in the skeleton of the molecule. A systematic search on the conformational space of arbutin was performed using molecular orbital methods, followed by the identification of structural similarities between the different conformers, using multivariate analyses. This approach allowed the grouping of conformers according to their structural affinity and the establishment of correlations between their structures and several properties. Intramolecular interactions involving OH groups were also investigated and correlations between spectroscopic, structural and thermodynamic properties established. The developed strategy might be useful to investigate the structure and structure/properties correlations in other conformationally flexible molecules.

1. Introduction

Arbutin (IUPAC name: (2R,3S,4S,5R,6S)-2-hydroxymethyl-6-(4-hydroxyphen oxy)oxane-3,4,5-triol, also known as hydroquinone-β-D-glucopyranoside) is an abundant solute in the leaves of many freezing- or desiccation-tolerant plants. It has been used pharmaceutically in humans for centuries, either as plant extracts or, in more recent decades, in the purified form. Arbutin acts as an antiseptic or antibacterial agent on the urinary mucous membranes while converting into hydroquinone in the kidney [1]. It is also used as a depigmenting agent (skin whitening agent) as it inhibits melanin synthesis by inhibition of tyrosinase activity [2].

From a chemical point of view, the arbutin molecule has eight conformationally relevant dihedral angles, five of them related with the orientation of the hydroxyl groups and the remaining three taking part in the skeleton of the molecule. The number of hydroxyl groups and multitude of possible conformations and intermolecular interactions for which they are relevant are responsible for most of the arbutin relevant physico-chemical properties and biological activity [3–6], but are also a source of complexity for molecular structural studies.

In this study, a systematic search on the conformational space of arbutin was performed, conformers were grouped according to structural similarities using multivariate analyses and correlations between their structures and several properties established. The strategy here used to analyze such a conformationally complex system as arbutin (with 35 atoms and eight conformationally relevant dihedral angles) might be useful to investigate the structure and structure/properties correlations in other conformationally flexible molecules, in particular carbohydrates and other biologically relevant substances.

Intramolecular interactions involving OH groups were also investigated and correlations between spectroscopic, structural and thermodynamic properties established.

2. Computational details

The semi-empirical PM3 method [7] was used to perform a systematic preliminary conformational search on the arbutin potential energy surface (PES). It provided a quick assessment of the main features of the conformational space of the molecule, which were later on taken into account in the subsequent, more reliable analysis performed at higher level of theory. This preliminary conformational search was carried out using the HyperChem Conformational Search module (CyberChem, Inc.© 2004) [8]. Taking into account the high flexibility of the arbutin molecule, a random search appeared as the most appropriate way to perform the conformational search [9–11]. In this approach, the generation of new starting conformations for the energy minimization uses a random

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variation of the dihedral angles of previously found conformers [9,10]. The method searches on until no new minima are generated.

The eight dihedral angles defining the conformational isomers of arbutin (Fig. 1) were considered in the random search: $C_2C_1O_{23}C_{24}$, $C_1O_{23}C_{24}C_{25}$, $O_6C_5C_7O_{11}$, $C_5C_7O_{11}H_{15}$, $C_3C_4O_{10}H_{14}$, $C_2C_3O_9H_{13}$, $C_1C_2O_8H_{12}$ and $C_{26}C_{27}O_{34}H_{35}$. Conformations with energies lower than 50 kJ mol^{-1} were stored while higher-energy conformations or duplicate structures were discarded. The structures obtained from this conformational search were used as start points for the construction of the input files later used in the higher level quantum chemical calculations. These latter were performed with Gaussian 03 [12] at the DFT level of theory, using the 6-311++G(d,p) basis set [13] and the three-parameter density hybrid functional abbreviated as B3LYP, which includes Becke's gradient exchange correction [14] and the Lee, Yang and Parr [15] and Vosko, Wilk and Nusair correlation functionals [16]. Conformations were optimized using the Geometry Direct Inversion of the Invariant Subspace (GDIIS) method [17]. The optimized structures of all conformers were confirmed to correspond to true minimum energy conformations on the PES by inspection of the corresponding Hessian matrix. Vibrational frequencies were calculated at the same level of theory.

The multivariate studies were performed using The Unscrambler software (v9.8) [18].

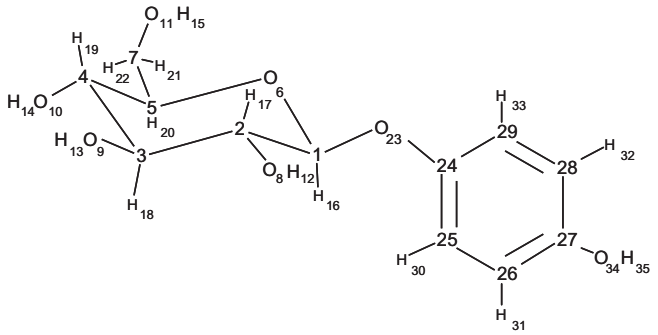

Fig. 1. Arbutin molecule, with atom numbering scheme.

3. Results and discussion

3.1. Geometries and energies

Arbutin has eight conformationally relevant rotational axes. After re-optimizing at the DFT(B3LYP)/6-311++G(d,p) level of theory the structures obtained from the preliminary semi-empirical random conformational search, 130 conformers were found, all of them belonging to the C_1 symmetry point group.

Table 1 presents the calculated relative energies and dipole moments of all the conformers calculated at the DFT(B3LYP)/6-311G++(d,p) level of theory. The values corresponding to the dihedral angles defining the conformers are provided in Table S1.

To group the conformers according to their main structural similarities, the following strategy was followed, which intends to be a fast and general procedure to perform such operation in medium size (30–60 atoms) conformationally flexible molecules:

Table 1
DFT(B3LYP)/6-311++G(d,p) relative energies, including zero point vibrational contributions (ΔE), and dipole moments (μ) for the 130 most stable conformers of arbutin.[a]

Form[b]	ΔE	μ	Form[b]	ΔE	μ	Form[b]	ΔE	μ	Form[b]	ΔE	μ
29 (B)	0[c]	1.90	110 (B)	14.88	4.00	221 (A)	20.64	4.03	113 (C)	27.40	3.14
60 (B)	0.54	4.29	115 (B)	14.98	3.70	1 (B)	21.09	2.48	133 (B)	28.34	2.69
57 (C)	0.93	2.80	141 (C)	15.30	3.43	4 (C)	21.20	3.97	107 (C)	28.52	2.95
88 (B)	1.18	4.12	26 (B)	15.58	2.71	204 (A)	21.40	3.06	123 (B)	28.57	3.10
53 (C)	1.82	2.77	36 (B)	15.62	2.22	16 (B)	22.17	3.52	104 (C)	28.98	2.94
47 (C)	2.18	3.91	76 (C)	15.63	3.39	100 (A)	22.17	4.18	253 (A)	29.15	2.67
52 (C)	2.68	2.96	211 (A)	16.15	3.38	130 (A)	22.27	1.65	237 (A)	29.17	2.64
56 (B)	2.88	2.04	143 (A)	16.67	5.00	153 (A)	22.32	3.51	157 (B)	29.27	3.72
200 (B)	3.29	4.48	22 (C)	16.69	1.71	39 (B)	22.42	2.01	99 (A)	29.32	4.99
112 (B)	3.88	2.36	51 (B)	16.87	2.36	44 (C)	22.51	2.78	222 (A)	29.75	2.56
274 (B)	4.43	4.15	83 (C)	16.89	2.95	168 (C)	22.71	3.37	137 (C)	29.82	4.21
134 (C)	8.97	1.70	280 (C)	16.90	4.23	164 (A)	22.73	3.96	289 (A)	29.83	3.80
33 (C)	9.64	0.93	24 (C)	16.95	1.31	262 (A)	22.94	3.43	284 (A)	30.00	2.32
136 (B)	9.75	2.88	59 (B)	17.01	3.84	161 (A)	23.03	1.91	145 (C)	30.01	4.73
75 (B)	10.04	3.46	40 (C)	17.37	1.47	119 (B)	23.78	2.62	261 (C)	30.11	5.34
120 (C)	10.73	1.14	303 (B)	17.50	4.32	175 (A)	23.92	1.65	270 (A)	30.27	3.57
185 (C)	10.84	2.48	9 (B)	17.53	2.35	139 (A)	24.02	4.28	69 (C)	30.43	3.24
173 (B)	11.10	3.07	202 (A)	17.56	2.08	250 (A)	24.66	1.75	298 (A)	30.60	3.69
103 (B)	11.28	2.32	7 (B)	17.61	3.72	263 (A)	24.68	2.75	246 (A)	31.08	3.42
178 (C)	11.32	2.92	58 (B)	17.62	2.60	180 (C)	24.96	3.61	306 (B)	31.16	4.58
150 (B)	11.36	3.66	45 (B)	17.94	3.91	95 (A)	24.97	3.00	114 (A)	31.42	2.61
41 (C)	11.53	2.72	209 (A)	17.96	3.30	73 (C)	24.97	0.68	232 (B)	32.71	5.65
288 (C)	12.40	3.05	10 (B)	18.07	1.36	142 (A)	24.97	3.00	215 (A)	32.72	1.30
109 (B)	12.59	2.07	98 (B)	18.12	4.12	195 (C)	25.13	2.32	307 (A)	34.23	3.47
154 (C)	13.25	4.68	6 (C)	18.21	3.00	151 (A)	25.20	2.32	282 (A)	35.46	4.52
63 (B)	13.36	3.15	304 (C)	18.81	5.25	79 (B)	25.30	2.78	297 (A)	35.75	4.05
74 (B)	13.77	4.23	158 (A)	18.98	2.06	177 (C)	25.72	5.28	301 (A)	36.94	3.67
85 (C)	13.82	2.21	3 (C)	19.22	2.52	186 (B)	25.86	3.48	207 (A)	37.31	4.34
111 (B)	13.98	3.47	11 (C)	19.34	2.91	43 (A)	26.03	4.82	293 (A)	39.42	3.63
62 (C)	13.99	2.30	166 (A)	19.37	2.97	160 (A)	26.19	3.93	264 (A)	41.46	3.01
70 (B)	14.07	3.42	311 (A)	19.77	5.33	198 (A)	26.27	1.55	313 (A)	45.68	6.40
121 (A)	14.16	3.45	225 (A)	20.25	1.93	105 (A)	26.37	2.98			
156 (A)	14.50	4.96	71 (C)	20.29	1.94	116 (B)	27.01	3.49			

[a] Energies in kJ mol^{-1}, Dipole moments in Debyes (1 D = 3.33564×10^{-30} C m).
[b] The numbers designating the conformers correspond to the number of the structure submitted to optimization in the preliminary PM3 calculations; the group to whom conformers belong is given in parenthesis.
[c] The calculated total energy (with zero point vibrational energy contribution) for the lowest energy conformer of arbutin (conformer 29) is −2608343.813 kJ mol^{-1}.