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REGULAR ARTICLE

Quantum-chemical study of the potential anti-cancer drug Ru–NAMI-A in complex with estrogen and the simulated VA and VCD spectra of estrogen, the Ru–NAMI-A drug, and possible/proposed estrogen–Ru–NAMI-A complexes

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Abstract Following up on an earlier theoretical report by Knapp-Mohammady (Phys Lett A 372:1881–1884, 2008) on the ground state of the neutral Ru complex NAMI-A (trans-imidazoledimethylsulfoxide-tetrachlororuthenate), we first report here a quantum-chemical study of the effect of both oxidation and reduction of the parent molecule to form the anionic and cationic species. The new structures are compared with the equilibrium nuclear structure reported earlier for the neutral complex. We anticipate that one such Ru cluster, with potential as an anti-cancer drug, will interact via an appropriate receptor, rather than directly with DNA. A receptor for NAMI-A binding in here proposed to be the steroid hormone, estrogen, $C_{18}H_{24}O_2$. The biomolecular structure of the dicomplex is predicted from restricted Hartree–Fock theory and density functional theory (DFT) calculations. The vibrational frequencies of NAMI-A and the dicomplex with estrogen are also reported. Some maps of the ground-state electron-density for the three neutral biomolecular species are finally presented. The use of vibrational spectroscopy, vibrational absorption (VA) and vibrational circular dichorism (VCD) are advocated to be measured, simulated and be used to understand the nature of the interaction of the Ru complex NAMI-A in complex with estrogen. Our aim in presenting these spectral simulations is to motivate the measurement of the VA and VCD spectra of estrogen, the Ru complex NAMI-A and finally of the estrogen–Ru NAMI-A complex. It should also be instructive to measure the VA and VCD spectra of estrogen and the estrogen receptor, both alone, together and finally together in the presence of the Ru NAMI-A complex to substantiate our claim that the Ru complex NAMI-A ties up estrogen, and hence prevents estrogen binding to the estrogen receptor.

Keywords Charged Ru complex · Anti-cancer drug · Estrogen receptor · Vibrational absorption · Vibrational circular dichroism · Competitive binding

Dedicated to Professor Sándor Suhai on the occasion of his 65th birthday and published as part of the Suhai Festschrift Issue.

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1 Introduction

In an earlier article [1], we have reported the equilibrium structure of the Ru complex NAMI-A in its neutral form. We mentioned there the interest in the possible changes in structure with anionic and cationic charging. In addition, we proposed, for the anti-cancer drug NAMI-A that indirect interaction with DNA will involve a receptor.

He et al. [2] have emphasized the potential of steroid hormones in treating tumors such as ovarian and cervical. This led us to an appropriate candidate hormones, and our attention was drawn to estrogen. The focus of the present study is a 'dicomplex', formed via hydrogen bonding between estrogen, our present choice of potential receptor for NAMI-A, and the NAMI-A Ru complex.

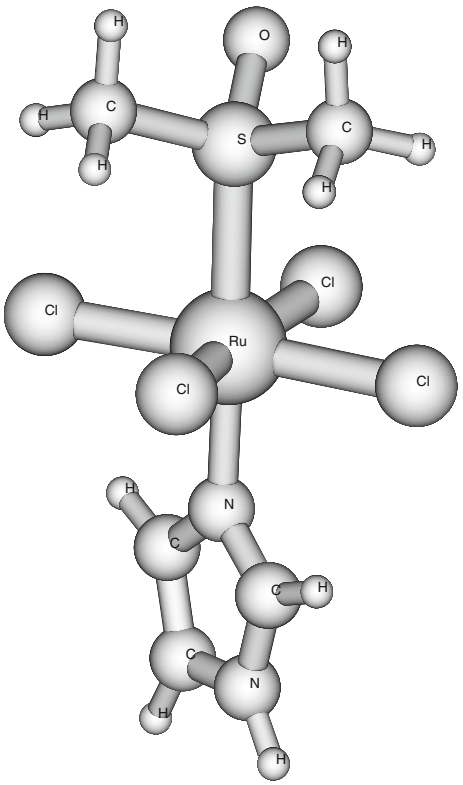

Fig. 1 The equilibrium nuclear structure of NAMI-A

In the following, we describe the main steps by which we have been led to propose a dicomplex between the NAMI-A Ru complex and estrogen based on theoretical grounds, which may hold clues as to why NAMI-A is presently undergoing promising clinical trials as an anti-cancer drug. In our concluding comments to this article, we propose that the interaction of the above dicomplex, containing the Ru cluster NAMI-A, with DNA may still be indirect. Thus, it seems to us feasible that the dicomplex proposed could act via DNA repair mechanisms, rather than by direct binding to DNA. Finally, we predict the vibrational absorption (VA) and vibrational circular dichroism (VCD) spectra of the NAMI-A Ru complex, of extrogen and of various dicomplexes we have found to date via theoretical modeling at both ab initio restricted Hartree–Fock (RHF) and density functional theory (DFT) using the B3PW91 hybrid exchange correlation (XC) functional. We hope that this work will motivate biomedical researchers to use VA and VCD spectroscopy as tools in investigating the mechanism and mode of action of the NAMI-A Ru complex.

2 Theoretical approach

As indicated, we have carried out theoretical studies on NAMI-A, estrogen and the dicomplex formed by bonding

Table 1 Nuclear coordinates of NAMI-A in angstroms

	x	*y*	*z*
Ru	2.985608	0.112790	−0.553021
Cl	3.074313	1.667552	1.255336
Cl	3.145168	−1.746819	−1.911886
Cl	3.096788	1.769273	−2.215462
Cl	2.828702	−1.512130	1.273271
N	0.931249	0.122835	−0.629734
C	0.139555	0.280625	−1.772354
C	−1.147238	0.218565	−1.394910
C	0.129954	−0.030885	0.401510
N	−1.138782	0.023790	−0.013151
H	0.438929	−0.183635	1.405849
H	0.565206	0.427083	−2.733090
H	−2.045859	0.291267	−1.955765
S	5.551576	0.155954	−0.448784
O	6.435968	−0.666303	−1.602662
C	6.118503	−0.427182	1.219750
H	5.641807	0.179903	1.970075
H	7.193149	−0.338280	1.232489
C	6.158594	1.910951	−0.436296
H	5.723913	2.416038	0.408253
H	7.234676	1.861595	−0.385519
H	5.836228	2.355086	−1.362583
H	5.813402	−1.455616	1.309102
H	−1.942518	−0.066259	0.569329

Ground-state energy is −7022.352913 in atomic units

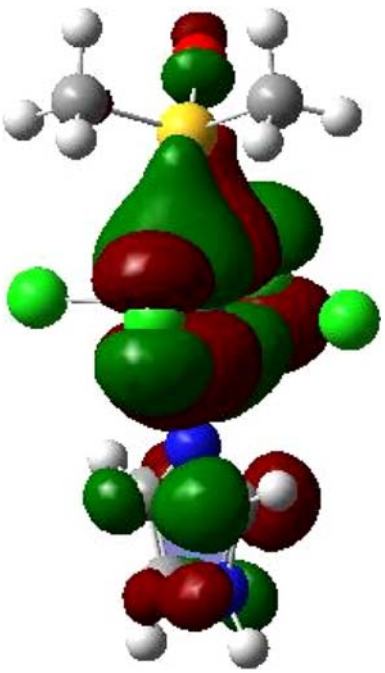

Fig. 2 HOMO of neutral NAMI-A

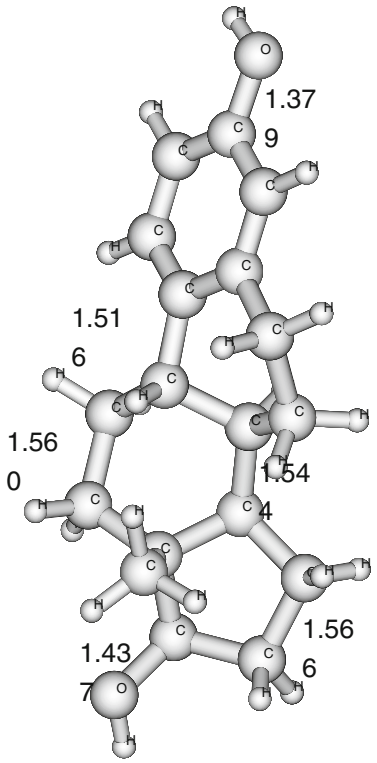

Fig. 3 The equilibrium nuclear structure of estrogen $C_{18}H_{24}O_2$, with bond lengths in Å reported

these two clusters. The ground-state equilibrium structures have been calculated by the restricted Hartree–Fock (RHF) approximation. The RHF calculations with the used basis set 6-31G were carried out by employing the Gaussian 03 package [3]. However, on a number of occasions throughout the article, we shall find it instructive to compare the RHF results with a form of density functional theory. This has latter proved particularly valuable in assessing the effect of expanding the basis sets employed on the vibrational frequencies discussed at some length below.

3 Results

Figure 1 shows the form of the nuclear structure of NAMI-A. As already mentioned above, we studied the influence of adding two additional electrons to this initially neutral Ru complex. The nuclear coordinates of NAMI-A are given in Table 1. The two electrons bind and the neutral and anionic complex structures are compared in the Appendix, where bond lengths are also shown. Though the neutral structure is fairly robust to the binding of the two additional electrons, the changes in bond length, especially the Ru–S distance, can be chemically significant. We also examined briefly the cationic complex obtained by removing two electrons from the HOMO orbital of the neutral Ru complex shown in Fig. 2. The structure was no longer robust against the charging and we shall not pursue the cationic case further therefore.

Table 2 Nuclear coordinates of estrogen

	x	*y*	*z*
C	−0.171341	1.650156	0.386896
C	−0.052829	0.147170	0.067874
C	0.400447	−0.075573	−1.400736
C	1.914725	−0.432627	−1.518456
C	2.733772	0.299832	−0.447197
C	4.241975	0.173624	−0.532535
C	4.939360	−0.498636	−1.511598
C	6.323352	−0.608719	−1.451969
C	7.012420	−0.048520	−0.400557
C	6.321061	0.627091	0.594486
C	4.951154	0.743171	0.533168
C	4.161128	1.519536	1.571088
C	2.845723	0.800133	2.025125
C	2.360594	−0.222674	0.975103
C	0.873349	−0.632525	1.025157
C	0.119558	−0.641228	2.378026
C	−1.390368	−0.637157	1.963370
C	−1.396225	−0.522640	0.413834
O	−2.487483	0.251115	−0.110092
O	8.383395	−0.120749	−0.269945
H	0.740567	2.181105	0.155666
H	−0.974854	2.062767	−0.206313
H	−0.407456	1.821146	1.429488
H	−0.180422	−0.874280	−1.849154
H	0.200965	0.820841	−1.975795
H	2.057418	−1.502896	−1.406455
H	2.258256	−0.160744	−2.510481
H	2.485192	1.353500	−0.505915
H	4.419692	−0.950054	−2.332224
H	6.848737	−1.135849	−2.225162
H	6.881773	1.052717	1.401077
H	4.782988	1.731155	2.431724
H	3.893528	2.474644	1.127976
H	3.018615	0.293659	2.967209
H	2.088747	1.554507	2.192322
H	2.943094	−1.126303	1.117237
H	0.840398	−1.658079	0.662925
H	0.373642	−1.512912	2.967381
H	0.350881	0.237113	2.962760
H	−1.901434	−1.531235	2.298965
H	−1.904578	0.223211	2.370087
H	−1.402623	−1.517973	−0.020557
H	−3.335565	−0.149437	0.121194
H	8.801170	−0.599085	−0.995296

Ground-state energy is −840.637815 in atomic units

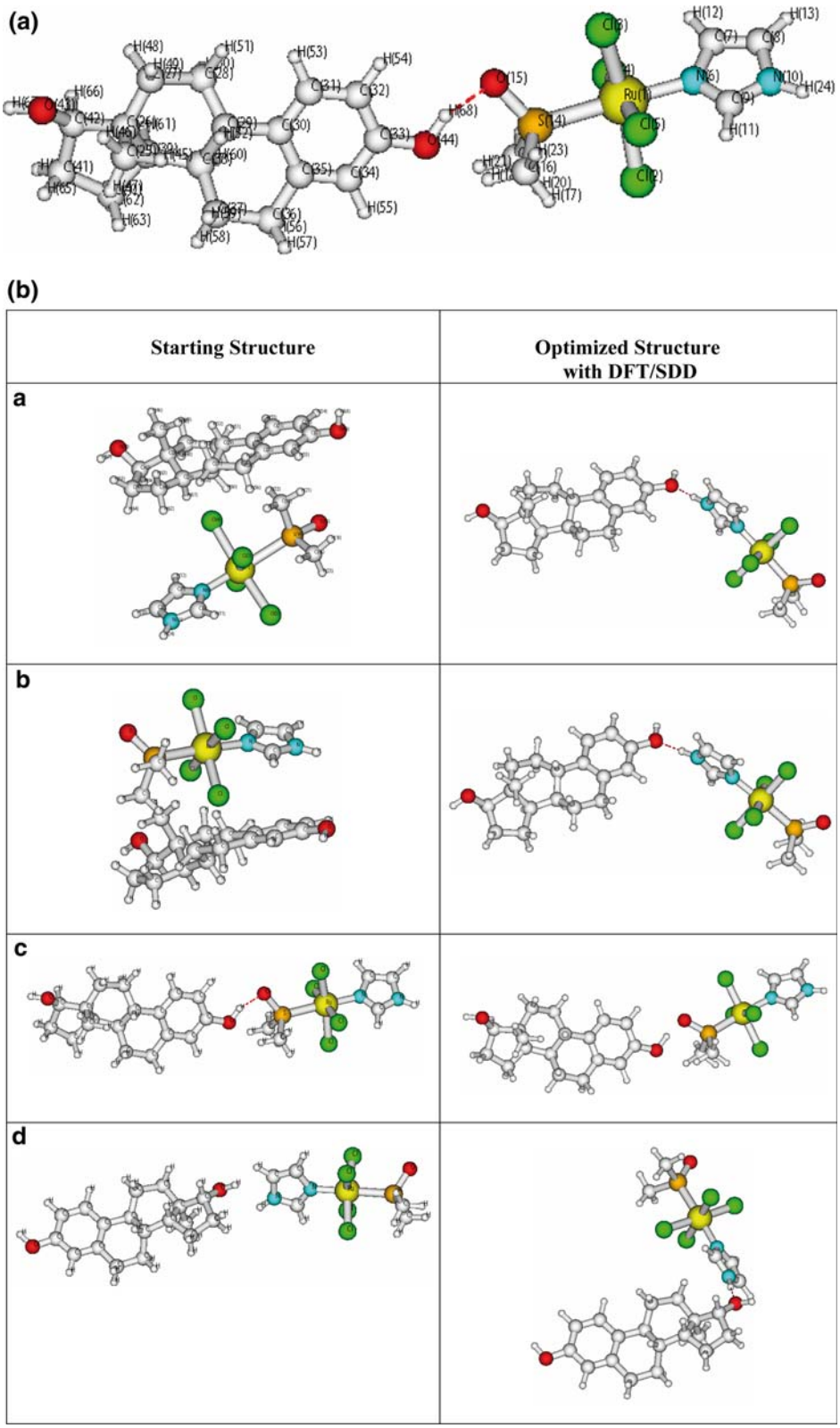

Fig. 4 (**a**) Structures of the bound dicomplex of NAMI-A and estrogen after optimization with RHF/3-21G. It is anticipated that this structure will correspond to one of the low-lying conformers of this cluster. (**b**) Structures of the bound dicomplex of NAMI-A and estrogen with different starting structures and different methods. Note that the best DFT configuration closely resembles the dicomplex from RHF theory in (**a**)

3.1 Estrogen and the dicomplex with neutral NAMI-A

Figure 3 shows the equilibrium nuclear structure of estrogen again given by RHF calculations. The nuclear coordinates are presented in Table 2. Then, because of our proposal in [1] that the anticancer drug NAMI-A interacts indirectly with DNA via a receptor, which we propose here to be estrogen, we have allowed the two clusters to interact.

Table 3 Nuclear coordinates of the neutral dicomplex of NAMI-A and estrogen

	x	*y*	*z*
Ru	−5.125917	−0.097687	−0.061267
Cl	−5.344426	2.270944	−0.193566
Cl	−4.669046	−2.259686	0.610635
Cl	−4.952998	−0.404798	−2.382374
Cl	−5.351125	0.344237	2.340662
N	−7.148409	−0.425320	−0.123883
C	−7.821306	−1.332345	−0.950171
C	−9.132279	−1.245931	−0.675229
C	−8.042424	0.183312	0.625045
N	−9.258262	−0.278918	0.323020
H	−7.832967	0.919573	1.360979
H	−7.306937	−1.939971	−1.651474
H	−9.967764	−1.762052	−1.078894
S	−2.581764	0.385671	−0.018510
O	−1.537895	−0.930342	−0.082895
C	−2.104275	1.375836	1.489109
H	−2.681361	2.284435	1.478683
H	−1.042214	1.534500	1.397739
C	−2.074789	1.522608	−1.409357
H	−2.636709	2.434475	−1.309052
H	−1.011408	1.652904	−1.290423
H	−2.321297	1.007078	−2.322051
H	−2.354386	0.768192	2.341866
H	−10.110976	0.015741	0.746890
C	9.098698	−0.199000	1.640502
C	8.938374	−0.745613	0.208321
C	8.112564	−2.058906	0.196684
C	6.626244	−1.840328	−0.228937
C	6.118589	−0.465428	0.242775
C	4.616731	−0.216942	0.135900
C	3.681641	−1.240145	0.090027
C	2.324079	−0.987093	0.047644
C	1.869856	0.317793	0.054983
C	2.788439	1.348324	0.097731
C	4.149747	1.100376	0.137996
C	5.088069	2.308357	0.132849
C	6.594355	1.968911	0.236868
C	6.860843	0.662396	−0.522988
C	8.328137	0.258832	−0.791299
C	9.413736	1.350456	−0.949767
C	10.756542	0.563031	−0.783583
C	10.344694	−0.887675	−0.405431
O	11.235032	−1.521704	0.527180
O	0.536437	0.631894	0.017422
H	8.145845	−0.082933	2.135039
H	9.701739	−0.895026	2.205955
H	9.602573	0.759023	1.649342
H	8.565562	−2.772661	−0.483034
H	8.137056	−2.504474	1.184182
H	6.524954	−1.905043	−1.307575
H	6.036561	−2.640342	0.199434
H	6.371151	−0.376947	1.292455
H	4.005730	−2.259885	0.087887
H	1.625123	−1.799124	0.010611
H	2.419840	2.354859	0.095587
H	4.922811	2.838150	−0.801058
H	4.803696	2.979944	0.936070
H	7.160095	2.793563	−0.180121
H	6.887131	1.858552	1.274207
H	6.378469	0.753301	−1.492811
H	8.310622	−0.278272	−1.737940
H	9.348944	1.842366	−1.911997
H	9.324771	2.103701	−0.180511
H	11.349067	0.584940	−1.690044
H	11.350624	0.970138	0.023524
H	10.263783	−1.485808	−1.308121
H	12.123181	−1.599798	0.155328
H	−0.085090	−0.141532	−0.025466

Ground-state energy is −7863.026332 in atomic units

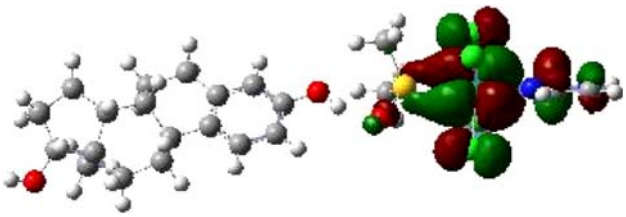

Fig. 5 HOMO of neutral dicomplex

We find a bound complex, having the structure shown in Fig. 4a. Of course, because of the tremendous complexity of the potential energy surface involved, we can claim no more than that the biomolecular structure shown in Fig. 4a must be one of the low-lying conformers of NAMI-A in interaction with the hormone estrogen. Figure 4b shows the dependency on the starting orientation of the dicomplex. The frequencies of these four optimized dicomplexes are shown in Fig. 6. The nuclear coordinates of the dicomplex of Fig. 4a are collected in Table 3. The HOMO of this neutral dicomplex is displayed in Fig. 5.

Vibrational frequencies: Table 4 shows the vibrational frequencies for the neutral Ru complex at the optimized RHF structure shown in Fig. 1. In units of cm^{-1}, these frequencies range from ∼20 to 4,000. For the isolated

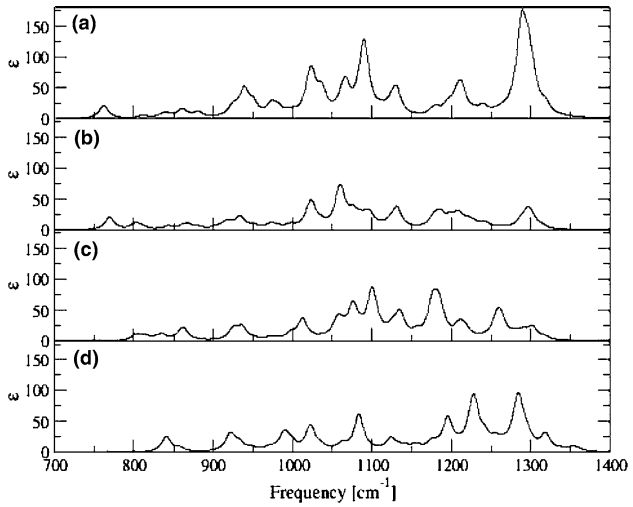

Fig. 6 Vibrational absorption spectra of the dicomplexes from Fig. 4b of neutral NAMI-A and estrogen calculated with DFT and the SDD basis set

Table 4 Frequencies of NAMI-A in units of cm^{-1}

20.26	35.69	58.74
64.61	82.46	97.37
120.25	133.84	137.20
150.20	158.26	170.17
186.81	187.69	198.54
203.93	239.79	250.09
262.97	264.72	269.38
308.13	329.75	337.05
379.51	392.85	627.09
697.65	712.52	732.17
739.95	824.35	906.08
1,032.78	1,072.67	1,080.02
1,082.46	1,096.03	1,100.18
1,117.04	1,145.13	1,181.48
1,189.43	1,230.07	1,298.06
1,414.88	1,430.46	1,504.01
1,530.01	1,581.81	1,599.84
1,612.53	1,617.22	1,627.95
1,631.15	1,721.99	3,254.45
3,256.62	3,363.76	3,364.60
3,377.79	3,382.41	3,492.06
3,501.59	3,519.01	3,831.79

complex estrogen, we have become aware of BLYP DFT calculations on estradiol in [4] where a comparison with experimental infrared results has been made. Therefore, in Table 5, we have recorded the basis set dependence of some selected vibrational frequencies of estrogen given by DFT. Figures 7 and 8 show the calculated vibrational absorption spectra (VA) and the VCD spectra of estrogen with different basis sets.

When the two above complexes are allowed to interact to form the dicomplex at the heart of this study, with nuclear structure as shown in Fig. 3, the frequencies are collected in Table 6. We draw attention to the gap between about 1,720 and 3,250 in Table 4 for NAMI-A. For the dicomplex in Table 6, the gap ranges from 1,800 to approximately 3,150, some low frequency modes (<20 cm^{-1}) now being present which appear to reflect the two molecules moving relative to one another in the dicomplex.

4 Discussion

Ground-state energies related to sum of occupied orbital energies: returning briefly to the ground-state energies E of NAMI-A, estrogen and the dicomplex formed from their bonding together, we wish to continue this present section by relating these energies to the sum of the RHF occupied orbital energies, denoted by E_s. In early theoretical work by March and Plaskett [5], using the Thomas–Fermi statistical method [6], the forerunner of modern density functional theory [7], it was demonstrated that for closed shell atoms, $E = (3/2)E_s$. Later, and independently, Ruedenberg [8, 9] analyzed self-consistent field studies on relatively small molecules to show that E was indeed proportional to E_s, with a coefficient near to (3/2) predicted theoretically for atoms. We have used the values of the ground-state energies E recorded at the head of Tables 1, 2 and 3, respectively, for NAMI-A, estrogen and their dicomplex to plot Fig. 9. The eigenvalue sum E_s has been obtained from the RHF program for the occupied orbitals, and the result is indeed showing a linear dependence, with a slope again quite near to 3/2 (see caption to Fig. 9).

Electron density map: A substantial part of modern quantum chemistry namely (often semi-empirical) DFT, makes use of the ground-state electron density, n(**r**) say, as the major calculational tool. Therefore, it is of interest to display maps of n(**r**) got by the summing the squares of the normalized RHF molecular orbitals we have calculated in the present study over all occupied states. The maps shown in Figs. 10, 11, and 12 apply to NAMI-A, estrogen, and their dicomplex, respectively. Eventually, in the densities shown in the three figures, the outermost contour taken to sufficiently large distances (i.e. low enough electron density) far from all nuclei will become circular, all traces of the 'molecular shapes' clearly in evidence here, then being lost. After this, the 'almost spherical' density will fall off with an exponential decay of the form $(-2\sqrt{2I} \cdot r)$ where r now measures the distance from the centre of mass of each molecular species, while I is the approximate ionization potential in atomic units. The further point to be

Table 5 Frequencies of estrogen in units of cm^{-1}, showing variations with choice of basis set for DFT

B3PW91/6-311++G**			B3PW91/CEP-121G			B3PW91/SDD			B3PW91/lanl2dz		
47.11	63.38	93.22	46.54	62.31	91.70	47.39	63.19	94.18	47.42	63.12	94.20
115.79	140.80	151.26	109.90	137.93	148.58	114.26	140.99	151.68	114.10	140.91	151.66
152.68	214.06	220.48	149.47	210.59	218.67	152.84	215.90	222.16	152.84	215.96	221.98
230.86	232.95	244.32	226.25	228.30	237.86	230.24	232.51	256.36	230.13	232.48	256.33
281.57	289.03	292.67	279.00	283.27	290.58	284.86	290.02	295.65	284.88	290.12	295.77
302.59	338.97	368.74	322.99	331.10	364.42	328.05	335.81	371.88	326.94	335.86	371.94
374.50	413.46	431.47	369.90	413.61	428.17	375.31	418.57	433.47	375.34	418.58	433.49
445.34	468.54	480.27	442.55	467.07	471.27	446.02	472.06	476.84	446.10	472.10	476.94
494.57	529.62	551.74	492.05	525.44	543.49	498.62	532.22	550.70	498.68	532.27	550.69
582.24	586.17	601.93	581.30	588.63	603.15	588.63	595.51	611.18	588.71	595.62	611.38
663.19	681.28	697.34	659.64	675.77	692.74	668.93	690.39	702.27	668.96	690.57	702.51
725.11	774.81	789.93	713.76	767.45	794.49	730.74	781.45	811.75	730.92	781.65	811.96
801.54	814.14	827.63	801.66	825.31	831.10	813.26	836.36	843.29	813.42	836.56	843.43
845.12	870.14	887.30	848.53	877.11	900.66	861.57	888.76	921.31	861.84	888.93	921.47
910.23	923.02	939.27	910.94	916.72	937.43	923.43	931.21	948.70	923.56	931.32	948.91
942.97	959.96	982.15	953.74	961.95	987.74	969.56	975.60	999.86	969.75	975.77	999.98
1,002.43	1,008.22	1,011.39	1,002.78	1,014.29	1,017.12	1,014.33	1,023.05	1,029.52	1,014.51	1,023.26	1,029.69
1,033.26	1,041.97	1,065.68	1,037.49	1,049.88	1,070.52	1,050.41	1,062.25	1,082.31	1,050.61	1,062.40	1,082.54
1,082.10	1,091.46	1,105.38	1,077.89	1,095.73	1,110.11	1,088.21	1,108.95	1,120.67	1,088.48	1,109.13	1,120.92
1,114.65	1,135.37	1,153.16	1,119.96	1,138.66	1,158.93	1,133.03	1,150.75	1,171.97	1,133.18	1,150.85	1,171.97
1,165.30	1,170.78	1,174.53	1,167.38	1,168.83	1,179.68	1,179.64	1,181.56	1,193.23	1,179.61	1,181.79	1,193.31
1,195.28	1,202.56	1,210.74	1,195.08	1,198.46	1,215.71	1,205.64	1,214.10	1,227.48	1,205.56	1,214.21	1,227.54
1,229.71	1,237.20	1,244.99	1,228.90	1,241.11	1,249.67	1,241.08	1,252.49	1,259.81	1,241.18	1,252.57	1,259.95
1,253.69	1,255.49	1,269.02	1,256.65	1,263.49	1,275.70	1,267.56	1,275.39	1,287.78	1,267.64	1,275.58	1,287.95
1,274.47	1,293.96	1,300.84	1,282.23	1,288.13	1,304.00	1,295.26	1,304.98	1,317.16	1,295.46	1,305.11	1,317.26
1,307.53	1,309.59	1,320.26	1,309.54	1,319.37	1,326.73	1,323.11	1,333.06	1,339.24	1,323.07	1,333.31	1,339.36
1,329.26	1,347.21	1,350.52	1,333.82	1,349.97	1,358.28	1,346.07	1,363.09	1,369.23	1,346.22	1,363.29	1,369.33
1,353.74	1,367.57	1,371.84	1,359.77	1,372.46	1,379.71	1,373.47	1,385.29	1,391.05	1,373.51	1,385.37	1,391.18
1,378.36	1,386.78	1,391.11	1,383.68	1,389.10	1,395.08	1,398.34	1,405.26	1,412.83	1,398.39	1,405.37	1,412.96
1,399.56	1,404.57	1,428.12	1,404.75	1,410.94	1,432.38	1,419.06	1,425.26	1,444.36	1,419.22	1,425.57	1,444.60
1,472.02	1,477.69	1,481.60	1,479.17	1,505.85	1,508.13	1,494.56	1,511.29	1,514.91	1,494.57	1,511.51	1,515.08
1,486.71	1,489.33	1,497.76	1,511.37	1,514.74	1,524.41	1,516.96	1,521.22	1,530.93	1,517.13	1,521.43	1,531.14
1,500.61	1,504.53	1,509.43	1,526.54	1,528.99	1,529.56	1,533.20	1,535.14	1,542.41	1,533.39	1,535.34	1,542.69
1,531.71	1,637.24	1,673.71	1,535.27	1,624.34	1,667.32	1,545.76	1,644.68	1,689.98	1,545.79	1,645.13	1,690.13
2,973.41	2,983.19	2,987.97	2,950.68	2,969.52	2,972.78	2,997.79	3,016.68	3,019.45	2,998.92	3,018.33	3,020.88
3,012.60	3,015.94	3,023.45	2,990.07	2,991.79	2,998.00	3,037.56	3,039.13	3,046.58	3,038.34	3,039.81	3,047.05
3,038.09	3,044.78	3,048.31	3,012.58	3,017.59	3,019.42	3,061.75	3,066.06	3,067.93	3,062.12	3,066.27	3,068.20
3,050.15	3,060.88	3,065.46	3,021.77	3,039.15	3,050.15	3,071.40	3,086.59	3,097.57	3,071.62	3,086.82	3,098.25
3,079.20	3,082.74	3,084.17	3,064.75	3,072.76	3,075.37	3,111.93	3,120.12	3,122.92	3,112.44	3,120.81	3,123.35
3,093.88	3,104.58	3,119.25	3,083.86	3,098.80	3,112.70	3,130.96	3,145.87	3,157.52	3,131.51	3,146.25	3,157.78
3,132.16	3,157.65	3,185.07	3,126.45	3,152.48	3,182.67	3,170.04	3,194.19	3,228.61	3,170.42	3,194.14	3,228.57
3,189.06	3,866.36	3,871.12	3,188.75	3,702.25	3,718.18	3,231.85	3,722.58	3,740.73	3,231.78	3,723.02	3,741.37

emphasized here is that the inhomogeneous electron liquids displayed in Figs. 10, 11, and 12, when refined sufficiently by either theory or by diffraction experiments, will determine the equilibrium nuclear positions (compare the present forms in Figs. 1, 3, and 4) as those points in the electron density distribution where the electric field vanishes, as is known from the early independent work of Hellmann [10] and Feynman [11].

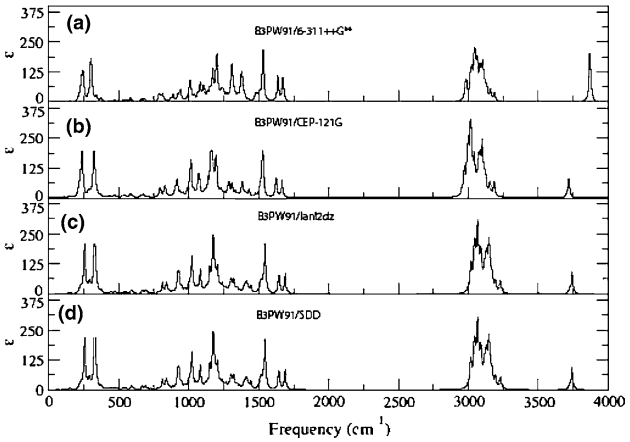

Fig. 7 Vibrational absorption spectra (VA) of estrogen with different basis sets

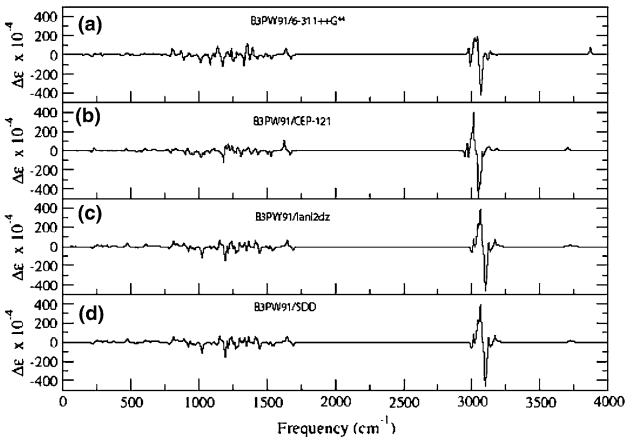

Fig. 8 VCD spectra of estrogen spectra with different basis sets

5 Conclusions

To summarize, we have first examined by restricted Hartree–Fock theory, the change in the equilibrium nuclear structure of the neutral Ru complex NAMI-A calculated in [1] when two additional electrons are added. The essence of the structure remains intact, but the important Ru–S bond undergoes considerable elongation on charging.

Then the neutral Ru complex is allowed to interact with a proposed receptor, estrogen, taken as neutral at the start of the energy minimization. The 'dicomplex', formed from 24 NAMI-A nuclei with 44 added from estrogen, is found quantum-chemically to have a binding energy of about 0.7 eV.

The calculated VA and VCD spectra of estrogen in Figs. 7 and 8 show that the influence of the different basis sets is negligible. This leads to some concluding comments on NAMI-A as a potential anticancer drug. We propose the possibility that the above 'dicomplex', with the Ru cluster

Table 6 Frequencies of the dicomplex of NAMI-A and estrogen in units of cm^{-1}

4.48	10.94	13.97
21.96	30.46	35.50
49.00	54.69	58.58
59.70	73.25	83.76
88.78	107.43	114.00
123.28	134.24	136.29
138.84	146.56	157.91
171.41	187.29	189.10
194.77	203.97	221.78
224.69	229.83	238.40
246.40	250.91	257.98
261.94	263.54	266.72
273.24	280.01	288.88
312.17	321.83	324.11
330.68	341.69	360.82
380.82	393.24	393.79
409.17	411.99	444.69
473.27	493.14	511.53
531.99	545.47	574.15
606.74	618.29	640.62
645.88	668.60	691.94
697.68	708.39	738.12
739.44	751.33	755.24
863.01	881.12	902.79
906.44	914.19	927.89
942.06	969.76	985.11
987.31	996.89	1,012.16
1,032.52	1,033.24	1,057.82
1,065.47	1,080.35	1,082.93
1,083.34	1,092.53	1,097.57
1,101.27	1,108.91	1,117.00
1,119.81	1,136.89	1,141.20
1,148.13	1,156.84	1,165.59
1,176.43	1,189.47	1,189.76
1,207.64	1,210.18	1,221.01
1,231.00	1,244.60	1,255.13
1,279.04	1,284.35	1,299.13
1,307.30	1,311.75	1,318.55
1,341.06	1,354.33	1,372.36
1,382.30	1,392.05	1,398.25
1,410.73	1,414.61	1,415.33
1,430.06	1,442.59	1,447.99
1,460.48	1,470.40	1,481.53
1,489.14	1,491.74	1,500.90
1,507.09	1,510.97	1,519.15
1,523.57	1,527.14	1,535.20
1,540.76	1,549.45	1,566.14
1,582.53	1,585.57	1,603.85
1,618.56	1,627.07	1,627.90

Table 6 continued

1,630.87	1,643.39	1,644.01
1,649.38	1,654.13	1,667.39
1,669.19	1,670.54	1,680.27
1,682.29	1,687.65	1,722.50
1,742.85	1,800.87	3,163.05
3,184.91	3,193.46	3,196.51
3,205.50	3,215.78	3,218.16
3,224.59	3,229.78	3,230.80
3,240.56	3,243.39	3,245.48
3,253.20	3,254.42	3,262.48
3,267.43	3,269.98	3,289.50
3,298.21	3,313.07	3,328.71
3,362.91	3,366.60	3,373.15
3,376.64	3,378.24	3,383.54
3,394.96	3,492.30	3,501.39
3,519.26	3,830.45	3,869.30

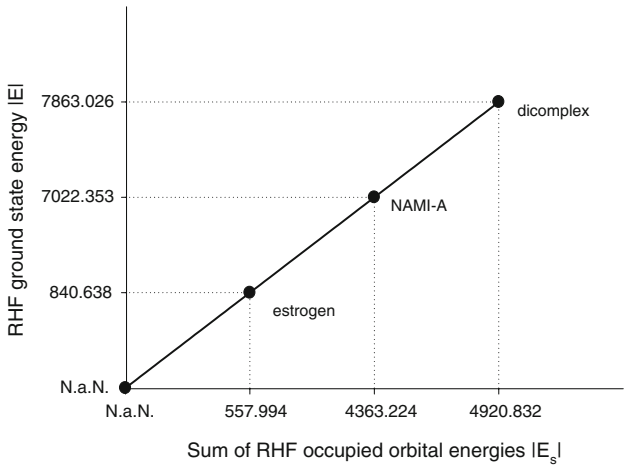

Fig. 9 The sum of the RHF occupied orbital energies against the RHF ground state energies of estrogen, NAMI-A and the dicomplex of estrogen and NAMI-A. Note that the straight line drawn has slope 1.59; quite near to the theoretical prediction of 3/2

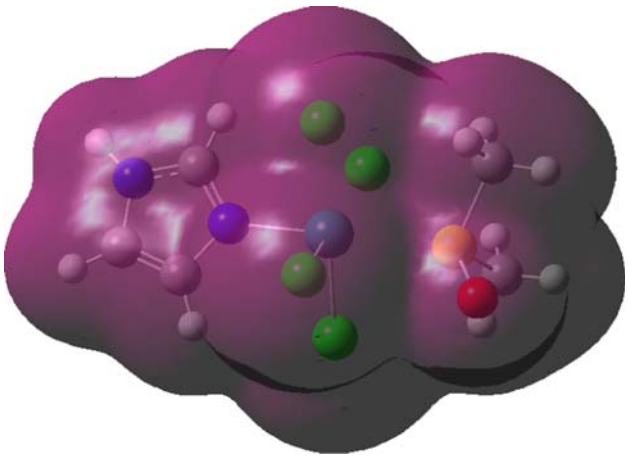

Fig. 10 Electron density map NAMI-A

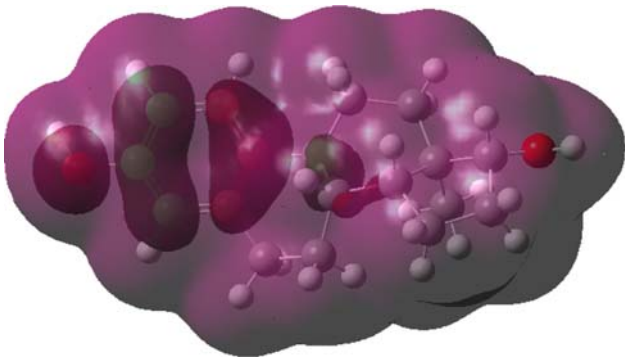

Fig. 11 Electron density map of estrogen

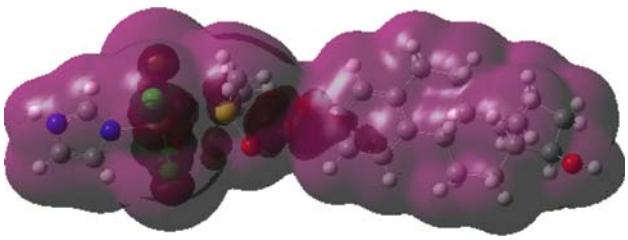

Fig. 12 Electron density map the dicomplex of estrogen and NAMI-A

embedded, is involved in prevention of cell division and multiplication. However, the mechanism to achieve this is not presently known. Interaction of the dicomplex studied here with DNA may still, we propose, be indirect. One possibility which comes to mind is that the dicomplex may be involved in maintaining, or even enhancing, DNA repair units. These seem to us to be issues of importance for the future understanding of the mechanisms involved in the use of the potential anticancer drug NAMI-A.

While, of course, the main achievement of the present study is to arrive quantum-chemically at the stable bio-molecular complex of estrogen and NAMI-A in free space shown in Fig. 4a, we wish to conclude with a general reference concerned with estrogen and its receptors in relation to cancer. A recent review of this area is that by Chen et al. [12]. It concerns itself with three categories of cancer, namely (1) breast and gynecologic, (2) endocrine organs and (3) lung and digestive system. It emerges from their review that estrogens have multiple functions in cell, which can be either adverse or beneficial and that the effects of estrogen may be of cell-type or organ dependent. Our final comment here is to stress that we were led to study theoretically the structure and dynamics of the

biomolecular complex in Fig. 4a because of our earlier interest in anticancer drug NAMI-A, presently undergoing clinical trials [1].

Little has been said, so far, as to the way the predictions of the present quantum-chemical study, of (a) estrogen and (b) the bonded complex formed from the Ru anticancer drug and (a), may be tested. To date, we are not aware of either infrared or Raman experiments on estrogen itself. In addition, as theorists, we are not competent to discuss the feasibility of such studies in the foreseeable future. Nevertheless, we record in the final two Tables of this article predictions of the DFT results for both infrared and Raman spectra. It would, of course, be important if such tests could be made, in order to confirm, or if necessary to point likely directions for refinement of, the results presented here (see also [13, 14]).

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Appendix

Effect of anionic charging on neutral complex NAMI-A and on the dicomplex with estrogen

The main purpose of this Appendix is to record the change in structure of the originally neutral complex NAMI-A discussed in the main text in some detail, when two additional electrons are added. The first point of considerable interest is that the nuclear structure shown in Fig. 1 is robust against this addition of two electrons in a spin-compensated orbital. However, Fig. 13 compares the anionic equilibrium structure with that of the neutral complex, with bond lengths recorded there. The main change in structure which is worth emphasizing here is the extension of the Ru–S distance to a value of 2.89 Å in the anionic species. This increase of some 0.3 Å is of course, chemically significant. The final point on $(NAMI\text{-}A)^{2-}$ is that the binding energy of two additional electrons is substantial. The HOMO of this anion is shown in Fig. 14. As mentioned briefly already in the main text, in marked contrast to the above behavior of NAMI-A on anionic charging, removing two electrons leads to structural

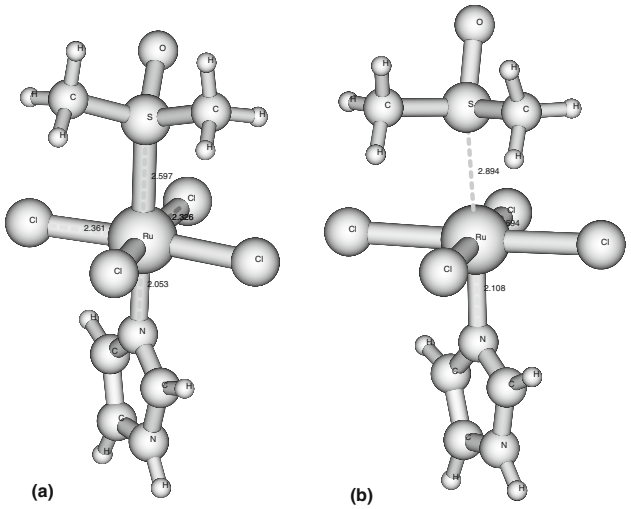

Fig. 13 Bond lengths of the neutral (**a**) and the anionic doubly charged NAMI-A (**b**) nuclear structures. Note the marked extension of the Ru–S bond length in the anion

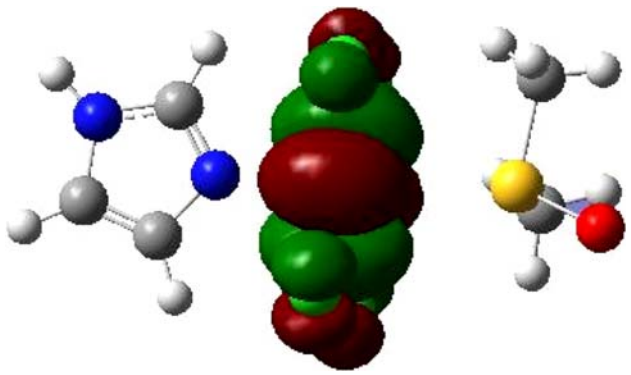

Fig. 14 HOMO of charged NAMI-A

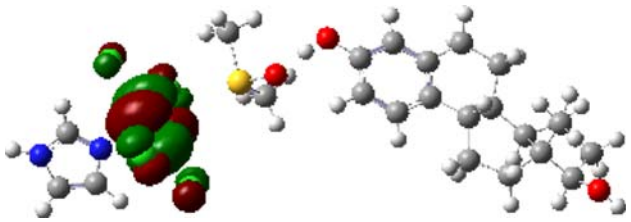

Fig. 15 HOMO of the doubly negative charged dicomplex of NAMI-A and estrogen

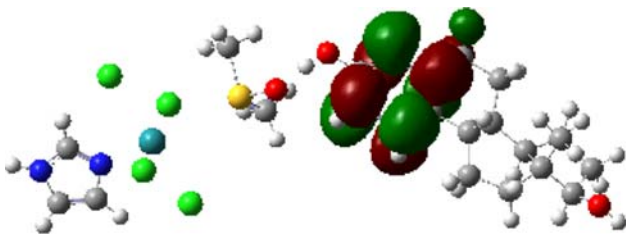

Fig. 16 LUMO of the doubly negative charged dicomplex of NAMI-A and estrogen

instability and we shall not therefore elaborate further on the cationic complexes.

Turning to the dicomplex of NAMI-A with estrogen, we have made a more limited study of the effect of ionic charging. We content ourselves therefore in stressing that the dicomplex anion is also quite stable. Figure 15 shows the shape at the HOMO for such a dicomplex, while Fig. 16 depicts the LUMO. Further details are available from M. Knapp-Mohammady on request.

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