Modeling the Interaction between Two- and Four-Ring Progestin Models and a Silicone-Based Polymer Model: A Density Functional Theory Study

Terttu I. Hukka*,† and Tuula T. Pakkanen‡

Tampere University of Technology, Institute of Materials Chemistry, P.O. Box 541, 33101 Tampere, Finland, and University of Joensuu, Department of Chemistry, P.O. Box 111, 80101 Joensuu, Finland

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In this paper, we introduce a relatively fast and reliable method for determining the feasibility of drug delivery from transdermal and implant materials. We are using density functional theory for modeling the interaction of progestins, that is, progesterone and six of its hydroxyl derivatives, with a silicone-based polymer. The silicone-based polymer model is a linear molecule, which consists of four dimethylsiloxane units. The progestin models are (1) complete progestin structures, which are called four-ring models, and (2) their two-ring models, which are comprised of the C and D rings of the basic steroid skeletons. We are investigating the interaction between the four- and two-ring models and the polymer model in three different interaction configurations. Altogether, 42 different equilibrium geometries of progestin−polymer model complexes and the corresponding interaction energies have been calculated. Our computational results are in very good agreement with the experimental findings reported previously in the literature, which state that the release rates and permeabilities of progestin pharmaceuticals in silicone-based drug delivery systems decrease when the number of hydroxyl groups is increased in the steroid skeleton. The four-ring models take the total interaction of the steroid into account slightly better than the two-ring models. However, the two-ring models are very good for predicting the local interactions between the steroid and the polymer model.

1. INTRODUCTION

It has been experimentally observed that the release rates of progesterone and six of its hydroxyl derivatives from biocompatible, silicone-based transdermal drug delivery systems decrease with an increasing number of hydroxyl groups.[1,2] The extent of reduction in the release rates has been determined to be a function of the position of the hydroxyl groups on the steroid skeleton. However, the experimental results do not explain how the interaction between the drug molecule and the delivery material that is surrounding the drug is altered when multiple hydroxyl groups are simultaneously present or when the position of the hydroxyl group in the drug molecule is altered.

In this work, we use density functional theory (DFT) to investigate local interactions of four- and two-ring models of progesterone and those of its six hydroxyl derivatives with a dimethylsiloxane-based polymer modeling the drug delivery material. Ab initio theory has been previously applied to calculating the electronic structures of some progesterone molecules[3−7] and other steroids.[8,9] DFT has recently been used to calculate the vibrational frequencies or structures of progesterone,[10,11] 17α-hydroxyprogesterone,[12] desoxycorticosterone,[13,14] and a few other progesterone derivatives.[15] The ab initio and DFT method has also been applied to cation affinity studies of some neurosteroids, including progesterone.[16] Structural optimizations[17,18] and conformational studies[19] of some progestins have been carried out by semiempirical calculations. The valence electronic structure of polydimethylsiloxane (PDMS) has been investigated by the ab initio Hartree−Fock linear combination of atomic orbitals crystal orbital method.[20] The interaction of PDMS with some organic compounds such as 1,3-dimethylurea has been studied by using semiempirical quantum mechanical methods with the Austin model 1 parametrization.[21] However, computational studies on progestins interacting with polydimethylsiloxane have not been published prior to the time of reporting of this work, although they are commonly used substances in hormone therapy.[22−25]

In this paper, we present results on the DFT calculations modeling progesterone and six of its hydroxyl derivatives interacting with a dimethylsiloxane-based polymer at three different interaction geometries. We model the progestins by the complete progestin structures, which are called four-ring models, as well as with their two-ring models. The silicone-based polymer model is a linear molecule, as described in the Computational Methods and Models section. We report the closest interaction distances and the corresponding angles within the interaction complexes as well as the interaction energies. The closest hydrophobic distances between the interacting complexes are also given. In addition, we compare the calculated relative stabilities of the model complexes to experimental results such as diffusivities, release fluxes, and permeabilities of these progestins through a polydimethylsiloxane polymer used in transdermal drug delivery devices. Moreover, we discuss the applicability of the computational methods and the ring models for predicting

* Corresponding author phone: +358 (0)3-3115 3632; fax: +358 (0)3-3115 2108; e-mail: terttu.hukka@tut.fi.
† Tampere University of Technology.
‡ University of Joensuu.

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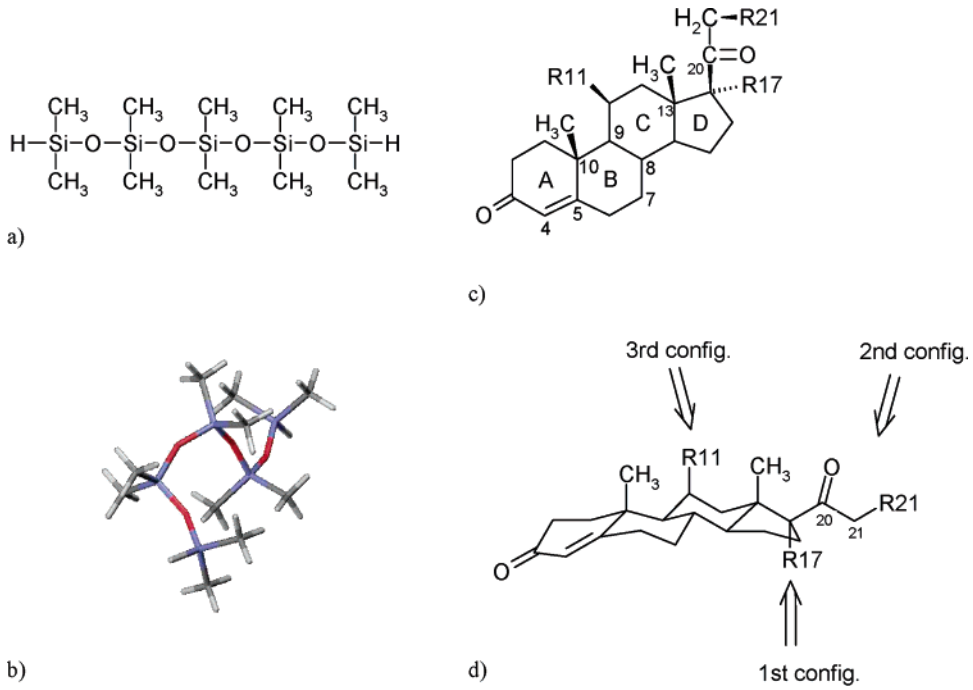

Figure 1. (a) Molecular structure and (b) the B3LYP/6-31G**-optimized structure of the polydimethylsiloxane polymer model. The rightmost Si−O−Si "leg" is pointing outward from the polymer model chain, and the other Si−O−Si end is pointing "forward" (to the right). (c) Steroid skeleton. Substituents R11, R17, and R21 are given in Table 1. (d) The locations of the PDMS model in three different interaction configurations.

experimental results. We will utilize the conclusions to benefit our ongoing research on the topic.

2. COMPUTATIONAL METHODS AND MODELS

Density functional theory calculations with the Becke 3LYP (B3LYP) hybrid functional[26−29] were carried out by using the Gaussian 98 program[30] and an SGI Origin 2000 computer at CSC, the Finnish IT Center for Science. The initial ground state geometries of separate models were constructed with the Spartan 02 software[31] and optimized to stationary points by ab initio self-consistent field molecular orbital calculations by using the spin-restricted Hartree−Fock method[32] and the polarized 6-31G** split-valence basis sets[33,34] within the Gaussian software. The DFT calculations were then carried out with the 6-31G** basis set.

A linear molecule consisting of four dimethylsiloxane units, $H(CH_3)_2SiO[(CH_3)_2SiO]_3Si(CH_3)_2H$, see Figure 1a, is terminated with hydrogen atoms, optimized, and used as a model of the PDMS. The optimized structure of the polymer model is presented in Figure 1b. The calculated Si−O bond lengths are ca. 0.06 Å longer and the Si−O−Si bond angles are within 0.5−0.8° if compared to the crystal structure of a molecule including a dimethylsiloxane chain consisting of three silicon and two oxygen atoms.[35]

The complete molecular structures of progesterone (pregn-4-ene-3,20-dione; 1), desoxycorticosterone (21-hydroxypregn-4-ene-3,20-dione; 2), 11-hydroxyprogesterone (11-hydroxypregn-4-ene-3,20-dione; 3), 17α-hydroxyprogesterone (17-hydroxypregn-4-ene-3,20-dione, 4), corticosterone [(11β)-11,21-dihydroxypregn-4-ene-3,20-dione; 5], 17α-hydroxydesoxycorticosterone (17,21-dihydroxypregn-4-ene-3,20-dione; 6), and hydrocortisone (11,17,21-trihydroxypregn-4-ene-3,20-dione; 7) are chosen for the steroid pharmaceuticals and named as four-ring models throughout the text. In addition, two-ring models that are comprised of the C and D rings, that is, one cyclohexane ring fused with the cyclopentane ring, plus the substituents R11, R17, and R21 present in the complete steroid skeletons[36] are chosen for the representatives of the local structures of progestins. Two-ring models were studied in order to determine how reliably smaller models predict the local interactions between progestins and a polydimethylsiloxane polymer. The two ring models were cut out from the four-ring models and were optimized. A basic steroid skeleton is presented in Figure 1c, and the names of progestins 1−7 and the compositions of the substituents R11, R17, and R21 are listed in Table 1. All four-ring steroid models are trans-trans-trans conformations like most natural and synthetic steroids such as progesterones. The calculated bond lengths are mostly within 0.01−0.03 Å and the bond angles within 0.6° of the corresponding values available in literature measured for crystal structures of the steroids[37−40] or their enantiomers.[41,42].

Table 1. Pharmaceuticals Modeled in this Work

steroid	R11	R17	R21
(1) progesterone	H	H	H
(2) desoxycorticosterone	H	H	OH
(3) 11-hydroxyprogesterone	OH	H	H
(4) 17α-hydroxyprogesterone	H	OH	H
(5) corticosterone	OH	H	OH
(6) 17α-hydroxydesoxycorticosterone	H	OH	OH
(7) hydrocortisone	OH	OH	OH

Three different progestin−polymer interaction model configurations are chosen at the first stage of this research in order to investigate the applicability of the computational methods and the ring models for predicting experimental results. No experimental structural data was found either from the literature or the Cambridge Structural Database for comparing the calculated interaction geometries. The configurations are chosen on the basis of the experimental

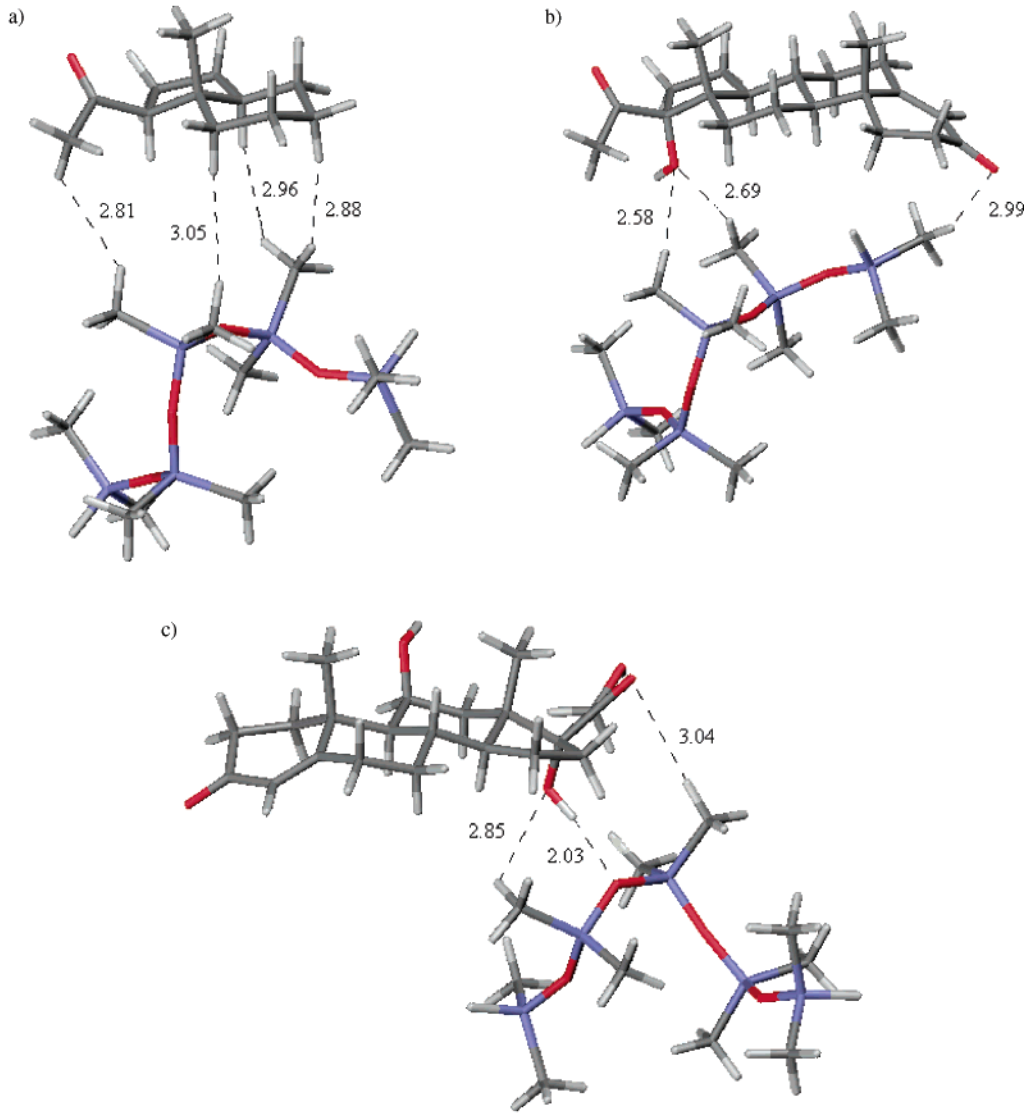

Figure 2. Optimized structures of three different steroid-model−polymer complexes in the first interaction configuration. A two-ring model of (a) the interacting progesterone (I1) and the four-ring models of the interacting (b) 17α-hydroxyprogesterone (I4) and (c) hydrocortisone (I7). The closest intermolecular distances are given in Å units.

conclusions found in the literature that the hydroxyl groups in positions 11, 17, and 21 seem to control the release rates of progestins from transdermal drug delivery systems. The polymer model is placed to a distance possible for an attractive interaction in close proximity to one of these three hydroxyl group positions and the interaction geometries are optimized to stationary points and the corresponding energies are calculated. It is assumed that these three positions are the keys for finding out the applicability of the computational method.

In the first chosen interaction configuration (I), the polymer model is "below" the steroid skeleton, which by convention is called the lower side, that is, close to the 17α-hydroxyl group of progestin models 4, 6, and 7, leaving the carbonyl and both 11- and 21-hydroxyl groups to the opposite side of the polymer, see Figure 1d. In the second chosen interaction configuration (II), the polymer is "above" the steroid skeleton, which by convention is called the upper side, that is, close to the 21-hydroxyl group and also to the carbonyl group at position 20 of progestin models 2, 5, 6, and 7, see Figure 1d. In the third chosen interaction configuration (III), the polymer is also "above" the steroid skeleton, but at the opposite end of it compared to II, that is, close to the 11-hydroxyl group of progestin models 3, 5, and 7, see Figure 1d. The complex geometries are constructed with the *Zoa 2.5* software[43] by positioning the optimized polymer model at an intermolecular distance of 3.5 Å from the carbon atom bonding the OH substituent at either position 11, 17, or 21 in the steroid skeleton. The initial polymer location is the same in all complex models also when the OH group is exchanged with H, because the distance is measured from the same carbon atom of the steroid skeleton used as a template for constructing the complexes. The two-ring complexes are constructed and optimized first. The optimized four-ring steroid models are then substituted in the optimized two-ring complexes by placing the four-ring models on top of the two-ring models, which are removed. The four-ring model complexes are then optimized. The interaction energy is calculated for each complex by subtracting the sum of the energies computed for a separate progestin model and the initial polymer model from the total energy computed for their optimized complex.

Table 2. Calculated Total Energies (hartree)[a] of the Four- and Two-Ring Models of Steroids, Polydimethylsiloxane, and their Interaction Complexes in the First (I) Interaction Configuration

model	four-ring model HF/6-31G**	four-ring model B3LYP/6-31G**	two-ring model B3LYP/6-31G**
1	−962.487	−968.800	−544.585
2	−1037.331	−1044.001	−619.786
3	−1037.338	−1044.009	−619.797
4	−1037.342	−1044.014	−619.798
5	−1112.182	−1119.210	−694.998
6	−1112.187	−1119.215	−694.999
7	−1187.038	−1194.425	−770.212
PDMS		−2149.272	
model & PDMS	four-ring model HF/6-31G**	four-ring model B3LYP/6-31G**	two-ring model B3LYP/6-31G**
I1		−3118.078	−2693.858
I2		−3193.275	−2769.059
I3		−3193.286	−2769.070
I4		−3193.291	−2769.074
I5		−3268.484	−2844.271
I6		−3268.495	−2844.278
I7		−3343.705	−2919.492

3. RESULTS AND DISCUSSION

Geometries and Energies. The First Interaction Configuration. In the first interaction configuration (I), the polymer model is "below" the steroid skeleton, that is, close to the 17α-hydroxyl group of the progestin models 4, 6, and 7, leaving the carbonyl group at position 20 and the 11- and 21-hydroxyl groups to the other side of the steroid skeleton, see Figure 1d. Some representative, B3LYP/6-31G**-optimized equilibrium geometries are presented in Figure 2a−c for a two-ring model complex of progesterone (I1) and for the four-ring model complexes of 17α-hydroxyprogesterone (I4) and hydrocortisone (I7), respectively.

Total energies calculated for the four-ring progestin molecules 1−7 as well as for their two-ring models are presented in Table 2 together with the total energy of the PDMS polymer model. The calculated total energies for their interaction complexes I1−I7 are also given in Table 2. The closest intermolecular H···H distances, the closest interaction distances, and the corresponding interaction angles, as well as the energies of interaction, are listed in Table 3a for the four-ring models and in Table 3b for the two-ring models.

The conformation of the polymer model is C_2-symmetric in two- and four-ring complexes I1, I2, I3, and I5. The conformation of the polymer model in complexes I6 and I7 is close to C_2-symmetric; however, the C17−O−H···O−Si interaction has bent the other Si−O−Si bridge inward and toward the neighboring Si−O−Si bridge. All steroid models are located above a Si−O−Si bridge. In complexes I4, no C17−O−H···O−Si interaction takes place, and also there is no C21−OH group in the steroid structure. The conformation of the polymer is similar to that found in complexes I6 and I7 but is clearly out of C_2 symmetry because the methyl groups of the polymer are tilted toward the C17−OH group because of the C17−O···HCH_2−Si interaction, and at the same time, the Si−O−Si chain end has moved up closer to the steroid skeleton. The main changes from the initial conformation of the polymer are the directions of the Si−O−Si ends of the PDMS chains. In the initial PDMS model, the other end (the Si−O−Si "leg") is directed outward from the PDMS main chain and the other end is bent forward. In the complexes of the first configuration, the Si−O−Si "leg" has moved to the front from the outward position and the other Si−O−Si end has bent back from the front.

In the first interaction configuration, the hydrogen atom of the 17-hydroxyl group of steroid models 6 and 7 locates closest to an oxygen atom of the polydimethylsiloxane backbone, see the C17−O−H···O−Si distances in Table 3a and b. These C17−O−H···O−Si distances in complexes I6 and I7 are 2.04 and 2.03 Å for the four-ring models and 2.33 and 2.04 Å for the two-ring models, respectively. Complexes I6 and I7 are also computed to be energetically the most stable, ca. −21 kJ mol^{-1} (the four-ring models) and −17 to −21 kJ mol^{-1} (the two-ring models), as discussed below. The largest O−H···O interaction angles of 166−168° are found in complexes with the largest interaction energies. In the third most stable complex I4, only the oxygen atom of the 17α-hydroxyl group is relatively close to the polymer (ca. 2.6−2.7 Å, see the C17−O···H−CH_2 distances in Table 3a and b), leading to ca. 7.0 kJ mol^{-1} (the four-ring model) or from 6.0 to 10 kJ mol^{-1} (the two-ring model) smaller interaction energies if compared to those of complexes I6 and I7. The O···H−C interaction angles are also slightly smaller, that is, 154−162°.

In I1, I2, I3, and I5, there is no 17-hydroxyl group in the steroid skeleton. The localized interaction energy of these complexes (calculated from the two-ring models) varies between −3.1 and −3.6 kJ mol^{-1}. In the case of complexes I1 and I3 with the four-ring models, the PDMS "leaves" its location next to the 17-hydroxyl group and moves close to the carbonyl group at position 3, where it interacts with the oxygen atom of the carbonyl group (C3═O···HCH_2−Si). However, the conformation of the polymer remains comparable to that found in the two-ring model complexes I1 and I3, where there is no C3═O group. In I1, two methyl hydrogens of the PDMS are interacting with the C3═O oxygen at distances of 2.55 and 2.61 Å, leading to an interaction energy of −16 kJ mol^{-1}. In I3, only one methyl hydrogen is interacting with the C3═O oxygen at a distance of 2.49 Å, and a slightly more positive interaction energy of −13 kJ mol^{-1} results. If we consider only the localized interactions of each configuration in this work, which in the first configuration means the interactions where the polymer is close to the 17-hydroxyl group of the progestin model as is the case in the two-ring complex models, we have to omit the C3═O···H interactions of the four-ring models when calculating the average interaction energies. If we do that, both the four-ring and the two-ring models predict energetically very similar molecular level interactions. Furthermore, the local interaction energies between the 17-hydroxyl group and the polymer in the four-ring model complexes I1 and I3 should be comparable to those given by the two-ring models or the other four-ring model complexes, that is, with the interaction energy from −3 to −4 kJ mol^{-1}.

Our results predict that hydrocortisone (7), which has three OH groups, interacts the most strongly with the polymer model in the first configuration, see Table 3a and b. The strength is most obviously due to the interaction between a slightly acidic hydrogen atom of the alcoholic 17α-hydroxyl group and a nucleophilic oxygen atom of the polymer backbone. In addition, the C17−O···HCH_2−Si interaction with two different methyl hydrogens of the polymer stabilizes the complex further. The combined C−O−H···O−Si and

Table 3. Interaction Distances (Å), Angles (degrees), and Energies of Interaction (kJ mol^{-1}) of the Four- and Two-Ring Steroid Models (1−7) and the Polymer Model in the First (I) Interaction Configuration[a]

model	H···H	C17−O−−H···H−CH_2	C3═O···H−−CH_2	∠O···HC	C17−O···H−−CH_2	∠O···HC	C17−O−H···O−−Si	∠O−H···O	E_I B3LYP/6-31G**
				a. Four-Ring Steroid Models					
I1	3.33		2.55, 2.61	139.4,138.3					−16
I2	2.77								−4.1
I3	2.50		2.49, 3.62	159,1,129.2					−13
I4	2.53	2.52, 2.64	2.89	155.0	2.58, 2.69	155.9,156.2			−14
I5	2.81								−3.8
I6	2.28	2.63			2.91, 3.06	119.1,129.2	2.04	165.8	−21 (−21.0)
I7	2.28	2.61			2.85, 3.49	117.8,126.5	2.03	166.7	−21 (−21.4)
				b. Two-Ring Steroid Models					
I1	2.81						−3.3		
I2	2.69						−3.5		
I3	2.77						−3.1		
I4	2.62	2.29, 2.56	2.55, 2.63	161.6, 153.9			−11		
I5	2.78						−3.6		
I6	2.45	2.70			2.56, 2.78	132.7, 128.5	2.33	138.5	−17
I7	2.25	2.63			2.90, 3.19	116.8, 127.8	2.04	167.7	−21

[a] Hydrophobic intermolecular H···H distances are given for comparison.

C−O···H−CH_2 interaction has an energy of −21 kJ mol^{-1} calculated at the B3LYP/6-31G** level of theory.

The interaction of 17α-hydroxydesoxycorticosterone (6) with the polymer model is calculated to be the second strongest in the first configuration, see Table 3a and b. The intermolecular C17−O−H···O−Si distance is found to be almost the same as that in I7, and the interaction energy is only slightly smaller, see Table 3a and b. 17α-Hydroxyprogesterone (4) forms the third most stable interaction complex with the polymer model (I4), if we focus only on the localized interactions and omit the C3═O interaction, as is discussed previously. Although in I4 the two C17−O···H distances are shorter than in either I6 or I7, there is no additional stabilizing C17−O−H···O−Si interaction as in I6 and I7, and therefore, the interaction remains slightly weaker than that in I6 and I7.

The Second Interaction Configuration. In the second interaction configuration (II), the polymer is "above" the steroid skeleton and close to the side chain, that is, close to the carbonyl group at position 20 and also close to the hydroxyl group at position 21, which exists in progestin models 2, 5, 6, and 7, see Figure 1d. The 11-hydroxyl group in progestin models 3, 5, and 7 locates at the opposite end of the steroid skeleton with respect to the polymer location and is therefore too far away to directly interact with the polymer. The B3LYP/6-31G**-optimized equilibrium structures of some representative interaction models II1, II5, and II7 are presented in Figure 3a−c.

Total energies calculated for the interaction complexes II1−II7 are given in Table 4. The closest intermolecular H···H distances, the closest interaction distances, and the corresponding interaction angles, as well as the energies of interaction, are listed in Table 5a for the four-ring models and in Table 5c for the two-ring models. The interaction energies are also listed in Table 5a and c, respectively.

In the optimized complexes, oxygen atoms of the polymer backbone remain far away from the 21-hydroxyl group and the O−H···O−Si interaction seen in the first configuration is not possible in the second configuration.

The conformations of the polymer models are very similar when the corresponding two-ring and four-ring complexes are compared. In complexes II1, II3, and II4, the Si−O−Si "leg" of the PDMS chain is pointing "forward" and the other end of the Si−O−Si chain is slightly forward like in the initial polymer model. In complexes II2, II5, II6, and II7, the "leg" is also pointing forward and the other end of the Si−O−Si chain is bent slightly backward. In addition, in complex II5, the other end of the Si−O−Si chain is bent asymmetrically also slightly outward and toward the C10−OH group breaking the crownlike structure of the top of the PDMS found in complexes II2, II6, and II7. Either the C20═O carbonyl group (II1, II3, and II4) or the bond between the carbonyl group and the C21−OH group (II2, II5, II6, and II7) of the steroid model locates above the Si−O−Si "top" bridge, which has bent downward. The main changes from the initial conformation of the polymer are the directions of the Si−O−Si ends of the PDMS chains. In the initial PDMS model, the other end (the Si−O−Si "leg") is directed outward from the main chain of the polymer and the other end is bent forward slightly more strongly than in the complexes.

According to the computed results, the methyl hydrogens of the polymer model locate closest to the oxygen atom of the carbonyl group at position 20 in all complexes II1−II7, see the C20═O···H distances in Table 5a and c. The methyl hydrogens of the polymer model are next closest to the oxygen atom of the 21-hydroxyl group (the C21−O···HCH_2 distances), which exists in complexes II2, II5, II6, and II7. The O···H−C interaction angle in these complexes varies from 168.0 to 159.8° in the four-ring models and from 168.1 to 139.7° in the two-ring models. The larger angles correspond to energetically stronger interactions as discussed below. In these complexes, also the intermolecular C20═O···HCH_2 distances are the shortest (2.53−2.62 Å in the four-ring models and 2.54−2.61 Å in the two-ring models). The corresponding C═O···H−C interaction angles are 146.3−156.8° and 145.3−157.8°, respectively, and are slightly smaller than those measured for the O···H−C interaction where the oxygen atom is sp^3-hybridized. Complexes II2, II5, II6, and II7 are also predicted to be energetically more stable than II1, II3, and II4, as discussed below.

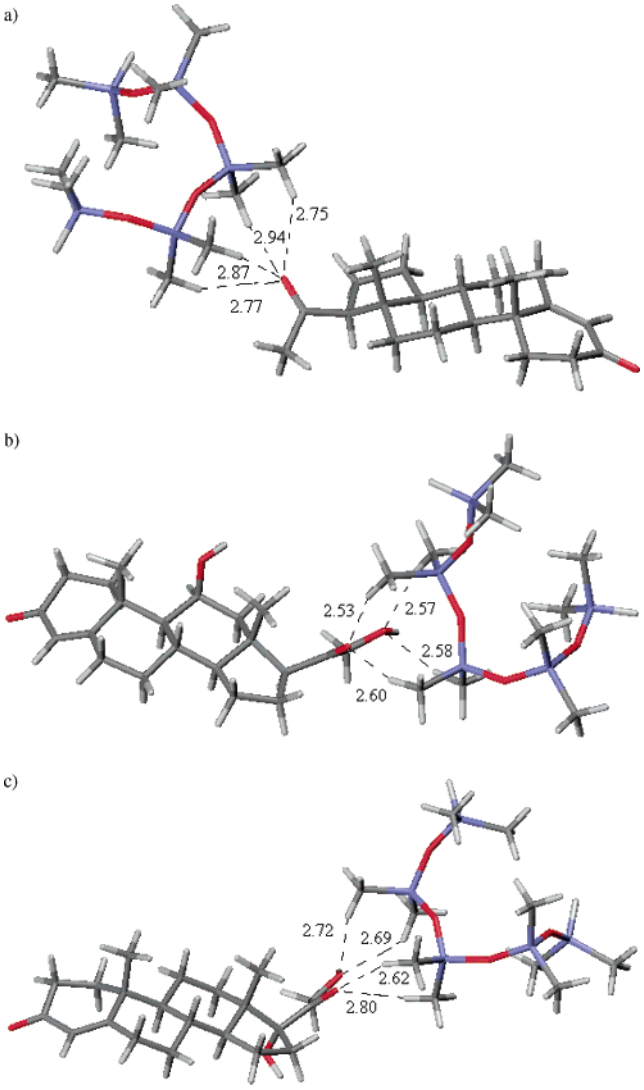

Figure 3. Optimized structures of three different four-ring steroid−polymer complexes in the second interaction configuration. Progestins are (a) progesterone (II1), (b) corticosterone (II5), and (c) 17α-hydroxydesoxycorticosterone (II6). The closest intermolecular distances are given in Å units.

Table 4. Calculated Total Energies (hartree) of the Four-Ring Steroid Model−Polydimethylsiloxane Complexes and the Two-Ring Model−Polydimethylsiloxane Complexes in the Second (II) and Third (III) Interaction Configurations

model & PDMS	four-ring model B3LYP/6-31G**	two-ring model B3LYP/6-31G**
II1	−3118.078	−2693.863
II2	−3193.281	−2769.065
II3	−3193.287	−2769.075
II4	−3193.290	−2769.074
II5	−3268.491	−2844.279
II6	−3268.494	−2844.279
II7	−3343.705	−2919.492
III1	−3118.073	−2693.858
III2	−3193.293	−2769.079
III3	−3193.289	−2769.079
III4	−3193.287	−2769.071
III5	−3268.490	−2844.280
III6	−3268.495	−2844.279
III7	−3343.707	−2919.495

In the second interaction configuration, both the two- and four-ring progestin models have the C20═O···H interaction with the polymer, and all interaction energies are within the range of −12 to −23 kJ mol^{-1} in this configuration, see Table 5a and c. Both the complete steroid structures and their two-ring models predict that the interaction between corticosterone (5) and the polymer is energetically the strongest. Also, the interaction angles are the largest in II5 complexes. In complexes II2, II6, and II7, which have the same additional C21−O···H interactions, the local interaction is practically as strong as that in II5 (from −19 to −21 kJ mol^{-1} in the four-ring models and from −20 to −22 kJ mol^{-1} in the two-ring models). In II1 and II3, the C21−O···H interaction is missing and the remaining C20═O···H interaction has an energy of ca. −15 kJ mol^{-1}. The 17α-hydroxyl group seems to have a decreasing effect on the interaction if compared to complexes that have an 11-hydroxyl group instead of a 17-hydroxyl group, in other words, if complex II4 (−12 kJ mol^{-1}) is compared to complex II3 (−15 kJ mol^{-1}) or complex II6 (−19 kJ mol^{-1}) is compared to complex II5 (−23 kJ mol^{-1}). The 11-hydroxyl group is farther away from the position of the local interaction than the 17α-hydroxyl group and does not therefore have a direct interaction. However, in complex II5, the polymer structure seems to stretch slightly toward the 11-hydroxyl group, and this may have a small stabilizing effect on the complex geometry.

If compared to the first interaction configuration, complexes II7 and II6 are practically as stable as complexes I7 and I6, with the stability decreasing with a decreasing number of hydroxyl groups.

According to the calculated results, the reason for the stability of the complexes in the second configuration is owing to the close interaction between the electron-rich, nucleophilic carbonyl oxygen of the steroid and the hydrogens of the methyl groups of the polymer. The Si−O bond of the polymer is slightly polarized, because the electronegativities of Si and O are 1.9 and 3.4, respectively. The CH_3 group is known to be an electron-donating group. Methyl carbons of the polymer locate at α positions with respect to the silicon atoms, and the neighboring electronegative oxygen atoms can withdraw electrons from them, delocalizing the electron distribution and making the methyl hydrogens slightly more electrophilic. This local interaction does not take place in other configurations, unless the molecules move with respect to each other to a completely different location during the energy minimization as happens in the case of complexes I1 and I3. In addition, steroids in complexes II2, II5, II6, and II7 have the 21-hydroxyl group that interacts with the polymer, stabilizing the complex further.

The Third Interaction Configuration. In the third interaction configuration (III), the polymer is also "above" the steroid skeleton as in the second configuration, but at the opposite end of it, that is, close to the 11-hydroxyl group of progestin models 3, 5, and 7, see Figure 1d. The polymer is also far away from the side chain so that there is no interaction with the oxygen atoms at positions 20 and 21. The B3LYP/6-31G**-optimized equilibrium geometries of the progestin−polymer interaction complex models III3, III5, and III7 in the third configuration are presented in Figure 4a−c. Total energies calculated for the interaction complexes III1−III7 are given in Table 4. The closest intermolecular H···H distances, the closest interaction distances, and the corresponding interaction angles, which are also visible in Figure 4, as well as the energies of interaction are listed in

Table 5. Interaction Distances (Å), Angles (degrees), and Energies of Interaction (kJ mol^{-1}) of the Four-Ring Steroid and Two-Ring Models (1−7) and the Polymer Model in the Second (II) and Third (III) Interaction Configurations[a]

a. Four-Ring Steroid Models/Second (II) Interaction Configuration

model	H···H	C21O−H···H	C21−O···H−CH_2	∠O···HC	C20=O···H−CH_2	∠O···HC	order	E_{II} B3LYP/6-31G**
II1	2.65				2.75, 2.77, 2.87, 2.94	145.7, 145.0, 141.8, 140.4	5	−15
II2	3.35	2.63	2.69, 2.70	146.9, 164.8	2.56, 2.69	151.3, 157.3	2	−21
II3	2.65				2.76, 2.80, 2.81, 2.83	145.0, 144.6, 143.8, 142.9	6	−15
II4	2.74				2.74, 2.84, 2.86, 2.98	146.2, 144.0, 143.1, 139.3	7	−12
II5	3.17	2.88	2.57, 2.58	168.0, 166.7	2.53, 2.60	156.8, 152.6	1	−23
II6	3.32	2.61	2.69, 2.87	138.4, 159.8	2.62, 2.85	146.3, 154.0	4	−19
II7	3.56	2.83	2.64, 2.97	141.1, 161.5	2.55, 2.86	154.2, 146.5	3	−21

b. Four-Ring Steroid Models/Third (III) Interaction Configuration

model	H···H	C21−OH···O−Si	∠OH···O	C21−O···H−CH_2	∠O···HC	C20=O···H−CH_2	∠O···HC	C11−OH···O−Si	∠O−H···O	C11−O···H−CH_2	∠O···H−C	order	E_{III} B3LYP/6-31G**
III1	2.53											7	−2.5
III2	2.86	2.02	151.5	2.52	147.7	2.54, 2.70	153.1, 157.8					1	−54
III3	2.54							2.06	171.5	3.10	144.5	4	−21
III4	2.83											6	−3.3
III5	2.44							2.03	166.8	2.64	158.5	3	−22
III6	3.04			2.54, 2.70	170.5, 156.4	2.60	147.7					5	−20
III7	2.47			2.54	158.2			2.11	164.9	2.61, 2.74	132.9, 163.7	2	−27

Table 5b for the four-ring models and in Table 5d for the two-ring models.

The interaction energies of complexes III2 and III6 do not, however, describe the local interaction energies of the third configuration, because the energy optimization of the geometries converged to structures which resemble more closely the second interaction configuration, in which the polymer is interacting with the C20=O and C21−OH groups of the progestin models. The correct local interaction should correspond to a similar interaction energy of −3 to −4 kJ mol^{-1} seen in complexes III1 and III4, as discussed below, because there is no 11-hydroxyl group to interact in these models.

The conformations of the polymer models are very similar when the corresponding two-ring and four-ring complexes are compared. In complexes III1, III3, III4, III5, and III7, the Si−O−Si "leg" of the PDMS chain is stretched "forward" and the other end of the Si−O−Si chain is stretched back. The interacting C11−OH group of complexes III3, III5, and III7 is pointing toward this back-stretching Si−O−Si chain bridge. In the previous interaction configurations, the interacting bridge is the next one toward the middle of the PDMS chain and not the end of the chain like in the third configuration. The main changes from the initial conformation of the polymer are the directions of the Si−O−Si ends of the PDMS and the notable stretching of the polymer model.

In the third interaction configuration, the hydrogen atom of the 11-hydroxyl group of the progestin models 3, 5, and 7 locates close to an oxygen atom of the polydimethylsiloxane backbone, see the C11−O−H···O−Si distances in Table 5b and d. The closest C11−O−H···O−Si distances in these complexes are 2.03−2.11 Å (the four-ring models) and 2.02−2.06 Å (the two-ring models). The corresponding O−H···O interaction angles are 164.9−171.5° and 163.0−164.7°, respectively. The interaction energies of complexes III3, III5, and III7 range from −21 to −27 kJ mol^{-1} in the case of the four-ring models and from −26 to −30 kJ mol^{-1} in the case of the two-ring models. The oxygen atom of the 11-hydroxyl group of progestin models 3, 5, and 7 is also relatively close to methyl hydrogens of the polymer. The 21- and 17α-hydroxyl groups are too far away to directly interact with the polymer except in complex III7, in which the polymer is stretching toward the hydroxyl group at position 21 (C21−OH). The stability of complex III7 is increased by ca. 5.0 kJ mol^{-1} with respect to III5 and III3 because of the additional C21−O···H−CH_2−Si interaction. Although the energy differences between III5 and III3 are very small, ca. 1 kJ mol^{-1}, we can conclude that the stability of the complex is increasing with an increasing number of

Table 5. Continued

c. Two-Ring Models/Second (II) Interaction Configuration

model	H···H	C21−O−H···H	C21−O···H−CH_2	∠O···HC	C20═O···H−CH_2	∠O···HC	E_{II} B3LYP/6-31G**
II1	2.81				2.70, 2.79, 2.81, 2.89	145.6, 143.6, 143.0, 140.3	−16
II2	3.40	3.59	2.61, 2.77	139.7, 133.6	2.61, 2.68	145.3, 141.6	−20
II3	2.80				2.73, 2.75, 2.79, 2.86	144.3, 145.3, 142.6, 142.1	−15
II4	2.63				2.72, 2.81, 2.91, 2.94	146.4, 144.7, 142.1, 139.9	−12
II5	3.15	2.98	2.55, 2.58	168.1, 167.7	2.54, 2.56	157.8, 153.1	−23
II6	3.34	2.61	2.69, 2.74	139.7, 141.3	2.60, 2.78	145.8, 136.6	−20
II7	2.94	2.73	2.61, 2.86	162.9, 144.2	2.54, 2.78	153.4, 150.7	−22

d. Two-Ring Models/Third (III) Interaction Configuration

model	H···H	C21−OH···O−Si	∠O−H···O	C21−O···H−CH_2	∠O···HC	C20═O···H−CH_2	∠O···HC	C11−OH···O−Si	∠O−H···O	C11−O···H−CH_2	∠O···HC	E_{III} B3LYP/6-31G**
III1	2.73											−3.3
III2	2.62	2.10	144.7	2.52, 2.88	149.8, 125.0	2.56, 2.78	149.4, 152.9					−54
III3	2.69							2.02	164.7	2.72, 2.80, 3.11	141.9, 139.1, 125.5	−27 (26.7)
III4	2.66											−2.9
III5	2.62							2.02	163.0	2.73, 2.73, 3.12	140.9, 141.3, 125.0	−26 (26.4)
III6	2.92			2.51, 2.72	166.7, 156.0	2.58, 2.80	146.9, 136.6					−21
III6	2.92			2.51, 2.72	166.7, 156.0	2.58, 2.80	146.9, 136.6					−21
III7	2.49			2.66	157.3			2.06	164.3	2.73, 2.82, 2.87	141.6, 129.4, 138.7	−30

[a] Hydrophobic intermolecular H···H distances are given for comparison.

hydroxyl groups interacting directly with the polymer, which is seen from the results of the four-ring model calculations; that is, the stability order is III3 < III5 < III7. The acidity of the hydrogen atom of the C11−OH group that is interacting with the electron-rich siloxane oxygen is increasing when the number of electron-withdrawing hydroxyl groups is increasing in the steroid skeleton.

Both the four- and two-ring model calculations predict that complexes II1 and II4 are ca. 9.0−13 kJ mol^{-1} more stable than complexes III1 and III4, in which there is no interaction between the polymer and either the carbonyl or the hydroxyl group of the steroid. On the basis of our calculations, the basic underlying interaction of complexes without any O···H interactions corresponds to an interaction energy of ca. 3−4 kJ mol^{-1}. Therefore, this interaction energy is used for complexes III2 and III6 when calculating the "corrected" average interaction energies of all three interaction configurations given in Table 6, in order to take the correct local interaction geometries into account.

If the four-ring model calculations in the second and third interaction configurations are compared, complex III3 is ca. 6.0 kJ mol^{-1} more stable than complex II3, see Table 5a and b. The direct interaction of the 11-hydroxyl group of the progestin with the oxygen atom of the polymer backbone (C11−O−H···O−Si) is ca. 6.0 kJ mol^{-1} stronger than a C20═O···H interaction. When a carbonyl oxygen is interacting with a methyl hydrogen of the PDMS polymer, a total interaction energy of ca. −15 kJ mol^{-1} is predicted. The interaction energies between the functional groups of the four- and two-ring models of the progestins studied and the PDMS polymer model estimated in this way from our interaction calculations are listed in Table 7.

Comparison to Experimental Literature Results. Our calculated stability order for steroids 7, 6, and 4 in their first interaction configuration is in very good agreement with experimental results published for the delivery of progestin molecules from poly(dimethysiloxane)-based devices. The experimental values are collected in Table 8. The best

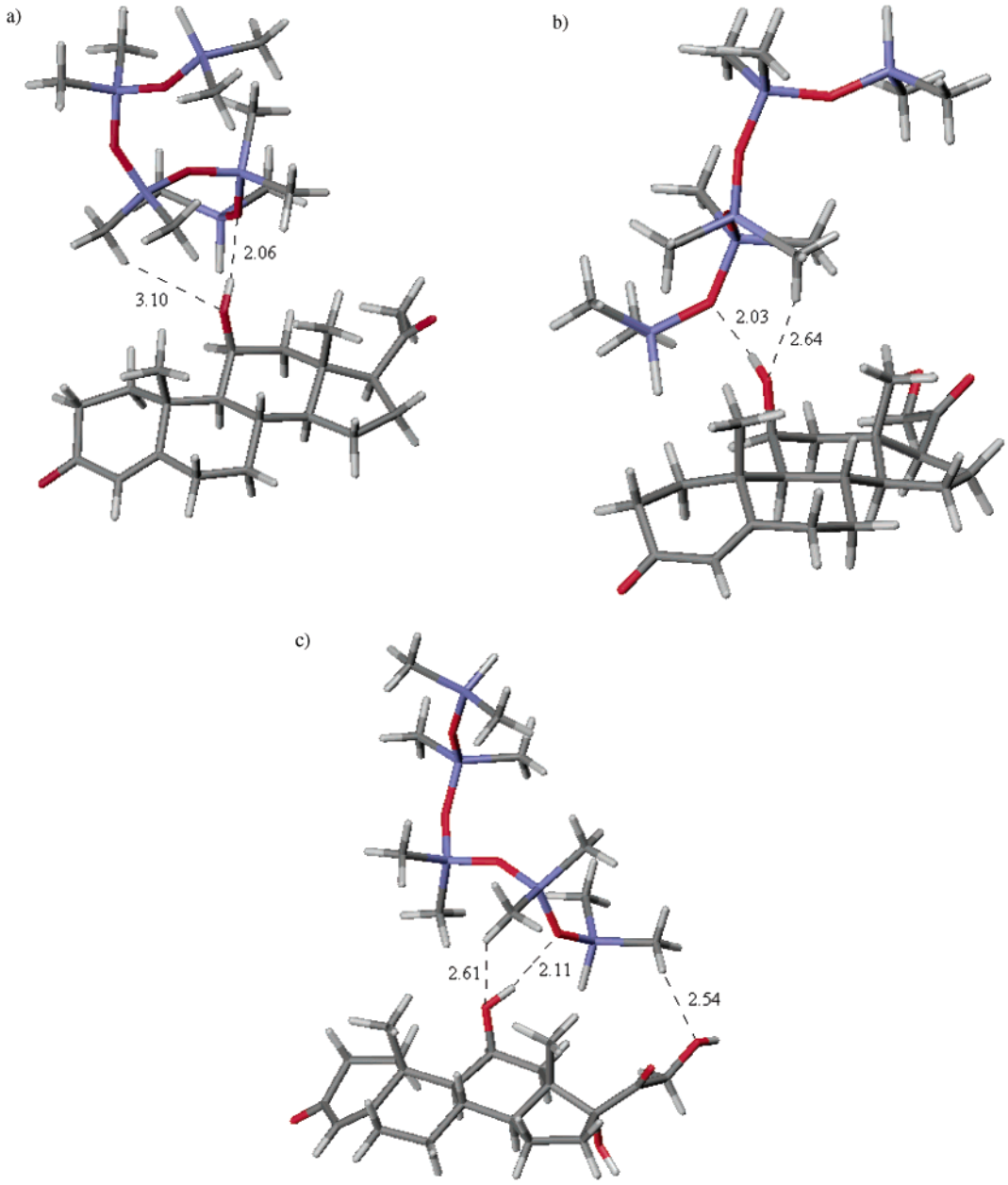

Figure 4. Optimized structures of three different four-ring steroid-model−polymer complexes in the third interaction configuration. Progestins are (a) 17α-hydroxyprogesterone (III3), (b) corticosterone (III5), and (c) hydrocortisone (III7). The closest intermolecular distances are given in Å units.

Table 6. Averages of the Interaction Energies (kJ mol^{-1}) of All Three Different Interaction Configurations (I−III)[a]

model & PDMS	$E_{(I-III)}$ four-ring model B3LYP/6-31G**	$E_{(I-III)}$ two-ring model B3LYP/6-31G**
1	−6.7	−7.4
2	−9.5	−8.8
3	−13	−15
4	−9.7	−8.5
5	−16	−18
6	−14	−13
7	−23	−24

[a] The local interaction energies have been corrected by removing the wrong geometries and replacing them with the correct calculated interaction energy of ca. 3 kJ mol^{-1}, as explained in the text.

Table 7. Interaction Energies (kJ mol^{-1}) between Single OH or C═O Groups and the PDMS Polymer Estimated from Calculations

functional group	E (four-ring model) B3LYP/6-31G**	E (two ring model) B3LYP/6-31G**
C3═O···H	−13 to −16	
C20═O···H	−12 to −15	−12 to −16
C11−O−H	−1.0 to −5.0	−5.0 to −6.0
C17−O···H	−14	−11
C21−O···H	−8.0 to −11	−4.0 to −11
C11−O--H···O−Si	−21	−21
C17−O−H···O−Si	−21	−21
C21−O−H···O−Si	−28 to −34	−33

agreement in the order of stability is found with the experimental $(D_pC_p)^{1/2}$ values, that is, (diffusivity × characteristic constant for the silicon adhesive matrix)$^{1/2}$.[1] The correlation is better for the two-ring models ($r = 0.74$), which do not have the C3═O group that is interfering with the local interaction in the four-ring models I1 and I3 ($r = 0.27$). The conclusion drawn from the experiments is supported by our calculations done at the first interaction configuration that

Table 8. Experimental Results from Literature

steroid	$(D_pC_p)^{1/2} \times 10^3$ ($mg^{1/2}$ $cm^{-1/2}$ $h^{-1/2}$)[a]	$D_p \times 10^5$ (cm^2 h^{-1})[b]	E (kcal/mol)[c]	$Q/t^{1/2}$ (mg cm^{-2}/$day^{1/2}$)[c]	$D_m \times 10^2$ (cm^2/day)[c]	PDS $\times 10^{-4}$ (cm^2 h^{-1})[d]
1	110.64	7.06	15.25	3.368	6.34	304
2	70.49	9.72	13.52	2.28	4.51	3.30
3	62.89	6.12	14.95	0.663	2.96	0.291
4	8.02	1.10	14.30	0.623	1.82	0.697
5	18.73	3.09	16.30	0.249	5.82	0.0915
6	7.06	1.30	23.62	0.12	4.16	0.194
7	0.45	0.59	16.70	0.096	0.76	0.0264

[a] A slope of the drug release flux ($Q/t^{1/2}$) vs $(2A - C_p)^{1/2}$, a characteristics of a silicone adhesive matrix, ref 1. [b] Diffusivity D_p of progesterone and its hydroxyl derivatives in the silicone adhesive matrix, ref 1. Adhesives have been prepared by reaction of a linear poly(dimethylsiloxane) fluid with a solvent-soluble low-molecular-weight silicate resin. [c] Release from a silicone device, which consists of the progesterone derivative, dimethyl polysiloxane elastomer, and a silicone fluid, ref 44. E is the energy required for a controlled release of progesterone or its hydroxyl derivative from a silicone device; $Q/t^{1/2}$ is the drug release flux through the silicone device, and D_m is the matrix diffusivity. [d] Normalized permeability through a polydimethylsiloxane (PDS) polymer, ref 2.

(a) the diffusivity decreases when the number of the hydroxyl groups increases and (b) the addition of a hydroxyl group to position 21 appears to improve the diffusivity, while the addition of a hydroxyl group to position 17 counteracts the enhancing effect of 21-OH.

All experimental results in Table 8 excluding the E values, suggest that hydrocortisone (7), which has three hydroxyl groups, has the strongest interaction with silicone-based materials. Our calculations in the first and third interaction configurations agree exactly with these experimental findings. Depending on the experiment done, either progestin 6, 5, or 4 is found to interact second strongest and 6 or 5 third strongest with the polymer. Also, our calculations with progestins predict small energy differences of 3−4 kJ mol^{-1} between II5 and II6, for example. The differences in calculated local interaction energies between II3 and II4 and between III3 and III5 are also small, that is, from 1 to 3 kJ mol^{-1} (Table 5a−d). Therefore, it is not surprising that the experimental values reported in the literature vary, especially with progestins 3−6.

The differences between the interaction energies of complexes III5, III6, and III7 are so small that in practice it can be concluded that the calculations are in good agreement with the experimental findings that the stability increases with an increasing number of hydroxyl groups and depends on the position of the hydroxyl group in the steroid skeleton. In the second interaction configuration, the addition of a C11−OH increases the stability with respect to C17−OH, which weakens the interaction of C20═O and C21−O by withdrawing electrons. The correlation coefficients r calculated for the experimental studies and our three interaction configurations vary between 0.74 $[(D_pC_p)^{1/2}]$ − 0.55 (PDS) for the two-ring models and 0.53 (D_m) − 0.11 (PDS) for the four-ring models in the first configuration; 0.44 (PDS) − 0.27 ($Q/t^{1/2}$) and 0.43 (PDS) − 0.24 ($Q/t^{1/2}$), respectively for the same models, in the second interaction configuration; and 0.23 (D_m) − 0.02 $[(D_pC_p)^{1/2}]$ and 0.26 (PDS) − 0.003 ($Q/t^{1/2}$) in the third configuration. The experimental property is given in parentheses after the correlation coefficient r. Negative correlation is found between all interaction configurations and the experimental E values except in the case of the four-ring model ($r = 0.12$). In the third configuration, either the two-ring or the four-ring model gives always a negative r value with all experimental results.

The experimental results take all possible interaction configurations into account, also between the same molecules. Our local interaction calculations predict the stabilities of one steroid−polymer model configuration at a time. However, if we take the average interaction energy, that is, sum the interaction energies computed for each four-ring progestin−polymer model in three different interaction configurations and divide by 3, after replacing the interaction energies of complexes I1, I3, III2, and III6 with the interaction energy of −3 kJ mol^{-1}, as accounted for above, the stability order is 7 > 5 > 6 > 3 > 4 > 2 > 1 (see Table 6). This stability order corresponds exactly to the order of the experimental normalized permeabilities of progestin molecules through a polydimethylsiloxane polymer, see Table 8. The correlation coefficient between the calculated energies and the normalized experimental permeabilities is 0.85. This agreement is expected, because the four-ring progestin models and the polymer model take the most important interacting atoms and molecular groups chemically into account in the modeling procedure.

The two-ring models yield results very similar to those given by the four-ring models with energy differences mostly within 1 kJ mol^{-1} and in few cases within 3 to 6 kJ mol^{-1}. Owing to these small differences in energies, the average interaction energy calculated in the same way as above yields a stability order of 7 > 5 > 3 > 6 > 2 > 4 > 1. The correlation coefficient between the average interaction energies of the four-ring and two-ring models presented in Table 6 is very high, that is, 0.98, proving that the energetic differences are really small. The interaction energies of 2 and 4 differ only by 0.2 kJ mol^{-1} and those of 3 and 6 by 1.4 kJ mol^{-1}. If these energies were in the opposite order, the experimental normalized permeability would be reproduced exactly like with our four-ring models. The correlation coefficient between the calculated average interaction energies of the two-ring models (Table 6) and the normalized experimental permeabilities (Table 8) is also high, that is, 0.80. In order to get a bigger average energy for 6 than for 3, the interaction energy of III6 should be at least −8 kJ mol^{-1}, that is, slightly bigger than the typical interaction energy of −3 kJ mol^{-1} used. The order of the stability of the two-ring models resembles most closely the order of the experimental matrix diffusivity D_m of progestins: 7 > 4 > 3 > 6 > 2 > 5 > 1; that is, 4 and 5 have changed places. However, the correlation coefficient between the calculated energies and the diffusivities D_m is not very high, that is, 0.57 (0.66 for the four-ring models). Better correlation is obtained between the calculated average interaction energies

and $Q/t^{1/2}$ or $(D_pC_p)^{1/2}$ values, namely, 0.58−0.69 for the two-ring models and 0.69−0.75 for the four-ring models, respectively. To summarize, the four-ring models predict the stability order and the energies of the most stable complexes very well, and the two-ring models yield very close results when compared to the experimental values.

4. CONCLUSIONS

We have carried out the first computational studies on commonly used substances in hormone therapy, namely, progestins, and their interaction with a model of a dimethylsiloxane-based polymer. Our calculations shed light on how the interaction between a drug molecule and a delivery material that is surrounding the drug is altered when multiple hydroxyl groups are simultaneously present or when the position of the hydroxyl group in the drug molecule is altered.

Our calculations predict that an interaction between a hydrogen atom of a hydroxyl group of a steroid and an oxygen atom of the polymer corresponds to an energy of −21 kJ mol^{-1}. This interaction is stabilized by C21−O···H interactions, leading to an energy of −28 to +34 kJ mol^{-1}. The carbonyl and hydroxyl groups can simultaneously interact with two to four methyl groups of the polymer. Both the complete steroid structures and the two-ring models yield the same results. When an oxygen atom of the hydroxyl group is interacting with a methyl hydrogen of the polymer alone without any other stabilizing interactions, a weaker complex is formed.

The calculated stability of the complex depends also on the position of the interacting hydroxyl group. A hydroxyl group at position C11 interacts the most weakly. On the other hand, a hydroxyl group at C17 interacts the most strongly and has therefore a tendency to decrease the release of the steroid from the polymer surroundings. This has been predicted also by the experimental results reported in literature. The stability of interaction is increasing when the number of the hydroxyl groups is increased in progestin, as reported in the experimental literature. However, the overall combined interaction between different C−O−H···O−Si + C═O···H + C−O···H groups and the polymer affects the stability of the complex the most and therefore the easiness of the release from a polymer structure.

In the future, we will expand our work by computing interactions between two or more steroid molecules. The purpose is to elucidate the effect of the steroid−steroid interaction on the calculated steroid−polymer interaction energies. Also, the number of the interaction configurations and of the steroid molecules will be increased. In addition, we will investigate a combined effect of two polymer models interacting simultaneously with one steroid model at two separate locations.

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