Electron densities of bexarotene and disila-bexarotene from invariom application: a comparative study†‡

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By the application of the invariom formalism, which provides aspherical atomic scattering factors, the electron densities of the RXR-selective retinoid agonists bexarotene (**1a**) and disila-bexarotene (**1b**) were derived from their known low resolution ($d = 0.76 \text{ \AA}$) crystal structures. The density distributions allowed us to make a comparison of the electronic properties of these pharmacologically relevant compounds. Differences were found to be restricted to relatively small regions in the terminal six-membered rings of the tetrahydronaphthalene and tetrahydrodisilanaphthalene fragments. In total, the replacement of two carbon atoms in **1a** by silicon atoms ($\rightarrow$ **1b**) does neither influence the electronic structures nor the pharmacological properties (RXR receptor activation) significantly. It should be noted that the almost completely software supported invariom formalism can yield electronic information for biologically interacting systems with moderate effort. This offers interesting possibilities for drug research, in that steric and electronic information can be combined for the analysis of intermolecular recognition and interaction on an atomic scale. This approach is also valuable for the design and development of silicon-containing drugs using the carbon/silicon switch strategy.

Introduction

The retinoid X receptor (RXR) agonist bexarotene (**1a**, Targretin®) is in clinical use for the treatment of cutaneous T-cell lymphoma (Fig. 1).¹ Recently, this agent raised additional attention in that therapeutic effects on Alzheimer's disease in mouse models were discussed.² Disila-bexarotene (**1b**), a silicon analogue of bexarotene (**1a**), was also shown to be a highly potent RXR agonist (Fig. 1),³ and a series of structurally related C/Si analogues were demonstrated to be very potent retinoid agonists as well.⁴ For a deeper understanding of pharmacological activities on an atomic scale, not only the geometric but also the electronic properties of the drug molecule should be examined. In the case of the C/Si analogues

Fig. 1 Chemical structures of the C/Si analogues bexarotene (**1a**) and disila-bexarotene (**1b**).

bexarotene (**1a**) and disila-bexarotene (**1b**), carbon and silicon differ not only in their covalent radii but also in their electronegativities. Therefore, considerable differences in the electronic properties, for example in the electrostatic potentials (ESPs), can be expected for **1a** and **1b**. Knowledge of these ESPs could be very helpful in characterising the pharmacological properties of these two compounds.

Electronic properties can not only be derived from theoretical calculations but also from the electron density (ED) distribution $\rho(\mathbf{r})$ obtained from an X-ray diffraction experiment in the crystal, having the advantage that the intermolecular influences of the crystalline environment are taken into account. However, this makes aspherical modelling of the involved atoms in the crystal structure necessary. For that purpose, the Hansen & Coppens multipole formalism is commonly used,⁵ having the disadvantage that much more structural parameters have to be considered than for the description of the spherical structure. This requires increased experimental efforts to

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‡Electronic supplementary information (ESI) available: Bond critical points; atomic properties (charges and volumes); atomic coordinates, displacement parameters and multipole parameters for bexarotene (**1a**) and disila-bexarotene (**1b**). See DOI: 10.1039/c3ob27346f

obtain high order X-ray data sets. Since the introduction of databases providing aspherical atomic scattering factors for the modelling of an X-ray structure, EDs can be derived with moderate effort from medium or low order data sets so that the time-consuming nature of high order X-ray diffraction data collection can be avoided, which hampered so far a broad application of experimental ED determinations.

One of these databases is the invariom database introduced and described earlier.⁶ An appropriate invariom entry of the database assigns aspherical multipole parameters to a given atom in a molecule. These parameters were obtained from theoretical calculations of a model compound of the same element in the same chemical environment as the atom in question. The total ED of a molecule is then obtained by a superposition of its constituting invarioms. This procedure relies on the concept of transferability of submolecular fragments proposed by Bader.⁷ Since the invariom multipole parameters are treated as fixed contributions, they do not increase the number of parameters needed for modelling the structure. Applications have been described for a number of problems in bioorganic chemistry.⁸

In this study, we made use of the existing X-ray diffraction data sets of the C/Si analogues **1a** and **1b**,³ which were collected at 173 K to a resolution of 0.76 Å ($\sin \theta/\lambda = 0.66 \text{ \AA}^{-1}$). For aspherical modelling, our invariom formalism was applied. The results of the obtained EDs are discussed and compared below.

Experimental basis and aspherical ED modelling

X-ray diffraction data of **1a** and **1b** were entered into the XD program system,⁹ which allows refinement and analysis of the ED as follows: The reflection data files (only non-negative F_o^2 values were further considered) were reformatted to fit the format of XD. For aspherical modelling, the software Invariom-Tool¹⁰ was applied, which automatically selects and assigns the corresponding invarioms after analysing the identity and chemical neighbourhood of each atom. Scattering factors up to the hexadecapolar level, including κ parameters, from the invariom library were assigned to all atoms. InvariomTool also generates an initial master and input file for XD. Since several atoms of the title compounds are chemically equivalent, 17/18 different invarioms were sufficient for the 54 atoms of **1a/1b**. After invariom transfer, refinement of positional and vibrational parameters (anisotropic for non-hydrogen atoms and isotropic for hydrogen atoms) was carried out until convergence was achieved. Selected crystallographic data and figures of merit for the two refinements are summarized in Table 1. A topological analysis of the obtained EDs according to Bader's quantum theory of atoms in molecules (QTAIM formalism)⁷ was performed with the *xdprop* subprogram of XD.

The Bader formalism⁷ uses the first and second partial derivatives of the ED to yield the gradient vector field $\nabla\rho(\mathbf{r})$ and the scalar Laplacian function $\nabla^2\rho(\mathbf{r})$. Both can be exploited

Table 1 Selected crystallographic data and refinement data for **1a** and **1b** (for further data, see ref. 3a)

Compound	1a	1b
Formula	C ₂₄ H ₂₈ O ₂	C ₂₂ H ₂₈ O ₂ Si ₂
Crystal system	Triclinic	Triclinic
Space group	<i>P</i> $\bar{1}$ (2)	<i>P</i> $\bar{1}$ (2)
<i>Z</i>	2	2
<i>V</i> [Å ³]	966.0(3)	1061.9(3)
($\sin \theta/\lambda$) _{max} [Å ^{−1}]	0.66	0.66
Unique reflections	4062	4595
Observed reflections [$F_o^2 \geq 3\sigma(F_o^2)$]	2854	3784
Multipole refinement:		
<i>R</i> (<i>F</i>)	0.0273	0.0242
<i>R</i> _{all} (<i>F</i>)	0.0427	0.0306
<i>R</i> _w (<i>F</i>)	0.0242	0.0246
<i>R</i> (<i>F</i> ²)	0.0440	0.0395
<i>R</i> _{all} (<i>F</i> ²)	0.0473	0.0409
<i>R</i> _w (<i>F</i> ²)	0.0493	0.0499
Min/max $\Delta\rho$ [e Å ^{−3}]	−0.154/0.152	−0.254/0.212
Gof	1.97	1.87
<i>N</i> _{ref} / <i>N</i> _v	8.22	10.9

to provide quantitatively a variety of bond topological and atomic properties.

Results and discussion

Structural properties

The molecular structures of **1a** and **1b** are displayed in ORTEP representations in Fig. 2a and 2b,¹¹ generated with PLATON.¹² The numbering scheme is the same as in ref. 3a. The molecular geometries in terms of bonding data are basically the same as reported before and need no further discussion. For example, the eight bond lengths from C101/C102 and Si1/Si2 to their adjacent carbon atoms are (average) 1.534(4) Å and 1.874(9) Å in the spherical model and 1.535(5) Å and 1.875(9) Å in the present aspherical model. Exceptions are the hydrogen atoms, which refine closer to neutron positions (and hence to longer X–H bonds, X = C, O), so that, for example, hydrogen bonding can more correctly be described.

The molecules are composed of a tetrahydronaphthalene (**1a**) or tetrahydrodisilannaphthalene (**1b**) fragment and a benzoic acid moiety linked by a C=CH₂ group. In both cases, the molecules form dimers *via* hydrogen bond pairs generated by the carboxy groups over crystallographic inversion centres.

Bond topological descriptors

Bond critical points (BCPs, defined by the property that the gradient $\nabla\rho(\mathbf{r})$ vanishes at this point, according to Bader's QTAIM formalism) were found on all covalent bonds and on the H(donor)⋯O(acceptor) linkage of the hydrogen bonds. ED values, the Laplacians and the ellipticities [$\rho(\mathbf{r}_{\text{BCP}})$, $\nabla^2\rho(\mathbf{r}_{\text{BCP}})$, ϵ] providing quantitative information about the strength and nature of a bond are summarized in Table 2. Only averages over equivalent bonds are given, and detailed lists for **1a** and **1b** are given in the ESI (Tables S1 and S2†).

Fig. 2 ORTEP representations of beaxortene (a) and disila-beaxortene (b) with atom numbering scheme. Displacement ellipsoids are plotted at a 50% probability level.^{11,12}

Table 2 Averaged bond topological properties for **1a** and **1b** (the first/second line: **1a/1b**)

Bond	Length [Å]	$\rho(\mathbf{r}_{\text{BCP}})$ [$\text{e} \text{ Å}^{-3}$]	$\nabla^2 \rho(\mathbf{r}_{\text{BCP}})$ [$\text{e} \text{ Å}^{-5}$]	ϵ^a	N^b	C–C bond order
C/Si–C	1.535(5)	1.63(2)	−10.2(2)	0.01(2)	8	0.98
	1.875(9)	0.85(1)	−2.3(5)	0.02(2)	8	
C3–C4	1.517	1.68	−11.38	0.01	1	1.04
	1.543	1.58	−9.08	0.02	1	0.93
C–C	1.398(8)	2.11(2)	−17.0(6)	0.21(1)	12	1.61
	1.399(7)	2.09(4)	−16.9(6)	0.19(2)	12	1.58
(aromatic)	1.344	2.33	−19.72	0.30	1	2.01
	1.337	2.35	−20.35	0.30	1	2.05
C=O	1.238	2.89	−32.16	0.09	1	
	1.229	2.93	−33.37	0.09	1	
C–O(H)	1.300	2.36	−29.19	0.11	1	
	1.307	2.33	−28.49	0.11	1	

^a The ellipticity ϵ is defined by $(\lambda_1/\lambda_2) - 1$ with λ_1 and λ_2 being the two principal negative curvatures of $\rho(\mathbf{r})$ at a BCP and is a measure for the asphericity and hence the double bond character of a bond. ^b N = the number of entries contributing to the average.

It can easily be seen that the only significant differences between **1a** and **1b** exist for those bonds where carbon in **1a** is replaced by silicon in **1b**. The eight bonds originating from C101 and C102 in **1a** have the typical properties of a C–C single bond. The average densities and Laplacians compare properly with the averages over 93 C–C single bonds reported by Scheins *et al.* ($1.68(7) \text{ e} \text{ Å}^{-3}$, $-11.7(25) \text{ e} \text{ Å}^{-5}$).¹³ The electron densities on the BCPs of the longer and polar Si–C bonds are much lower than those on the shorter C–C bonds. The value of

$\rho(\mathbf{r}_{\text{BCP}}) = 0.85 \text{ e} \text{ Å}^{-3}$ is in proper agreement with an average given by Kocher *et al.* ($0.87(2) \text{ e} \text{ Å}^{-3}$)¹⁴ and is in line with previous studies by Scherer *et al.*¹⁵ The Laplacians on the Si–C BCPs are negative (but close to zero), which is an insignificant finding. On this polar bond the Laplacian has a steep slope and changes its sign close to the BCP so that a slight experimental uncertainty of the BCP position may cause a slightly positive or negative Laplacian (see Fig. 3, left). This has already been observed earlier for these types of polar bonds.^{14,16,17} For comparison, the Laplacian on the non-polar C3–C4 bond of **1b** is also shown (Fig. 3, right). We note that this bond is not affected by the replacement of carbon by silicon, despite being the direct neighbour of the C/Si replacement site. This holds also for all further covalent bonds.

For the C–C bonds, bond orders n_b were calculated using a formula given by Bader⁷ ($n_b = \exp[C_1(\rho(\mathbf{r}_{\text{BCP}}) - C_2)]$, C_1 and C_2 from an earlier calculation¹⁸) and are listed in the last column of Table 2. The nature of the bonds as single/aromatic/double is also confirmed quantitatively by the ellipticities ϵ , which increase with increasing double bond character.

Hydrogen bond topological descriptors are given in Table 3. The D...A and H...A distances as well as the hydrogen bond energies^{19,20} indicate comparable and rather strong hydrogen bonds for both compounds. Further relevant intermolecular interactions are not seen in the crystal structures.

Atomic properties and molecular surfaces

Atomic volumes and charges were calculated⁹ by integration over the atomic basins enclosed by the zero-flux surfaces of the ED gradient vector field $\nabla \rho(\mathbf{r})$ corresponding to Bader's definition.⁷ The commonly used criteria whether the integration has worked properly are the sum of the charges, which should be zero (for a neutral molecule), and the sum of the atomic volumes, which should be equal to the volume of the asymmetric unit volume of the unit cell. In the case of **1a/1b** these criteria are properly satisfied, the charges add up to 0.05/0.08 e, while the sum of atomic volumes differs from the asymmetric unit volume by 0.2/0.8%.

In Table 4 only those atomic properties are summarized having charges $|q| > 0.2 \text{ e}$ (a complete list is given in the ESI, Tables S3 and S4†). Relevant charges common to both compounds are seen at the atoms of the carboxy group of the benzoic acid fragment. The two oxygen atoms carry a strong negative charge close to -1 e , which is widely compensated for by the positive charges at the atoms C22 and H2. The oxygen atom O2, being the donor of the above mentioned strong hydrogen bond, is by more than $\frac{1}{4} \text{ e}$ more negatively charged than the acceptor atom O1. The volume of the hydrogen atom H2 is much smaller than those of all the other hydrogen atoms, where the average volumes are $7.3(9)/7.8(9) \text{ Å}^3$ for **1a/1b** (the contribution of 27 hydrogen atoms).

Significant charge differences between **1a** and **1b** exist in the terminal six-membered ring of the tetrahydronaphthalene and tetrahydrodisilanaphthalene fragments. Both silicon atoms of **1b** have strong positive charges of 2.5 e each, which is almost entirely compensated for by the eight carbon atoms

Fig. 3 Laplacian distributions along the Si1–C3 (left) and C3–C4 (right) bonds in disila-bexarotene (**1b**). Vertical lines indicate bond critical point positions.

Table 3 Summary of hydrogen bonding topologies of **1a** and **1b**

Compound	D–H...A	D...A [Å]	H...A [Å]	$\rho(r_{\text{BCP}})$ [$\text{e } \text{\AA}^{-3}$]	$\nabla^2 \rho(r_{\text{BCP}})$ [$\text{e } \text{\AA}^{-5}$]	E_{HB}^a [kJ mol $^{-1}$]	E_{HB}^b [kJ mol $^{-1}$]
1a	O2–H2...O1 ^c	2.658(1)	1.71(2)	0.36	1.21	53.65	62.48
1b	O2–H2...O1 ^d	2.654(1)	1.64(2)	0.41	1.41	69.03	77.18

^a E_{HB} calculated after Espinosa's expression.¹⁹ ^b E_{HB} calculated after Abramov's expression.²⁰ ^c Symmetry code: $-x, 3 - y, 1 - z$. ^d Symmetry code: $2 - x, -y, -1 - z$.

Table 4 Atomic properties of **1a/1b** (charges q and volumes V_{tot}). Only atoms with $|q| \geq 0.2$ e in either **1a** or **1b** are listed. Fragments are T = tetrahydronaphthalene or tetrahydrodisilanaphthalene and B = benzoic acid

Atom	Fragment	q [e]	V_{tot} [$\text{\AA}^3$]
C101/Si1	T	0.01/2.51	6.52/6.07
C102/Si2	T	0.01/2.53	6.44/6.10
C1	T	−0.10/−0.45	9.83/12.41
C2	T	−0.11/−0.44	10.01/14.01
C3	T	−0.05/−0.93	8.09/12.96
C4	T	−0.05/−0.93	8.42/12.17
C5	T	−0.11/−0.41	10.38/13.09
C6	T	−0.10/−0.44	10.20/13.58
C7	T	−0.05/−0.68	10.73/14.63
C8	T	−0.06/−0.68	10.32/13.70
C22	B	1.20/1.21	7.04/7.57
O1	B	−0.90/−0.91	17.56/19.17
O2	B	−1.19/−1.26	19.47/20.30
H2	B	0.69/0.74	1.40/1.10

C1...C8, where the charges vary from -0.41 e to -0.93 e, a charge range that has also been reported earlier.¹⁷ Further atoms are not involved in this charge exchange. In the case of **1a**, all atoms of the tetrahydronaphthalene fragment carry negligible charges. The atomic volumes of C101/C102 in **1a** and Si1/Si2 in **1b** are rather alike, whereas the volumes of the eight carbon atoms, which compensate for the positive silicon charge, are by about $3.5 \text{ \AA}^3$ larger in **1b** than in **1a**.

The agreement/disagreement in charge distribution is related to the distribution of the ESP, which was calculated also with the *xdprop* subprogram of XD⁹ that makes use of a procedure introduced by Volkov *et al.*²¹ The ESP is plotted as a

colour code on the electron density isosurface at $0.0067 \text{ e } \text{\AA}^{-3}$ ($= 0.001 \text{ a.u.}$); see Fig. 4a and 4b.²² The study of the ESP surface is highly useful for the analysis of the reactive behaviour of a chemical system. Negative regions can be regarded as preferred nucleophilic centers, and regions with positive ESPs are potential electrophilic sites.^{8e} In the benzoic acid fragment, a polarization of the ESP exists at the carboxy group in both molecules, and both molecules exhibit a weak negative region at the phenyl ring. The difference between **1a** and **1b** is significant in the region of the ethylene bridge C3H₂–C4H₂. In **1b** this region between the silicon atoms has a negative potential, while the corresponding site in **1a** is completely positive. We have also generated an electrostatic difference potential between **1b** and **1a** (see Fig. 5), which illustrates this difference even more clearly and shows that outside the terminal six-membered ring of the tetrahydronaphthalene and tetrahydrodisilanaphthalene fragments the difference potential is practically zero.

Hirshfeld surfaces of **1a** and **1b** as obtained from the invariom applications are displayed in Fig. 6a and 6b. This surface is defined by the ratio of the molecular ED *versus* the crystal density, which should be equal to 0.5.^{23,24} The invariom ED was mapped onto this surface by a colour code indicating ED concentrations and hence sites and strengths of intermolecular interactions. The only significant signals in Fig. 6a and 6b are at the carboxy groups, where the ED concentration is caused by the strong hydrogen bond pair. Otherwise, the Hirshfeld surfaces are featureless, confirming that further relevant intermolecular interactions do not exist, as was mentioned before.

Fig. 4 Electrostatic potentials of bexarotene (a) and disila-bexarotene (b) mapped onto the isoelectron density surface $\rho = 0.0067 \text{ e } \text{\AA}^{-3}$ ($= 0.001 \text{ a.u.}$); Mollso representation.²²

Fig. 5 Electrostatic difference potential disila-bexarotene/bexarotene.²²

Conclusion

The application of the invariom formalism made it possible to complement steric information from conventional low-order X-ray diffraction data with electron density derived properties. This allowed a direct comparison of the electronic structures of the title compounds bexarotene (**1a**) and disila-bexarotene (**1b**). Differences were found to be limited but significant, while restricted to relatively small regions of the molecules. Intramolecular properties in terms of bond topological

Fig. 6 Hirshfeld surfaces of bexarotene (a) and disila-bexarotene (b).²²

descriptors were found to differ only in the eight bonds involved in the replacement of carbon by silicon.

More important for chemical systems of biological relevance are molecular surface properties,^{8c,f,25,26} because for biologically interacting species the mutual recognition takes place in a first step *via* the surfaces of the involved molecules.

The Hirshfeld surfaces displayed in Fig. 6a and 6b confirmed the findings from the conventional X-ray analyses³ in that, except from the strong hydrogen bonds in the dimer, no relevant intermolecular contacts exist for **1a** and **1b**.

Differences in the electrostatic potential between **1a** and **1b** (Fig. 4 and 5) were found, in that negative potential exists in the region between the two silicon atoms in **1b**, whereas this region is positive in **1a**. Common to both molecules is a pronounced negative region at the carboxy groups. There are indications that preferred strong interactions in the crystal can serve as a model for comparable interactions under biological conditions.^{8c,f} In this respect, experimental ED properties obtained from the crystal are suited to simulate physiological conditions.^{8a,27,28} However, in the case of **1a** and **1b**, it is unlikely that the dimeric structures of these compounds are conserved under physiological conditions. As shown experimentally by X-ray diffraction studies of the structurally related C/Si pairs **2a/2b** and **3a/3b** (Fig. 7), all four compounds bind to the retinoid receptor (**2a/2b**, RAR β ; **3a/3b**, RXR α) as the monomer.^{4a,c} Regarding the similar RXR receptor activation potentials of the retinoid agonists **1a** and **1b**, the different electronic structures and sizes of the terminal six-membered rings of their tetrahydronaphthalene and tetrahydrodisilanaphthalene skeleton are not sufficiently different to influence the pharmacological properties significantly.

Fig. 7 Chemical structures of the C/Si analogues **2a/2b** and **3a/3b**.

We note that the almost completely software supported invariom formalism¹⁰ is a fast and convenient procedure to derive electronic properties of a chemical structure provided that conventional X-ray diffraction data exist. The procedure is less time consuming than high level theoretical calculations, especially if periodic calculations are considered to simulate an intermolecular environment.

An important question is whether the results of an invariom approach can compete with those obtained from multipole refinement against high resolution X-ray data at low temperatures. This has been examined before in a comparative study on sucrose,^{6f} where an invariom modelling of a room temperature low order data set ($d = 0.85 \text{ \AA}$) was compared with a multipole refinement of a 20 K high resolution data set ($d = 0.43 \text{ \AA}$).²⁹ The obtained bond topological and atomic properties agreed well with the recently introduced experimental transferability indices, which were found to be $0.09 \text{ e \AA}^{-3}$ and $2.8 \text{ e \AA}^{-5}$ for the EDs and the Laplacians at the bond critical points, respectively, and $0.7 \text{ \AA}^3$ and 0.11 e for the atomic volumes and charges, respectively.³⁰ Hence, it was concluded that the invariom data are quantitatively reliable within the transferability indices quoted above.^{6f}

For biologically relevant molecules, it is an advantage that the crystal structure automatically provides an environment that can account for physiological conditions. So the invariom formalism can deliver valuable electronic information for biologically interacting systems almost routinely with moderate effort. This offers very interesting possibilities for drug research, not least for the design and development of silicon-containing drugs using the carbon/silicon switch strategy.^{4,31,32}

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