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Structure and Cooperativity of the Hydrogen Bonds in Sodium Dihydrogen Triacetate

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Geometry and energetics of low energy conformers of sodium dihydrogen triacetate (SDHTA) and its anion are studied using density functional theory (DFT) at the Becke, Lee-Yang-Parr hybrid functional (BLYP) and Becke, three-parameter, Lee-Yang-Parr hybrid functional (B3LYP) levels. For both cases, two structures of comparable energy are found, which have different symmetry with respect to the two hydrogen bonds (HBs). DFT-based Born–Oppenheimer molecular dynamics simulations are performed for SDHTA, which show that both structures are visited at room temperature conditions. The trajectory analysis further reveals that the two HBs behave anticooperative, that is, on average elongation of one HB is accompanied by a compression of the other one. This is in accord with nuclear magnetic resonance (NMR) experimental studies for a similar counter ion–dihydrogen triacetate complex. © 2012 Wiley Periodicals, Inc.

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Introduction

Hydrogen bonding and dynamics plays a prominent role in biological systems.[1,2] A detailed study of the properties of hydrogen bonds (HBs) is usually hampered by complexity, making it necessary to work with models that mimic the behavior of the real system. A prominent example is carboxylic acids, which are considered to be good models for aspartic and glutamic acid side chains. These often make homoconjugates and participate in various charge relay chains in hydrophobic pockets of proteins (see, e.g., the aspartic acid dyad in the Human immunodeficiency virus (HIV)-1 protease[3]). Homoconjugated anions of organic acids are known as classical sources of strong HBs (so-called Speakman-Hadži complexes). The hydrogen diacetates of ammonium, sodium, and potassium have been investigated intensively.[4–6] However, there are few reports on the dihydrogen triacetates only.[7–9] Here, we will consider one of the simplest systems, that is, sodium dihydrogen triacetate (SDHTA, Fig. 1) and its anion, dihydrogen triacetate anion (DHTA). These are nonplanar molecules that possess two HBs involving oxygen donors and acceptors.

For tetrabutylammonium dihydrogen triacetate, Limbach and coworkers[9] found, using ^1H nuclear magnetic resonance (NMR) that the two protons in the two HBs give rise to a single line at $\delta H = 16.39$ ppm, that is, they are chemically equivalent. Using ^{13}C NMR, it was further observed that all the carboxylic carbon atoms are chemically equivalent at 130 K on the NMR time scale. This has been interpreted in terms of a fluxional structure, being characterized by a very fast exchange of all carboxylic protons without dissociation of the complex. Upon single deuteration, it has been observed that the remaining proton signal was shifted to low field, which indicates an anticooperative coupling of both HBs (see also Refs. [10,11]). Despite this fascinating suggestion, there appears to be no detailed quantum chemical investigation of dihydrogen triacetate.

This work has two goals: First to characterize the structure of the double hydrogen bonded complexes, SDHTA as well as its anion DHTA. To this end, a quantum chemical characterization of the equilibrium geometries is performed on the basis of density functional theory (DFT). Second, the issue of HB cooperativity is addressed using DFT Born–Oppenheimer molecular dynamics (DFT-MD) simulations,[12] which previously have been shown to provide valuable insight into the dynamics of double HB systems.[13,14] Notice that for computational convenience and purpose of demonstration the basic effect of cooperative HB dynamics in this class of systems, we have chosen the much simpler sodium counter ion as compared with the experiments in Ref. [9] where tetrabutylammonium had been used.

Computational Details

To investigate the equilibrium geometry of DHTA, a set of possible starting structures was defined. DHTA is composed of two acetic acid molecules and an acetate anion (cf. Fig. 1). The two acetic acid molecules, through the carboxylic hydrogen atoms, may bind to the acetate ion by one of two possible ways to form two HBs. One of them through both carboxylate oxygen atoms and the other one through only one carboxylate oxygen atom. Taking into account conformers arising from free rotations around different single bonds, there have been in total 12 guessed structures (see Fig. 1, Supporting Information). For SDHTA, we have used the same guessed structures and placed the sodium ion such that it is close to as many

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Figure 1. Chemical structure of SDHTA.

Figure 2. The B3LYP/6-31++G(d,p) optimized geometries of different conformers of DHTA starting from the guess structures given in Figure 1, Supporting Information (relative electronic energies in kcal/mol in parentheses).
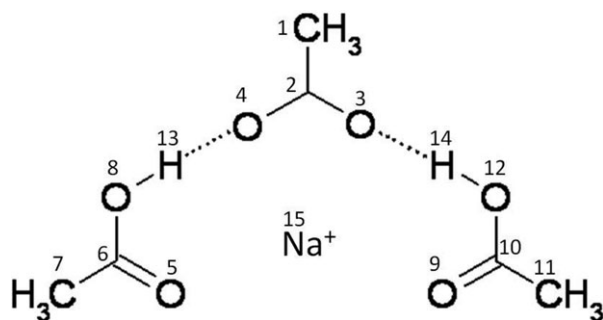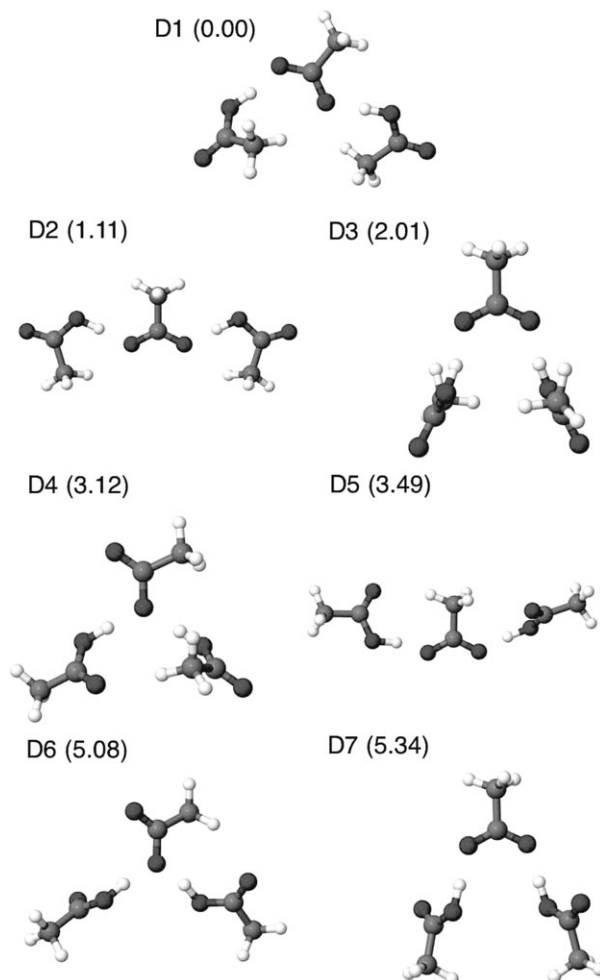
oxygen atoms as possible. Thereby, different positions in the plane defined by the oxygen atoms have been used, but also the possibility of including Na to be out of plane has been explored.

Starting from the guessed conformers, geometry optimizations have been performed using DFT with the Becke, three-parameter, Lee-Yang-Parr hybrid functional (B3LYP) and the 6-31++G(d,p) basis set. The convergence with respect to the basis set has been checked for DHTA using 6-311++G(d,p) as an alternative. For SDHTA, we have also used the Becke, Lee-Yang-Parr hybrid functional (BLYP) for geometry optimization, starting from the B3LYP (6-31++G(d,p)) optimized conformers, because this functional was further used in the DFT-MD simulations. The molecular geometries were fully optimized using the gradient minimization technique. The minima are characterized by having zero gradient norms and by diagonalizing the matrix of the second derivatives to give harmonic vibrational frequencies. Optimizations with and without C_s symmetry restriction were considered. All quantum mechanical calculations have been performed using the Gaussian03 program package.[15]

DFT-MD simulations have been started from the BLYP lowest energy structure of SDHTA in the gas phase using the Terachem package.[16] The simulation was done at the BLYP/6-31++G(d,p) level and using the DIIS algorithm for wave-function convergence with a threshold 10^{-4} and double precision. The temperature along the trajectory was fixed at 300 K by scaling the velocity every two MD steps (NVT ensemble). The DFT-MD simulation was run for 12.6 ps with a 0.3-fs time step. From the analysis of kinetic energy and temperature, we concluded that the first picosecond should be assigned for equilibration, the remaining trajectory was analyzed in terms of the HB dynamics.

Notice that for the present system the central processing unit (CPU) time saving when going from B3LYP to BLYP has been a factor of about 12.

Results and Discussion

DHTA

The geometries of stationary points of distinct conformers obtained from the guess structures are collected in Figure 2

Table 1. The B3LYP/6–31++G(d,p) optimized values of the HB parameters of DHTA (reference energy for D1 is −686.83121 and −686.657167 E_h without and with ZPE correction, dipole moments in Debye, ΔE in kcal/mol (ZPE corrected values in parentheses), bond lengths in Å, angles in degrees).

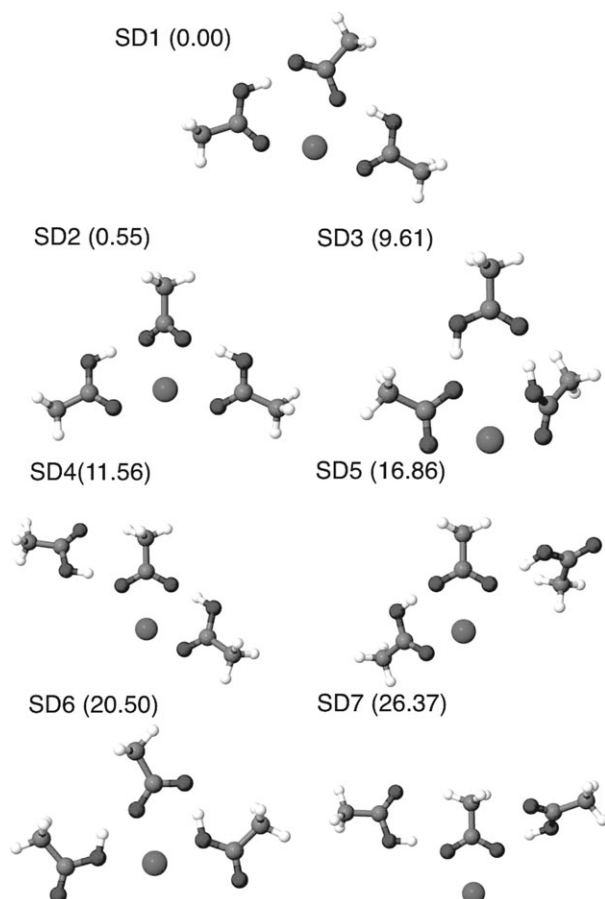| Struct.	Dipole	ΔE	O8—H13	O4—O8	∠O4H13O8	O12—H14	O3—O12	∠O3H14O12
D1	3.88	0.00 (0.00)	1.02	2.58	171.7	1.03	2.55	179.7
D2	3.76	1.11 (0.76)	1.03	2.54	178.4	1.03	2.54	178.4
D3	11.75	2.01 (2.24)	1.02	2.57	170.1	1.02	2.57	170.3
D5	3.66	3.49 (1.87)	1.07	2.48	166.2	1.09	2.46	170.0
D7	9.07	5.34 (4.29)	1.04	2.52	171.0	1.04	2.52	171.1
				O3—O8	∠O3H13O8			
D4	10.69	3.12 (2.85)	1.02	2.59	176.0	1.05	2.54	177.2
D6	4.70	5.08 (4.08)	1.06	2.50	169.1	1.04	2.55	169.8

Figure 3. The B3LYP/6-31++G(d,p) optimized geometries of different conformers of SDHTA starting from the guess structures as described in the 'Computational Details' section (relative electronic energies in kcal/mol in parentheses). Notice that SD1 is the only structure which has C_s symmetry.

(B3LYP/6-31++G(d,p)). Important geometric parameters as well as dipole moments and relative energies are given in Table 1. It should be noted that to obtain these structures it was necessary to release the C_s symmetry restriction (see Table 1). This requirement becomes obvious, for example, for structure D3. Here, the two hydrogen atoms of the HBs tend to be away from one another to reduce the repulsion force. As a result, the two methyl groups of the acetic acids rotate to reduce the steric hindrance and finally become upward and downward relative to the plane spanned by the heavy atoms of the acetate.
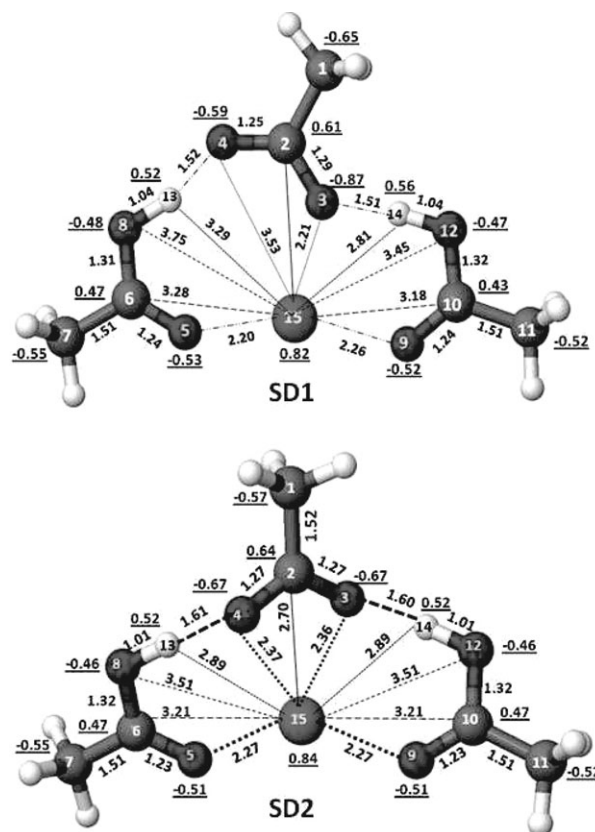

Figure 4. The B3LYP/6-31++G(d,p) optimized geometry of the proposed SDHTA conformer SD1 (upper panel) and SD2 (lower panel) containing distances in Å and Mulliken charges (underlined).

To scrutinize the basis set effect, we have performed geometry optimization using the triple zeta B3LYP/6-311++G(d,p) basis set. The results are given as Supporting Information. It turns out that the geometric parameters of the HBs are only slightly affected by the choice of the basis set. The energetic ordering does not change at all. Therefore, we will continue our discussion on the basis of the B3LYP/6-31++G(d,p) results.

The conformers are ordered by increasing energy (without including zero point energy (ZPE) correction) from D1 to D7. According to Table 1, the conformers D1 and D2 still have the same order even after including ZPE. The energetic difference between D1 and D2 decreased to 0.76 kcal/mol after including ZPE, and D5 becomes the third with the difference of 1.87 kcal/mol. The main difference between D1 and D2 is that the

Table 2. The B3LYP/6-31++G(d,p) optimized values of the HB parameters of SDHTA, compare with Figure 3 (reference energy for SD1 is −849.14918 and −848.973232 E_h without and with ZPE correction, dipole moments in Debye, ΔE in kcal/mol (ZPE corrected values in parentheses), bond lengths in Å, and angles in degrees).

Struct.	Dipole	ΔE	O8—H13	O4—O8	∠O4H13O8	O12—H14	O3—O12	∠O3H14O12
SD1	3.23	0.00 (0.00)	1.04	2.53	165.6	1.04	2.54	171.9
SD2	1.68	0.55 (0.94)	1.01	2.61	174.6	1.01	2.61	175.3
SD3	2.97	9.61 (9.00)	1.02	2.55	176.7	1.39	2.46	179.2
SD4	5.70	11.56 (12.14)	1.00	2.64	167.3	1.01	2.60	173.8
SD5	9.55	16.86 (17.36)	1.00	2.68	173.2	1.01	2.62	174.1
SD6	4.03	20.50 (19.62)	0.99	2.52	136.4	1.08	2.46	168.2
SD7	8.41	26.37 (26.94)	1.00	2.65	164.4	1.00	2.65	172.0

Note that SD3 is in *trans* form, compare with Figure 3.

Table 3. The BLYP/6–31++G(d,p) optimized values of the HB parameters of SDHTA (reference energy for SD1 is −848.95517 E_h, dipole moments in Debye, ΔE in kcal/mol, bond lengths in Å, and angles in degrees).

Struct.	Dipole	ΔE	O8—H13	O4—O8	∠O4H13O8	O12—H14	O3—O12	∠O3H14O12
SD1	3.24	0.00	1.05	2.55	163.7	1.05	2.55	171.1
SD2	1.72	0.87	1.03	2.60	176.0	1.02	2.63	176.7
SD3	2.62	9.04	1.04	2.55	176.9	1.36	2.47	179.2
SD4	5.79	11.60	1.02	2.65	163.3	1.02	2.63	175.9
SD5	9.57	16.36	1.01	2.71	170.7	1.02	2.65	174.7
SD6	4.12	19.43	1.01	2.55	137.0	1.10	2.50	170.0
SD7	8.77	25.41	1.01	2.67	162.3	1.02	2.68	169.2
Trajectory	3.29		1.03	2.67	167.3	1.03	2.67	167.3

The last row shows the geometric parameters averaged along the DFT-MD trajectory.

latter structure possess a higher symmetry with respect to the HBs. Thus, we conclude that at the present level of theory the less symmetric structure is preferred, although the energetic difference to a more symmetric structure is comparable to k_BT at room temperature such that one could expect both conformers being present under these conditions.

SDHTA

Geometry optimization of SDHTA at the DFT/B3LYP/6-31++G(d,p) level of theory yielded stationary points with geometries reported in Figure 3 and Table 2. The conformers are ordered with increasing energy from SD1 to SD7. Including ZPE in this case does not change the energetic order of the conformers. The table includes the dipole moments and relative energies without and with ZPE of the different conformers. First, notice that as compared with DHTA in Table 1, there is a clear energetic separation of different conformers. Further, we find that SD3 looks different from the rest, that is, the two HBs are pointing in opposite direction (*trans* conformers). In passing, we note that such a *trans* structure is not in accord with the findings of Limbach and coworkers,[9] which have been obtained, however, for a different counter ion. Overall, the effect of the counter ion is to increase the O—O and to decrease the O—H bond length. Further, we do not observe formation of HBs through only one acetate oxygen like in D4 and D6.

As far as the two lower energy structures are concerned Table 2 reveals that SD1 and SD2 differ only by 0.55 kcal/mol (without ZPE) or 0.94 kcal/mol (with ZPE) and represent structures of different symmetry concerning the HBs. Hence, the situation is similar to the case of DHTA in the previous section. For a more detailed discussion of these conformers, we give their structures with important distances and Mulliken charges in Figure 4. The different situations of the two HBs in SD1 and SD2 are reflected not only in the distances like HB lengths and angles but also in the partial charges, for example, SD1 has charges of −0.87 and −0.59 at O3 and O4, respectively, whereas they are equal to −0.67 in SD2. Furthermore, the two structures differ in the coordination of the sodium atom, which has almost equal distances to O3, O4, O5, and O9 in SD2, in strong contrast to SD1.

From the experimental point of view, there are two sets of data to compare with. First, a crystal structure has been reported in Ref. [8] that reveals chains of sodium coordination polyhedra, which are strengthened by the HBs between the $CH_3CO_2^-$ ion and the two CH_3CO_2H. According to this crystal structure, the two HBs are only slightly nonsymmetric, that is, the HB lengths are 2.503 and 2.509 Å (difference probably within expected error). Second, the NMR investigation of tetrabutylammonium dihydrogen triacetate in a freon mixture by Limbach and coworkers[9] gives indication of the chemical equivalence of the carboxylic carbon atoms, which would also favor the more symmetric structure SD2. However, even leaving aside the difference in the counter ion, the presence of the aprotic polar
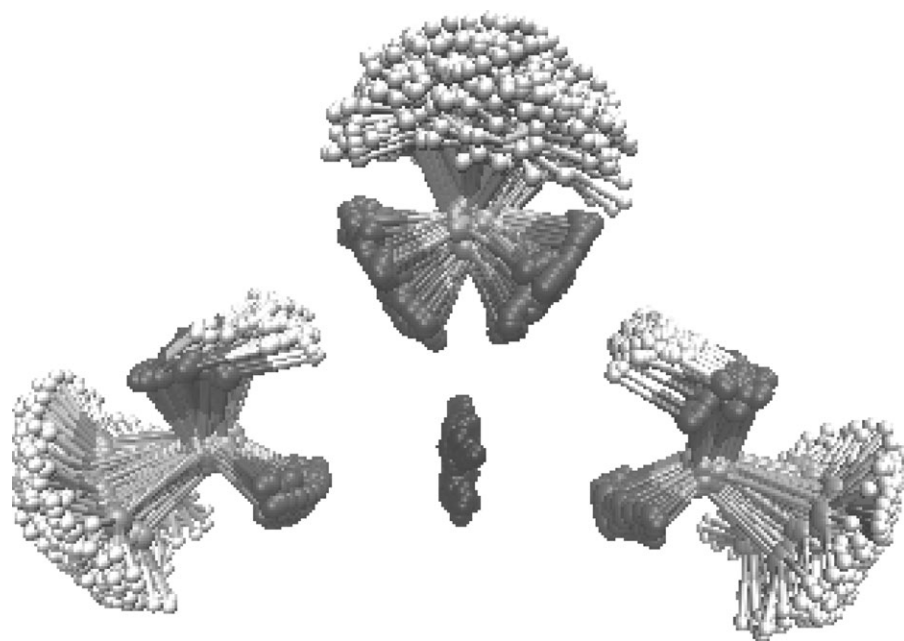

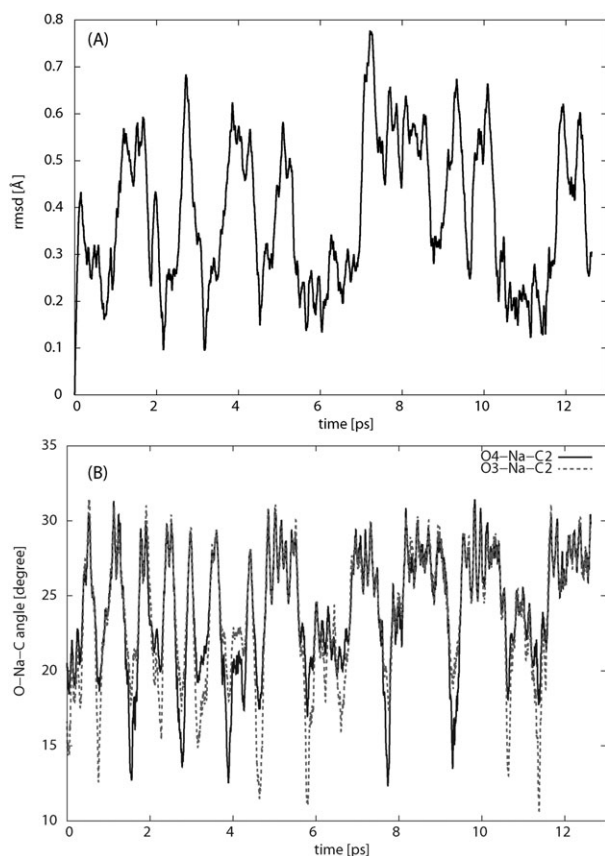**Figure 5.** Overlay of 210 structures sampled along the trajectory.

Figure 6. The RMSD with respect to the starting configuration (A) and the O—Na—C angles in degree (B) along the trajectory.

Figure 7. The O3—O12 (A) and the O4—O8 (B) H-bond parameters in Å along the trajectory.

solvent renders the situation to be not comparable with the present gas phase calculations similar to the crystalline phase.

The DFT-MD simulations will be performed using the BLYP functional. Comparing B3LYP and BLYP optimized structures in Tables 2 and 3, we notice that the changes are rather minor. In particular, there is no change in the energetic ordering of the conformers and the root mean square deviation (RMSD) values are in the range of 0.027–0.053 Å.

HB cooperativity in SDHTA

The DFT-MD trajectory has been analyzed putting special emphasis on the HB parameters. In Figure 5, we show 210 structures sampled along the trajectory to give a global view on the thermal fluctuation dynamics. A more detailed look is provided by inspecting the RMSD with respect to the starting
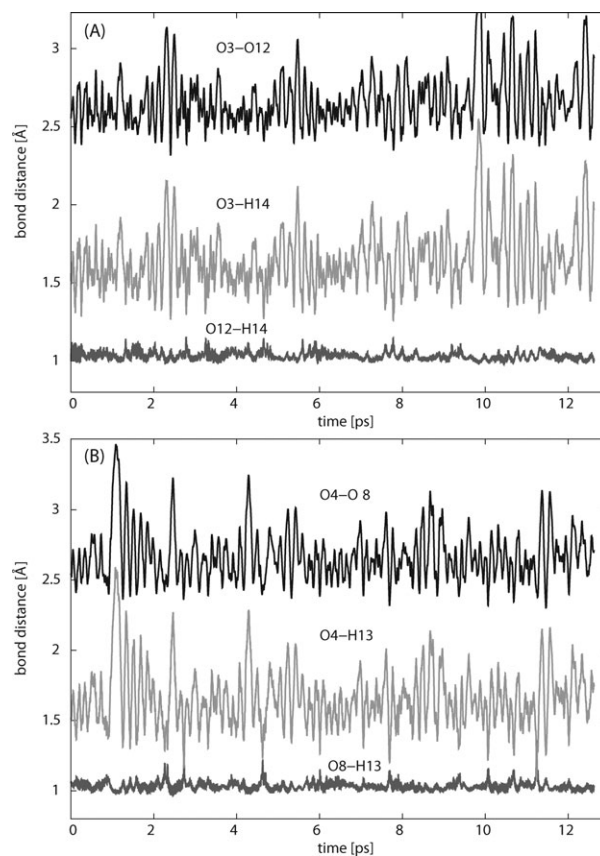
Table 4. RMSD, which was started from the SD1 conformer geometry taken along the trajectory after equilibration.

Conformer	RMSD (Å)
SD1	0.34
SD2	0.41
SD3	1.22
SD4	1.54
SD5	1.38
SD6	1.21
SD7	1.55

structure, which is shown in Figure 6A. The figure reveals an oscillatory behavior along the trajectory that turns out to be mostly due to an interconversion between SD1 and SD2 conformers. This becomes apparent when looking at the time-dependence of the O3—Na—C2 and O4—Na—C2 angles in Figure 6B. It should be noted that the main difference between SD1 and SD2 is that these two angles have the same value in case of the more symmetric SD2 (27.9○), but they are different for SD1 (O3—Na—C2: 16.6○, O4—Na—C2: 20.5○). Notice that the values of these angles are also found to be reversed at some points, indicating a structure that has approximately mirror symmetry with respect to a plane going through the C2 and Na atoms. The average values for these angles along the trajectory are 23.9○ and 24.1○. The overall importance of the different conformers in terms of the RMSD can be judged from Table 4, which gives indication that only conformers SD1 and SD2 are visited during the simulation. Evidence for the importance of the SD1 conformer comes from the average dipole moment, which is 3.29 D, that is, is close to SD1 conformer value (see Fig. 3, Supporting Information).

Next, we take a closer look at the HB dynamics in Figure 7. Overall, the individual HBs follow the common rule that HB compression leads to a shift of the hydrogen atom toward the center of the HB. In principle, this could lead to proton transfer, and indeed, we find two transfer events in the O4—H12—O8 HB at 2.72 and 11.23 ps. Notice that no transfer events are recorded for the O3—H12—O12 HB. The dynamics

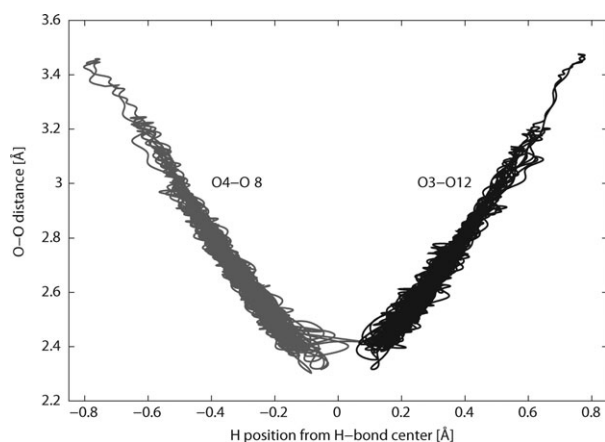**Figure 8.** The O—O HB lengths versus the deviations of the H atoms from the centers of the HBs ($(R_{O—H} − R_{H\cdots O})/2$). Notice that for the purpose of visualization, we have plotted the negative of the H position for the O3—O12 case.

of the two HBs can be alternatively represented in a correlation plot of HB length and H position with respect to the HB center as shown in Figure 8. This type of correlation plots are widely used for the interpretation of NMR data, because they provide a means for assigning H positions to a given HB lengths.[17] However, in contrast to experimentally derived correlations, where each point represents an averaged position for a single system, the present correlation plot gives indication for the correlated motion of single HBs along an equilibrium trajectory. It is to be noted that the range spanned by the HB distances is substantial, that is, covering HB lengths that could be classified to represent weak to strong HBs. The averaged HB parameters are 2.67 Å for both O4—O8 and O3—O12 HB, −0.312 Å for the H positions with respect to the HB center, and 167.3○ for both O4—H13—O8 and O3—H14—O12 angles (cf. Table 3). These values confirm our previous observation that the two HBs are on average rather symmetric.

Next, we focus on the issue of cooperativity in the HB motion. For the related system, tetrabutylammonium dihydrogen triacetate Limbach and coworkers[9] had found indication for an anticooperative behavior of the two HBs. This implies that provided one of the two HBs is contracted, the other one will be elongated. To elucidate this effect with the help of the present trajectory, we have considered the following simple measure: First, we record the O—O distances along the trajectory, that is, $R_{O3—O12}(t)$ and $R_{O4—O8}(t)$. Next, we calculate the difference $\delta R_{O3—O12}(t + \Delta) = R_{O3—O12}(t + \Delta t) − R_{O3—O12}(t)$ and likewise $\delta R_{O4—O8}(t + \Delta)$. These difference can be either positive or negative. Finally, we calculate $\delta R_{O3—O12}(t) \times \delta R_{O4—O8}(t)$ and count each instance where the result is positive/negative as cooperative/anticooperative. Performing the sampling along the trajectory yielded a small preference 54.8%/45.2% for anticooperative behavior. Notice that by performing this calculation for trajectories of different length one obtains ratios of 52.5%/47.5% and 55.5%/44.5% after 1/3 and 2/3 of the production interval, respectively, that is, given the available data there is a clear trend toward anticooperativity. Additional evidence for the anticooperativeness of the HBs

comes from the conjugation of the carboxylate group (O3—C2—O4), that is, when C2—O3 increases and C2—O4 decreases, the O3—O12 decreases and the O4—O8 increases (see Fig. 4, Supporting Information). We conclude by pointing out that although our findings are in accord with the observations of Limbach et al. it does, of course, give no explanation for these data due to the different counter ion as well as the lacking solvent. However, one may take the present simulation as a further support for the anticooperativeness of the HB dynamics in dihydrogen triacetate/counter ion complexes.

Conclusions

In summary, we have reported on a quantum chemical study of the structure and energetics of SDHTA and its ion. In both cases, it was found that there are two structures of comparable energy (within ∼1 kcal/mol), which differ in their symmetry with respect to the HBs. A subsequent DFT molecular dynamics investigation of SDHTA yielded a scenario, where both structures are visited along the room temperature equilibrium trajectory.

The DFT-MD trajectory data have been further analyzed placing emphasis on the issue of cooperativity in the dynamics of the two HBs. Here, an anticooperative behavior has been found, that is, on average the elongation of one HB will be accompanied by a compression of the other HB. This is also reflected in the conjugation of the carboxylate group and in the fact that only single proton transfer is observed. This result is in accord with experimental results obtained for a similar dihydrogen triacetate system but in solution phase.[9]

Having at hand the equilibrium structures one is in the position to explore the potential energy surfaces for HB dynamics and in particular to analyze the quantum mechanical wave function for different isotopologs (HH, HD, and DD). This would provide complementary information on the cooperativity by virtue of the Ubbelohde effect (cf. Refs. [10,11]). Preliminary investigations using a simple normal mode based model of SDHTA confirm the present finding of anticooperative HBs.[18]

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