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# Reply to “Comment on Effects of Ionizing Radiation on Crystalline Cytosine Monohydrate”

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In the above comment Close et al. raise criticism against the comparisons made between theoretical results of various radical forms of cytosine<sup>1</sup> with experimental EPR and ENDOR data primarily obtained in single crystals of cytosine monohydrate.<sup>2</sup> The essence of the comments made are certainly sound, namely, that there are differences between some of the observations made. Primarily, the authors claim that OH radical adducts are unlikely to be formed in the monohydrate crystals, and that the *net* effect of ionization is the removal of one hydrogen from the N1 position of some cytosines, and the addition of the H radicals to the N3 position of other cytosines. The formation of N1 dehydrogenated radicals was questioned in the theoretical study<sup>1</sup> to which the comment was made.

The main source for the difference between the experimentally and theoretically deduced hyperfine coupling constants (HFCC) is, according to Close et al., that the amino groups of cytosine (N4) should be planar from interactions within the crystals, whereas calculations in vacuo render slightly puckered structures. Employing planar models for the N1 dehydrogenated and N3 hydrogenated radicals is claimed to render theoretical data that will support the interpretations made by Close et al. We present new data below that partly supports and partly disagrees with these statements. For the N3 hydrogenated species (labeled **N3H**), we can see from Table 1 that the large isotropic coupling arising from the out-of-plane amino proton vanishes. The remaining proton couplings undergo minor adjustments from the planarity, as expected, and the overall agreement with ENDOR data is most satisfactory. We may thus conclude, even more strongly than previously in ref 1, that the **N3H** radical is one of the major species formed when exposing crystalline cytosine monohydrate to ionizing radiation.

Performing the same type of computation for the N1 dehydrogenated species (**N1**), Table 2, does however not lead to any improvements over previous results. The rationale for this is that the puckering is very small already for the unconstrained geometry, and the net effect is thus minor. The out-of-plane angle H–N4–C4–N3 (for atomic labeling, see ref 1) of unconstrained **N1** is 8.5°. In neutron diffraction experiments on crystalline cytosine monohydrate,<sup>3</sup> the HNCN out-of-plane angle was determined to be 3.4°, and a slight puckering of the ring was observed. Including hydrogen bonding moieties in the optimization calculations (four water molecules surrounding the N1 radical of cytosine) lowered the amino group puckering to HNCN = 3.2 angles. As expected, no major change in HFCCs was observed. From this data, together with the results listed in Table 2, we may thus conclude that planarity itself does not

**TABLE 1. Comparison of Calculated HFCCs (gauss) for the N3-Hydrogenated Radical (N3H) in Puckered and a Planar Geometries with Experimental Results (Reference 2)**

atom		calcd puckered	calcd planar <sup>a</sup>	exptl
N1H	A <sub>iso</sub>	−3.0	−2.7	
	T <sub>XX</sub>	−2.8	−2.5	
	T <sub>YY</sub>	−1.2	−1.2	
	T <sub>ZZ</sub>	4.1	3.7	
N3H	A <sub>iso</sub>	0.6	−2.9	−2.0
	T <sub>XX</sub>	−2.5	−2.6	−2.1
	T <sub>YY</sub>	−1.0	−0.9	−0.5
	T <sub>ZZ</sub>	3.5	3.5	2.6
N4H	A <sub>iso</sub>	19.6	−2.7	−1.6
	T <sub>XX</sub>	−1.0	−2.3	−1.7
	T <sub>YY</sub>	−1.0	−0.7	−0.8
	T <sub>ZZ</sub>	2.0	3.0	2.4
N4H	A <sub>iso</sub>	−1.1	−2.4	
	T <sub>XX</sub>	−1.5	−2.0	
	T <sub>YY</sub>	−0.5	−1.0	
	T <sub>ZZ</sub>	2.0	3.0	
C6H	A <sub>iso</sub>	−13.7	−14.8	−13.5
	T <sub>XX</sub>	−8.3	−8.9	−8.8
	T <sub>YY</sub>	0.2	0.5	0.8
	T <sub>ZZ</sub>	8.2	8.5	8.0

<sup>a</sup> Planar structure lies 3.6 kcal/mol higher in energy than the unconstrained (puckered) form.

**TABLE 2: Comparison of Calculated HFCCs (gauss) at Puckered and Planar Geometries with Experimental Results (2) for the N1 Dehydrogenated Radical**

atom		calcd puckered	calcd planar	exptl
N4H	A <sub>iso</sub>	−0.7	−0.9	−5.1
	T <sub>XX</sub>	−0.5	−0.5	−3.3
	T <sub>YY</sub>	−0.4	−0.4	−0.6
	T <sub>ZZ</sub>	0.9	0.9	4.0
N4H	A <sub>iso</sub>	−0.5	−0.5	−4.6
	T <sub>XX</sub>	−0.7	−0.7	−2.2
	T <sub>YY</sub>	−0.4	−0.4	−1.3
	T <sub>ZZ</sub>	1.1	1.1	3.5
C5H	A <sub>iso</sub>	−11.2	−11.2	−14.8
	T <sub>XX</sub>	−6.9	−7.0	−7.5
	T <sub>YY</sub>	−0.4	−0.3	−0.3
	T <sub>ZZ</sub>	7.2	7.4	7.8

<sup>a</sup> Planar structure was obtained from a full optimization at the B3LYP/6-31G(d,p) level using Onsager’s reaction field method. This method was chosen on the basis of previously reported work (ref 4).

**TABLE 3: Comparison of Calculated HFCCs (gauss) for Unprotonated and Protonated Model System of the N4 Dehydrogenated Radical with Data from Crystalline Cytosine Hydrochloride (ref 5)**

atom		calcd	calcd protonated <sup>a</sup>	exptl
C5H	A <sub>iso</sub>	−2.2	−7.6	−9.7
	T <sub>XX</sub>	−1.0	−3.5	−4.1
	T <sub>YY</sub>	−0.5	−1.1	−0.7
	T <sub>ZZ</sub>	1.5	4.6	4.9
N1H	A <sub>iso</sub>	−2.1	−5.3	−2.8
	T <sub>XX</sub>	−1.9	−4.3	−2.7
	T <sub>YY</sub>	−0.6	−1.1	−0.9
	T <sub>ZZ</sub>	2.4	5.4	3.6
N4H	A <sub>iso</sub>	−15.5	−13.0	−13.1
	T <sub>XX</sub>	−12.5	−10.4	−8.7
	T <sub>YY</sub>	−2.8	−2.4	−1.7
	T <sub>ZZ</sub>	15.3	12.8	10.5
N3H	A <sub>iso</sub>		−1.3	
	T <sub>XX</sub>		−1.2	
	T <sub>YY</sub>		−0.2	
	T <sub>ZZ</sub>		1.4	

<sup>a</sup> Protonated structure is completely planar. No vibrational effects or Cl anions were included, which may improve results further.

lead to **N3H** + **N1** as favored radical products, as suggested by Close et al. in their comment. The alternative mechanisms discussed in ref 1 should thus not be discarded on the basis of those arguments.

Close et al. finally end their comment by stating that the theoretical results obtained for the species dehydrogenated at the amino group (**N4**) disagree with their more recent findings,<sup>5</sup> performed on crystalline cytosine hydrochloride. This is indeed correct. What they overlook is, however, that we then need to investigate *the protonated form* of the **N4** radical, not the unprotonated form one would expect in monohydrate crystals, and which is reported in ref 1. In Table 3 we list data for the un-protonated and N3 protonated forms of the **N4** radical. As seen, when comparison is made between the correct molecules, there is a very close agreement between experiment and theory.

We are currently reinvestigating the cytosine monohydrate and hydrochloride problems, in which a large fraction of the local surrounding is included directly in the calculations. These results will hopefully shed more light on the detailed processes leading to the excess formation of certain radicals, whereas others are only formed in minor quantities.

### References and Notes

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