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Letter

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Are Bond Critical Points Really Critical for Hydrogen Bonding?

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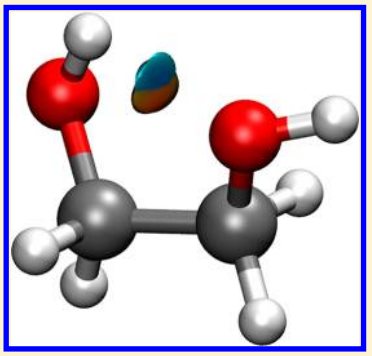
Supporting Information

ABSTRACT: Atoms in Molecules (AIM) theory is routinely used to assess hydrogen bond formation; however its stringent criteria controversially exclude some systems that otherwise appear to exhibit weak hydrogen bonds. We show that a regional analysis of the reduced density gradient, as provided by the recently introduced Non-Covalent Interactions (NCI) index, transcends AIM theory to deliver a chemically intuitive description of hydrogen bonding for a series of 1,*n*-alkanediols. This regional definition of interactions overcomes the known caveat of only analyzing electron density critical points. In other words, the NCI approach is a simple and elegant generalization of the bond critical point approach, which raises the title question. Namely, is it the presence of an electron density bond critical point that defines a hydrogen bond or the general topology in the region surrounding it?



Hydrogen bonding interactions are of importance in a wide range of applications including self-assembly of nanomaterials, solvation, enzyme−substrate binding, and protein folding. Consequently, the precise definition of what constitutes a hydrogen bond arouses passionate discourse among even the most mild-mannered chemists. It is perhaps because of this that a broad definition was recently adopted by the International Union of Pure and Applied Chemistry (IUPAC): *The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule of a molecular fragment X−H, in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.*[1] The IUPAC definition provides several theoretical and experimental characteristics that typify hydrogen bond formation. The absence of one or more of these characteristics is sometimes inappropriately used as evidence that a hydrogen bond is also absent. This letter highlights and attempts to resolve one such situation where an otherwise intuitive hydrogen bond cannot be identified by conventional topological analysis.[2,3]

One of the difficulties in determining the presence or absence of a hydrogen bond relates to the more general difficulty of defining what constitutes a bond itself. Unfortunately, the very tangible object of a bond to a classical chemist is not a direct solution of the Schrödinger equation. An approach that has gained many followers in the past few decades is based on a topological analysis: where chemical bonds, just like atoms, are assumed to be three-dimensional entities, and thus their location in space is defined before quantifying their properties. This division is completed in terms of the gradient of some scalar field, the choice of which should be a physical observable that is defined in coordinate space. The electron density, denoted $\rho(r)$, meets these requirements because it is an experimentally accessible scalar field and it is a local function defined within the exact many-body theory, supported by the Hohenberg−Kohn theorem (HKT).[4] The relationship between electron density topology and physical/chemical properties can be understood from the HKT, which asserts that a system's ground-state properties are a consequence of its electron density. Furthermore because chemical reactions proceed by $\rho(r)$ redistributions, methods that analyze $\rho(r)$ distributions should help to understand the electron structure of molecules and thus chemical reactivity.

A spatial topological decomposition of $\rho(r)$ itself is the basis of the popular Atoms in Molecules (AIM) theory.[5] AIM was introduced by Bader, who noted that the essence of a molecule's structure must be contained within the topology of $\rho(r)$ and resorted to mathematical tools to (i) describe the properties of chemical systems and (ii) extract observable information from the electron density. Thanks to this machinery, it is possible to correlate topological properties of $\rho(r)$ with elements of molecular structure (atoms and bonds), making quantum chemistry concepts compatible with traditional chemical ideas. Since the electron density is at a maximum at the nuclei, the localization of maxima enables the identification of atomic positions. Once atoms are identified,

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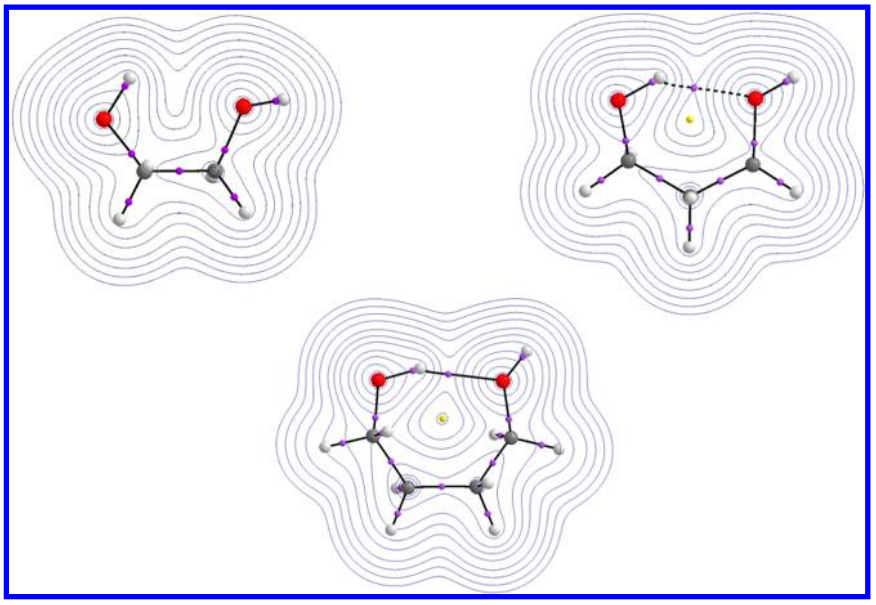

Figure 1. Electron density contour maps for **ED** (top left), **PD** (top right), and **BD** (bottom). Large spheres represent atoms: C in gray, O in red, and H in white. Small spheres represent critical points: BCPs in purple and RCPs in yellow. Whereas all three molecules show experimental evidence of hydrogen bonding, only **PD** and **BD** exhibit BCPs.

chemical bonds can then be defined as saddle points between the maxima. These saddle points are known as bond critical points (BCPs) and represent the minimum along the bonding direction, and the maximum in all others. Mathematically, this is defined by the sign of the second derivatives, λ_1, λ_2, λ_3, along the main axes of variation (eigenvalues): at a BCP, λ_1 and λ_2 are negative whereas λ_3 is positive.

While the mathematical concepts of AIM theory have been extensively applied and generally accepted in the literature, a number of criticisms and heated discussions still exist with regard to their precise chemical meaning. Many of these controversies involve the application of AIM theory to systems with weak long-range bonds. Examples are known where either an intuitive bond does not exhibit a BCP or a BCP exists despite there being no apparent bonding interaction.[6−8] The former case is commonly observed for intramolecular hydrogen bonds such as those considered in the present work. The latter case is most noted for repulsive H···H steric interactions in biphenyl derivatives.[9]

In this Letter, we argue that the BCP criterion of AIM theory is too stringent, more specifically, that the absence of a BCP should not necessarily be considered evidence as to the absence of a chemical bond. To illustrate this, we consider a series of 1,*n*-alkanediols: 1,2-ethanediol (**ED**), 1,3-propanediol (**PD**), and 1,4-butanediol (**BD**). Previous experimental[10,11] and present theoretical data (Supporting Information) suggest that the strength of the intramolecular hydrogen bonding interactions in these three molecules increases as the alkane chain length increases. For example, the OH-stretching vibrational mode of the hydroxyl group involved in hydrogen bonding becomes progressively more red-shifted in the fundamental and overtone regions, with a corresponding increase in intensity in the fundamental region and decrease in intensity in the first overtone region from **ED** to **BD**.[10,11] However, when AIM theory is applied to this 1,*n*-alkanediol series, only **PD** and **BD** are found to exhibit BCPs but not **ED**. This result is controversially interpreted by some groups as evidence "proving" that **ED** does not exhibit an intramolecular hydrogen bond.[12]

In order to analyze the changes in the densities that introduce these disagreements, we start by looking at the general topology from which Bader's theory departs along the series. In Figure 1, we present electron density contour maps for the lowest energy conformers of **ED**, **PD**, and **BD**. The molecules have been optimized with the CCSD(T)-F12a/cc-pVDZ-F12 method as implemented in MOLPRO 2010.1.[13] Full details can be found in the Supporting Information. The topology of the three molecules is generally similar. However, for **ED** there is a single flatter region between the two hydroxyl groups rather than the two discrete regions seen in **PD** and **BD**. In Figure 1, critical points are also shown for comparison. For **BD** and **PD**, the BCPs (in purple) clearly appear between the hydroxyl groups and are accompanied by ring critical points (RCPs; in yellow) toward the center of the ring. Ring critical points are second order saddle points ($\lambda_1 < 0$; λ_2 and $\lambda_3 > 0$) that are generally associated with ring-type structural features. For **ED**, the two types of critical points collapse on each other. Consequently, only **PD** and **BD** satisfy the AIM criteria for hydrogen bonding, but not **ED**. This is despite the fact that all three molecules appear to demonstrate experimental evidence of hydrogen bonding[10,11] and the fact that the three electron density topologies look very similar. Two possible conclusions can therefore be drawn: Either there is no hydrogen bond in **ED** and the experimental evidence is due to some other effect[12] or a hydrogen bond really does exist and the AIM criteria are too stringent.

If we accept the relevance of the electron density topology as a quantity directly related to the state of a system, it seems logical to look at a more general quantity that describes changes in the density rather than simply its local values. The gradient of the electron density seems a natural starting point, and this quantity has received renewed interest lately. Several authors have proposed different indices that utilize the electron density gradients to reveal chemical bonding interactions.[14−17]

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As the name suggests, the Non-Covalent Interactions (NCI) index of Johnson and co-workers has been specifically developed to reveal non-covalent interactions, such as hydrogen bonding, in 3D space.[15] The NCI index is based on the normalized and dimensionless reduced density gradient ($s = 1/[2(3\pi^2)^{1/3}]|\nabla\rho|/\rho^{4/3}$). Regions where the electron density $\rho(r)$ and reduced density gradient s are low correspond to regions where non-covalent interactions occur. It follows that isosurfaces of the reduced density gradient at low densities can be used to visualize the position and nature of non-covalent interactions in 3D space.

In Figure 2, we present NCI isosurfaces for **ED**, **PD**, and **BD** to illustrate the nature of the intramolecular hydrogen bonding

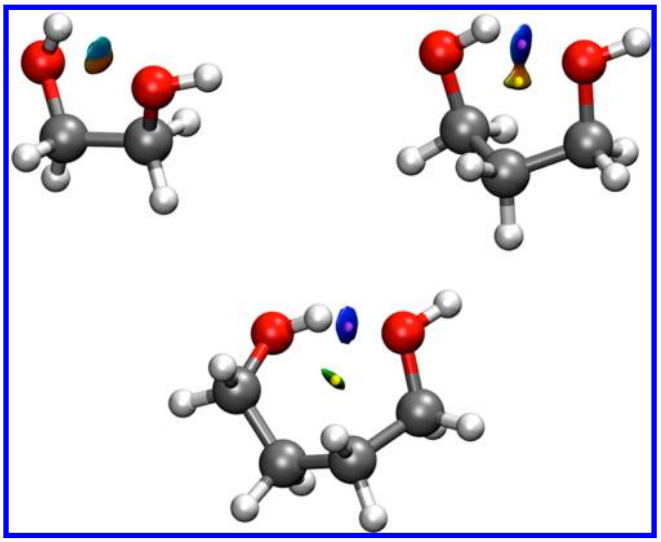

Figure 2. NCI isosurfaces for **ED** (top left), **PD** (top right), and **BD** (bottom): s = 0.5 and a blue-green-red color scale from −0.02 < sign(λ_2) $\rho(r)$ < +0.02 au. Small spheres represent critical points: BCPs in purple and RCPs in yellow. A continuous change is observed in the isosurfaces from **ED** to **BD**.

interactions. A continuous color-coding scheme based on the second derivatives is used, where strong attractive interactions are represented in blue, weak interactions in green, and strong repulsive interactions in red. Also included in Figure 2 are the corresponding BCPs (small purple spheres) and RCPs (small yellow spheres) that highlight the complementarity of the AIM and NCI approaches.

The image for **BD** corresponds to a typical strong hydrogen bond within the NCI framework, blue in color and very disk-shaped, that is, a very localized interaction, which expands from the BCP. A second weaker interaction is evident from the green isosurface at the center of the ring, which is related to the RCP. For **PD**, both interactions start to mix, which is consistent with the flatter density profile observed in Figure 1. However, the presence of critical points is still clearly marked by a distinct blue region centered at the BCP corresponding to a moderate hydrogen bond and a distinct yellow region centered at the RCP. Finally, the absence of critical points in **ED** is reflected as a unique NCI isosurface. This isosurface is a single circular volume between the two OH moieties due to collapse of both regions of interaction in the intramolecular bonding. So the question arises as to whether the unique region in **ED** can be identified as a hydrogen bond, or is it something else (as has been sometimes suggested in the literature[20])?

To answer this question, we must more closely analyze the behavior of the electron density and the electron density gradient across the 1,*n*-alkanediol series. In Figure 3, we present

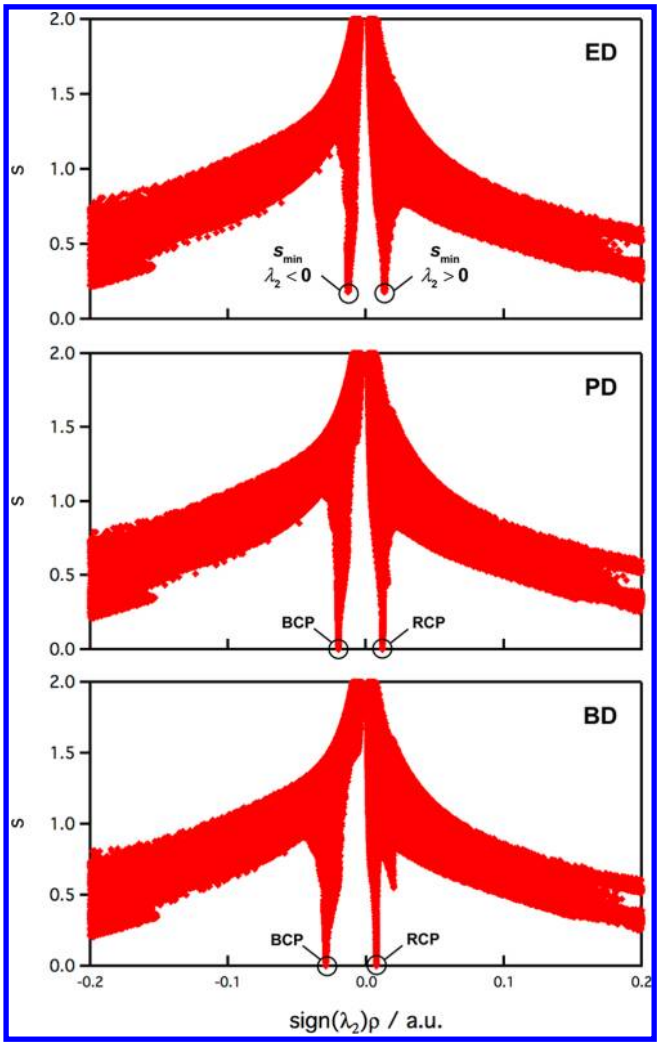

Figure 3. Plot of the reduced density gradient s and sign(λ_2)ρ for **ED** (top), **PD** (middle), and **BD** (bottom). The density features are qualitatively the same with a continuous change observed from **ED** to **BD**.

plots of s versus $\rho(r)$ oriented by the sign of the second eigenvalue (λ_2). In the absence of non-covalent interactions, these plots should behave like exponentials, whereas the presence of non-covalent interactions is characterized by troughs in $s(\rho)$.[15] Points where s = 0 correspond to electron density critical points due to annihilation of the density gradient. In the region immediately surrounding a critical point, the change in ρ dominates, and as $s(\rho)$ is continuous, a trough appears in that region. The nature of a point where s = 0 can be further characterized as either a BCP or RCP from the sign of λ_2. This distinction corresponds to the color-coding used in the 3D plots to differentiate attractive from repulsive interactions (Figure 2). Thus, NCI recovers AIM results and provides an intuitive isosurface that characterizes changes in the electron density gradient.

We find that the plot of s versus sign(λ_2)ρ for **ED** is not qualitatively different than that for **PD** or **BD**. In all three molecules, two troughs are obtained for the interaction, with

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one trough at negative sign(λ_2)ρ corresponding to an attractive hydrogen bonding interaction and a second trough at positive sign(λ_2)ρ corresponding to a repulsive steric interaction due to ring formation.[15] The only difference arises in the minimum values of s attained in the graphs. Whereas the troughs in s for **PD** and **BD** go down to zero, those for **ED** tend to a small positive value. Consequently, the fact that the troughs for **ED** do not reach zero only reiterates that these interactions are not associated with critical points in the electron density. But does this change the nature of the interactions? The HKT dictates that the same density characteristics [density and reduced density gradient are the main components of generalized gradient approximation (GGA) functionals] point to the same type of interaction, only different in strength. Such an understanding is also consistent with the experimental data for **ED**, **PD**, and **BD**, which suggests that the intramolecular hydrogen bond strength increases as the alkane chain length increases.[10,11] This raises the question whether it is only at critical points that we should look to determine the existence of a bond or rather more generally to the whole region that encompasses them?

In summary, we find there to be no clear distinction between the nature of the intramolecular hydrogen bonding interactions in **ED**, **PD**, and **BD**, despite the absence of a BCP in **ED**. As shown in Figures 1−3, there are no qualitative differences between the density characteristics of the interactions in **ED** as compared to **PD** and **BD**. To that end, the fact that the geometry of **ED** is favorable for intramolecular hydrogen bonding and that its vibrational spectra[10,11] are consistent with hydrogen bonding indicates that a hydrogen bond is actually present. Therefore the absence of a BCP in **ED** should not be viewed as evidence *against* hydrogen bonding but rather more simply as the absence of one piece of evidence *for* hydrogen bonding. Finally, we suggest that the AIM criteria for hydrogen bonding are unnecessarily stringent, particularly for intramolecular hydrogen bonds where the geometry constrains the electron density topology.

While the present work is limited to hydrogen bonding interactions, it is likely that the conclusions drawn can also be applied to other weak bonding interactions. We have demonstrated that the NCI index provides a more global description of bonding than analysis of critical points, overcoming some limitations of AIM theory. Very recently attempts to extend AIM theory to overcome these limitations have also been proposed.[18,19] The NCI approach introduces a simple and elegant generalization of the bond critical point approach, which has been shown to be too restrictive because of its locality.

■ ASSOCIATED CONTENT

Supporting Information

Additional theoretical details and results, including the software that was used for the AIM and NCI analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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