

ideally suited for ^{18}F -radiolabelling (Fig. 1). It was then demonstrated that this new chemistry allows access to ^{18}F aryl fluorides from ^{18}F I with radiochemical yield ranging from 8% to 40%. ^{18}F I can be made within 10 minutes from **2** and ^{18}F F $^-$ /18-crown-6 in acetone at room temperature. Inductively coupled mass spectrometric analysis of a representative HPLC-purified ^{18}F radiolabelled aryl fluoride indicated that this material contains 5 ppb Pd residue, which is comfortably below international

recommendation for samples to be injected into humans (the upper limit is 1,000 ppb).

With this work, the ^{18}F radiolabelling of electron-neutral and electron-rich aromatics with ^{18}F fluoride now seems possible. This is a beautiful illustration that smarter chemistry today can certainly facilitate and support tomorrow's patient care. \square

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QUANTUM CHEMISTRY

Quadruply bonded carbon

Determining molecular bond orders can be a delicate and sophisticated task, especially if the electronic structure of the studied system is complex. Now, two different *ab initio* methods have revealed that C_2 and analogous species have a fourth bond, rather than the previously assumed maximum of three.

Jörg Grunenberg

In chemistry, many useful concepts that offered conspicuous service over the last few decades, now seem to stand on shaky ground: looking at the literature, we see more and more reports of abnormalities and exemptions to long-standing chemical rules^{1,2}. Even the paradigm of aromaticity seems to be in doubt³. Many of these peculiarities were triggered by the recent advent of affordable computers, but such discoveries would not be possible without the pivotal, and probably more important, stimulus stemming from the need to create algorithms and numeric recipes able to effectively solve the Schrödinger equation. Quantum mechanics, developed in the first two decades of the last century, had to wait quite a long time until its application to chemical problems was made possible. Today, the coupled power of hard- and software has allowed for an 'electronic' resolution, which was not thinkable 15 or 20 years ago.

Now, writing in *Nature Chemistry*, Sason Shaik and co-workers present⁴ the newest and, if it proves true for other systems too, one of the most significant paradigm shifts in chemistry triggered by computer simulations: they provide evidence that two carbon atoms bonded together can be described as having a quadruple bond. This finding implicates an augmentation of the, so far, maximum bond order of three for carbon and other first-row elements.

The C_2 molecule is well characterized both in its electronic ground state and in many excited states⁵ and has a (ground state)

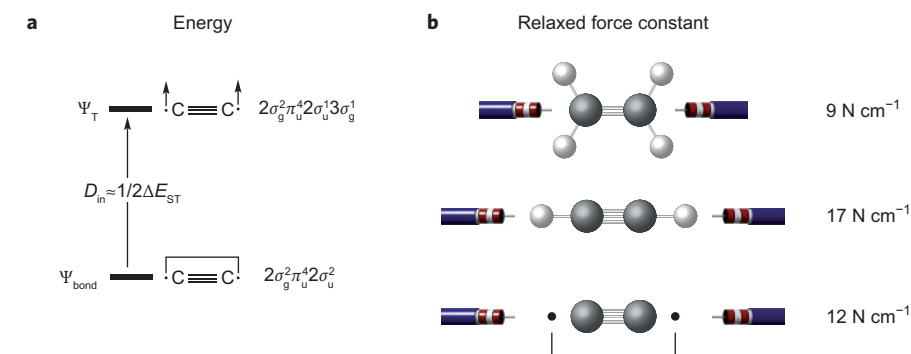


Figure 1 | The bond strength and restoring force in C_2 . **a**, Schematic plot⁴ of the corresponding singlet and triplet states in C_2 , used for the calculation of the bond strength in terms of energy (where the bond energy (D_{in}) is half the energy gap (ΔE_{ST}) between the full bond state (Ψ_{bond}) and the triplet state (Ψ_{T}). **b**, Representation of a comparison of the restoring force of a C–C double, C–C triple or C–C quadruple bond distorted from its equilibrium position using a dynamometer.

bonding distance of 1.24 ångströms. Despite its seeming simplicity, C_2 is one of the most notoriously troublesome cases in quantum chemistry. In fact, it is a member of the famous molecular 'sick list', the roll call of molecules for which particular *ab initio* computational methods give poor results. This sick list is rather long because electrons are particles with intricate dynamics, a fact that is only rudimentarily accounted for by most of the 'out of the box' methods of computational chemistry. Because C_2 is a small molecule with many electrons imprisoned in a relatively small space, it represents a perfect model for studying both dynamic and static correlation. As graphic

and appropriate as it might be in some cases, the simple one-electron picture breaks down when electron correlation — that is their instantaneous evasive manoeuvres out of the way of one another — gets out of hand. Anyway, this picture still dominates many discussions in the chemical literature, including applications of the very popular density-functional-theory methods.

Using differing electronic-structure methods Shaik and co-workers tackled the problem from two directions. Their first strategy was used to fix the errors introduced when representing multi-electron systems with a single electron configuration (that is the 'text book' explanation whereby two

electrons line-up in one molecular orbital). This method is straightforward and simply involves the inclusion of more and more possible configurational line-ups into their wave function, permuting the electrons also into higher 'virtual' orbitals. Shaik and co-workers included as many as 200 million of those configurations in their full-configuration-interaction calculation. This leads to a wave function flexible enough to describe the multi-configurational character of the C_2 moiety. Their second strategy, applying valence-bond theory, does not rely on molecular orbitals at all and therefore is free from any assignments of 'electrons into orbitals'. Actually, the first quantum chemical calculation of a chemical system by Heitler and London in 1927 was based on this theory. In a typical valence-bond calculation, the input consists of strictly localized atomic orbital combinations (covalent and ionic valence-bond structures) familiar to chemists as Lewis structures. If one constructs these possible valence-bond structures adequately for all eight valence electrons in C_2 , dynamic and static correlation is accounted for.

Having solved the electronic-structure problem Shaik and co-workers were finally ready to tackle the maybe even more challenging task: the determination of the bond order. Many disputes in the chemical literature rest on the dichotomy between the mere numerical solutions of quantum chemical calculations and their interpretation in terms of descriptive chemical concepts. Even right at the beginning of the quantum era, Erwin Schrödinger fiercely opposed the probabilistic interpretation of his strictly deterministic equation (actually, Schrödinger created his famous cat in order to ridicule the

probabilistic Copenhagen interpretation)⁶. The concept of bond orders suffers from the same antagonism. Additionally, their definition and therefore calculation is by no means unique.

Historically, the concept of multiple bonds — or *verbundene Affinitäten* (bonded affinities) in the language of E. Erlenmeyer (1862) — between carbon atoms was rooted long before the development of quantum mechanics, it was even before the discovery of the electron. The concept was nevertheless retained into the post-quantum age, but the issue became even more delicate: In valence-bond theory, a bond order is given by the number of electron pairs in a weighted Lewis valence-bond structure. Applying the molecular-orbital approximation, different schemes of localization give rise to different — and there are many around — definitions of bond orders. Which definition should be applied? Using the canonical molecular-orbital scheme, the suggested bond order in C_2 would be 2, for example.

Recognizing this obstacle, Shaik and co-workers had to make a detour: the strength of the potential fourth bond was determined indirectly as the energy difference between two states: the full-bond state and the quasi-classical state, where the two odd electrons maintain only classical interactions (Fig. 1a). Doing so, they were after all able to bracket the strength of the fourth bond between 12 and 15 kcal mol⁻¹, which is much stronger than typical hydrogen bonds. Shaik and co-workers describe the fourth bond given as an "inverted bond", that is, additional to the well known σ and π bonds in acetylene, the outwardly pointing *sp* hybrids in C_2 are thought to contribute to their interaction

too, through the two electrons pointing in opposite directions.

Still, there are some peculiarities in need of further explanation. The description of C_2 as a quadruply bonded molecule implies a pronounced restoring force that keeps the atoms in its equilibrium position (Fig. 1b). According to Shaik and co-workers, the mechanical bond strength, calculated as a compliance constant (relaxed force constant)⁷, in C_2 is around 12 N cm⁻¹, just between the value of a typical C–C double (9 N cm⁻¹) and a C–C triple bond (17 N cm⁻¹). The authors explain this discrepancy in terms of an avoided surface crossing, however, this hardly accounts for the flamboyant slackness compared with a typical triple bond (30% decrease). The same holds true for the other diatomics between first-row elements studied by Shaik and co-workers, CN⁺ BN and CB⁻. Is the ground-state energy surface actually flattened near the minimum for these species? And what about the other candidates for a quadruple bond, for example N₂²⁺? C_2 still seems not to have jumped from the test bench. □

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NUCLEIC ACID HYBRIDIZATION

Robust sequence discrimination

Careful consideration of thermodynamics has allowed the design of nucleic acid probes that are highly specific and virtually unaffected by changes in reaction conditions.

Grégoire Altan-Bonnet and Fred Russell Kramer

Hybrids formed by the binding of single-stranded oligonucleotides to complementary sequences are the strongest and most specific macromolecular complexes that can be formed. However, the ability to use hybridization probes to distinguish target sequences that differ from each other by as little as a single base (called a single-nucleotide polymorphism) has challenged assay designers for decades.

Discrimination can only be achieved under carefully optimized conditions that control the salt concentration, oligonucleotide concentration, pH and temperature. If, for example the temperature is too high, very few perfectly complementary hybrids are formed, resulting in too little signal for reliable detection. Conversely, if the temperature is too low, mismatched hybrids also form, preventing discrimination from

similar sequences. Dauntingly, small, natural variations create noisy environments that compromise reliability.

This narrow range of reliable conditions is a consequence of thermodynamic constraints. When two single-stranded oligonucleotides hybridize, energy is released by the formation of every base pair. Moreover, the complementary sequences are confined within a rigid double helix