

REVIEW

Dieter Cremer's contribution to the field of theoretical chemistry

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Abstract

This legacy article reviews the contributions of Dieter Cremer (1944-2017) to the field of theoretical chemistry, highlighting his major accomplishments in method development and applied quantum chemistry, which has led to many advances in the field. His work reflects an extraordinary breadth and deep understanding of theory, which is needed to solve complex chemical problems. His passion for science has inspired many colleagues in the past and will do so in the future.

KEYWORDS

local modes, MP6, NESC methods, NMR spectroscopy, puckering coordinates

1 | INTRODUCTION

Dieter Cremer's lifelong scientific goal was the development of quantum chemical methods, programs, and protocols for (1) complementing and/or correcting experimental data; (2) extracting additional information from experiment; (3) providing information about compounds not amenable to experiment; and (4) designing new environmentally friendly materials and chemical reactions. He was always open to explore new territories and off-mainstream paths and to listen to new ideas. His unique and notable achievements have strongly contributed to the development of the field of theoretical/computational chemistry and its recognition as an important partner for experimental chemistry.

In this review, some of the most important techniques and advances pioneered by Dieter Cremer are presented, and it is shown how these advances have affected the current state of our field. At the end of this article, Dieter Cremer's legacy will be summarized as an inspiration to continue in his spirit.

2 | DESCRIPTION OF PUCKERED RING SYSTEMS

The idea of ring puckering was first postulated by Sachse in the late 1800s when describing rigid and flexible forms of six-membered rings.^[1] In the middle of 20th century, the first evidence for ring puckering in five-membered rings was found by Aston et al. during the study of cyclopentane thermochemical data,^[2] supported by other experimental studies, and summarized by Kilpatrick, Pitzer, and Spitzer.^[3] The planar ring form was identified as having a higher energy than the puckered forms, and it was proposed that there is a pseudorotation of the phase of puckering that moves around the ring.^[3] However, the concept of pseudorotation was not instantly accepted by the chemical community. Alternative analyses of spectroscopic data claimed that there was no need to invoke it to explain the existing data.^[4,5] Nevertheless, various groups worked on the development of mathematical procedures defining ring puckering and pseudorotation, as for example Hendrickson,^[6] or Pickett and Strauss.^[7] (For a more comprehensive review, see Cremer and Szabo.^[8]) These attempts to define ring puckering were useful steps along the way but still resulted in approximate descriptions. The important breakthrough was made in 1975 when Cremer and Pople published their landmark paper on the Cremer-Pople puckering coordinates.^[9] This article has received more than 7000 citations to date.

2.1 | Cremer-Pople puckering coordinates

In 1972, Dieter Cremer joined Nobel Laureate John Pople at Carnegie Mellon University as a postdoctoral associate. His first task was to look into the problem of calculating cyclopentane conformations of a specific pucker. Dieter Cremer studied the literature and came up with several solutions, none without flaws. Then, he read Herzberg's vibrational mode analysis of cyclopentane.^[10] He realized that there were exactly $N-3$ out-of-plane vibrations that convert, for example, a pentagon ($N = 5$) into an envelope or twist form. Hence, he concluded that the description of the out-of-plane vibrations with fixed, finite vibrational amplitudes must lead to the envelope and twist conformations of cyclopentane, and that linear combination of these two modes must yield any desired conformation along the pseudorotation path of the molecule. Within weeks he could present to John Pople a unique mathematical solution. John Pople's comment was "This is indeed a splendid solution. If you do a Fourier transform, you can easily generalize these equations and have a description for any N -membered ring."

Besides the important observation that an N -membered planar ring possesses $N-3$ out-of-plane displacements, Cremer and Pople elegantly solved the question of a suitable reference form, which can be used to define degree and type of puckering of a ring molecule by introducing the *mean ring plane*, for example, the planar form being placed into the geometric center and the first ring atom along the positive y -axis. In this way, the out-of-plane deviations of the puckered N -membered ring are measured by the z coordinates of the ring atoms.^[9,11] The $N-3$ puckering coordinates can be split up in pairs of hypercylindrical conformational coordinates $\{q_m, \phi_m\}$ ($m = 2, 3, \dots, N-3$), with q_m describing the puckering amplitude, for example, the amount of puckering and the pseudorotational phase angle ϕ_m describing the type of puckering of puckering mode m .^[9]

The pseudorotational pairs $\{q_m, \phi_m\}$ ($m = 2, 3, \dots, N-3$) are uniquely connected to the z_j coordinates, ($j = 1, 2, \dots, N$) of the ring atoms via^[9]:

$$z_j = \left(\frac{2}{N}\right)^{1/2} \sum_{m=2}^{(N-1)/2} q_m \cos \left[\phi_m + \frac{2\pi m(j-1)}{N} \right] \quad (\text{Nodd}) \quad (1)$$

$$z_j = \left(\frac{2}{N}\right)^{1/2} \sum_{m=2}^{(N-2)/2} q_m \cos \left[\phi_m + \frac{2\pi m(j-1)}{N} \right] + \left(\frac{1}{N}\right)^{1/2} q_{(N/2)} (-1)^{j-1} \quad (\text{Neven}) \quad (2)$$

with the displacement z_j coordinates being normalized according to

$$\sum_{j=1}^N z_j^2 = q_2^2 \quad (3)$$

where $m = 0$ and $m = 1$ correspond to translation and overall rotation of the planar reference ring in the mean plane.^[9,12] The three-membered ring is always planar and does not possess any out-of-plane vibrations. Puckering starts with the four-membered ring ($N-3 = 1$; puckering amplitude q_2 , eg, one out-of-plane vibration leading to *crown puckering*), continues with a pseudorotational cycle for the five-membered ring ($N-3 = 2$; puckering amplitude q_2 and pseudorotation phase angle ϕ_2) as shown in Figure 1A for the sugar ring of deoxyribonucleosides; a globe for the six-membered ring ($N-3 = 3$; puckering amplitudes q_2 and q_3 and pseudorotation phase angle ϕ_2) as shown in Figure 1B for cyclohexane, etc.

Besides being uniquely defined and independent of the ring size or symmetry, the Cremer-Pople ring puckering coordinates offer two major advantages.^[9,12-14] (1) They form the basis for a quantitative analysis of ring conformations and the determination of the conformational energy surface (CES) of a puckered ring in analytical form. Any conformer located on the CES can be described and a physically meaningful pseudorotation path as a function of ϕ_m can be obtained, which is not possible in terms of Cartesian Coordinates. (2) Properties P of a puckered ring, such as energy, dipole moment, charge distribution, frequencies, magnetic properties, etc. can be expressed as a Fourier series of the puckering coordinates. In summary, the Cremer-Pople puckering coordinates can be considered as today's standard tool for the description of ring puckering.

2.2 | Deformation coordinates

In addition to out-of-plane motions, for example, vibrations moving atoms up and down to create puckering, rings can simultaneously perform in-plane motions that initiate in-plane deformations or rearrangements of the ring molecule. However, the connection between these two types of motion was not clear for a long time. Dieter Cremer solved this problem by introducing deformation coordinates for describing intrinsic deformations as well as rearrangements of planar rings in analogy to the puckering coordinates for the out of plane motions.^[15] He partitioned the $(3N-6)$ -dimensional configuration space of an N -membered ring into two subspaces, one in which specific ring puckering and one in which ring deformation processes take place. In view of the fact that ring-puckering can be described in an $(N-3)$ -dimensional subspace, the deformations of a planar N -membered ring should take place in a $(2N-3)$ -dimensional subspace. He introduced a special set of curvilinear deformation coordinates describing the $(2N-3)$ -dimensional deformation space. The deformation coordinates are directly derived from the normal vibrational modes of the N -membered ring and referenced to a regular polygon ("N-gon") of unit length.^[15]

Figure 2A shows as an example the deformation modes for a six-membered ring, for example, the ("6-gon"). There are 4 pairs of deformation coordinates $\{t_n, \tau_n\}$ ($n = 2, 3, \dots, 5$) with the n -th deformation mode changing bond lengths and bond angles of the hexagon in such a way that the impression of a $(6-[n-1])$ -membered planar ring is provided as illustrated in Figure 2B.

With the deformation coordinates for the first time, dynamic Jahn-Teller processes could be described and bond pseudorotation quantitatively discussed.^[16,17] Investigating Jahn-Teller, and Pseudo-Jahn-Teller systems such as cyclopentadienyl cations and their

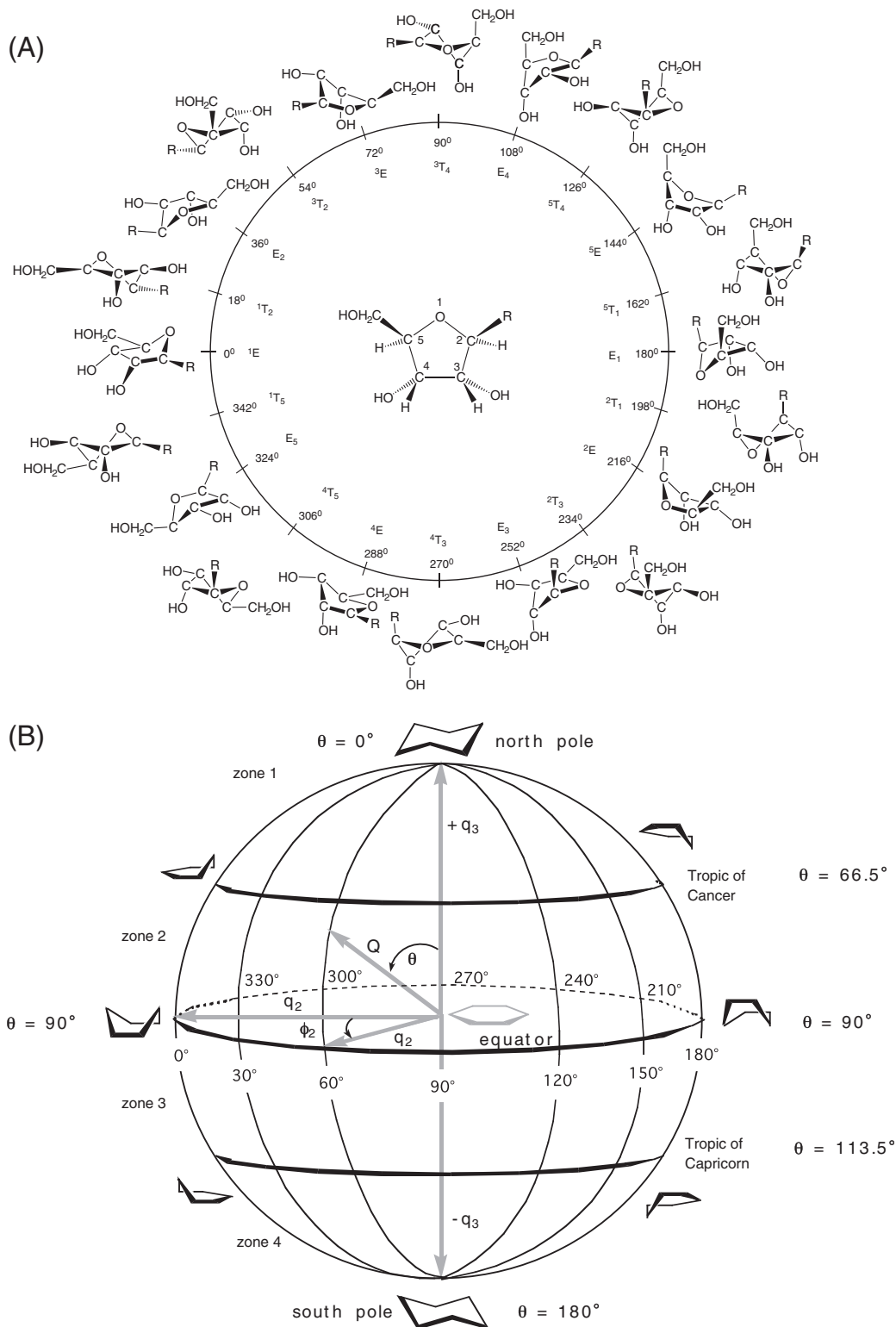


FIGURE 1 A, Pseudorotational cycle ($0^\circ \leq \phi_2 \leq 360^\circ$) of the sugar ring of deoxyribonucleosides, (R represents the nucleic base). Ten envelope (E) and 10 twist (T) conformations are shown at $\phi_2 = (0 + n360)/10$ and $\phi_2 = (18 + n360)/10$ with ($n = 0, 1, 2, \dots, 9$), respectively, for a fixed puckering amplitude q_2 . At the center of the pseudorotation cycle, the planar form with $q_2 = 0 \text{ \AA}$ is located. ϕ_2 values differing by 180° correspond to original and inverted form. B, Conformational globe of cyclohexane. Puckering coordinates q_2, ϕ_2, q_3 that span the globe, as well as some distinct longitudes and latitudes, are shown. The positions of distinct ring forms are shown in steps of 30° along the equator, the tropic of Cancer, and the tropic of Capricorn

penta-halogenated derivatives, Dieter Cremer and his group discovered a new, spectacular molecular process: In a Jahn-Teller unstable ring molecule, the atoms rotate simultaneously, however each with an individual well-defined phase shift around the corners of a highly symmetrical reference ring. This leads to a wave-like shifting of the chemical bonds along the perimeter of the molecule, a process with a very small energy barrier so that it can only be detected using pulsed laser spectroscopy. In some cases, Pseudo-Jahn-Teller driven molecules

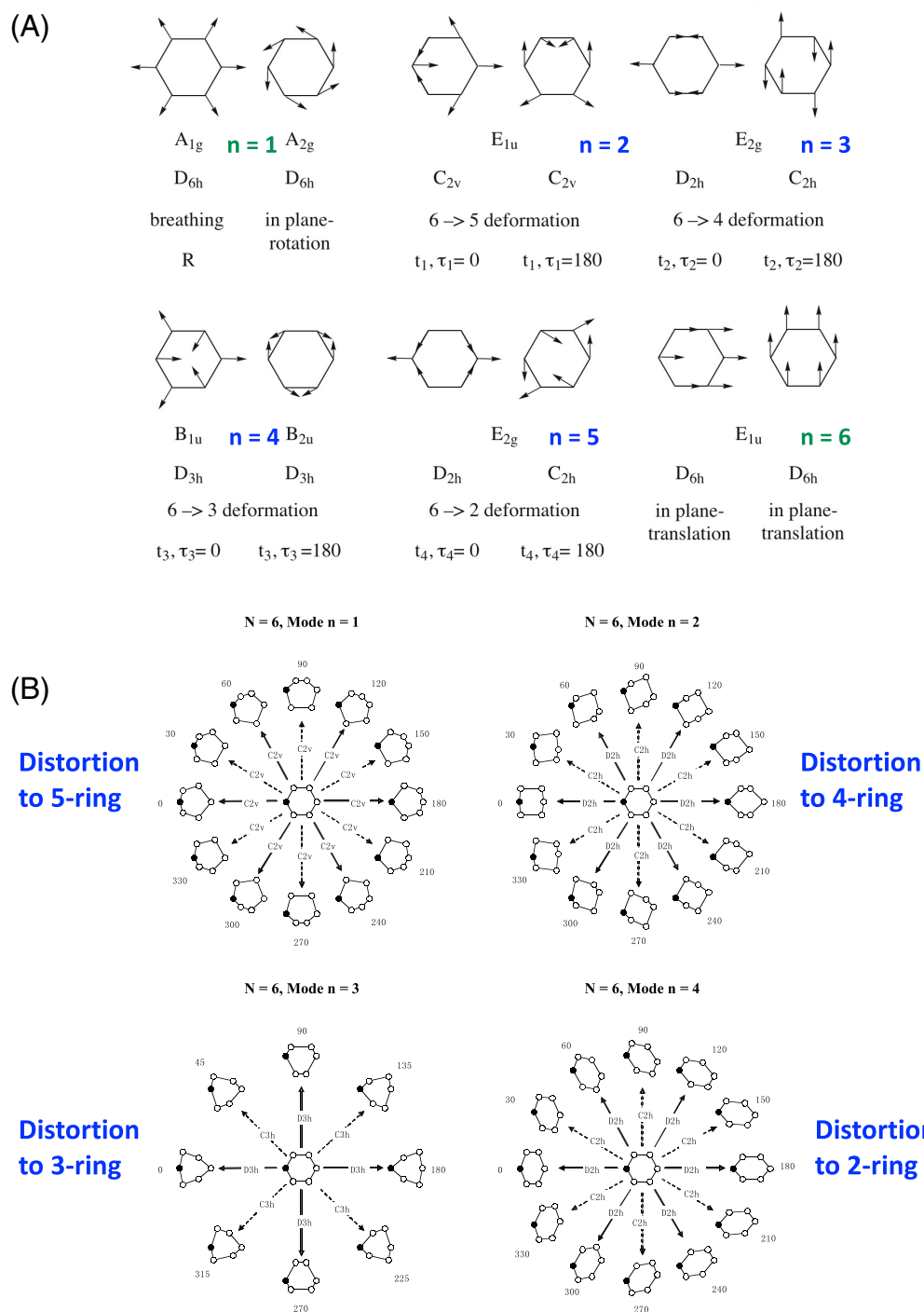


FIGURE 2 A, 12 basic in-plane motions of a “6-gon”; breathing mode and in-plane rotations ($n = 1$ and $n = 6$, green color), 4 pairs of deformation coordinates $\{t_n, \tau_n\}$ ($n = 2, 3, \dots, 5$ blue color). B, Pseudorotational cycles for the “6-gon”

rearrange so rapidly that they do no longer adopt a fixed structure. These molecules without a structure will definitely enter our textbooks in the near future.

Another important outcome of these studies worth mentioning is that the pseudorotational process in these systems could be identified as the interaction of ground and excited states via a vibronic coupling. What Dieter Cremer had not expected turned out to be a big bonus of the deformation analysis: The curvilinear deformation coordinates are an efficient tool shortening a tedious vibronic coupling analysis to just seconds, providing an exact description of Jahn-Teller and pseudo-Jahn-Teller effects.^[16]

In summary, any ring molecule can be exclusively described by puckering and deformation coordinates without using a single bond length, bond angle, or dihedral angle. Dieter Cremer's RING program^[18] offers the calculation of molecules of specified pucker and/or deformation, including analytical gradients and second derivatives for the determination of puckering and deformation force constants and frequencies.

3 | MAGNETIC PROPERTIES

During his graduate studies in Harald Günther's laboratory at the University of Cologne, Dieter Cremer was exposed to Nuclear Magnetic Resonance (NMR) spectroscopy, which shaped his later idea to develop quantum chemical methods and programs for the calculation of magnetic properties in order to (1) complement incomplete experimental data and (2) to use calculated magnetic properties as hypersensitive tools for determining electronic structure features of molecules.

3.1 | NMR chemical shifts

In the early 1990s, Dieter Cremer implemented the Individual Gauge for Localized Orbitals (IGLO) method of Kutzelnigg and Schindler^[19,20] into his COLOGNE quantum chemistry program.^[21] However, the accuracy of the calculated chemical shift values was limited by the model chemistry applied, predominantly Hartree Fock (HF) at that time.^[22] Therefore, he considered Malkin's idea of a sum-over-states density functional perturbation theory (SOS-DFPT) method.^[23] Combining the HF exchange part with a numerically determined correlation part within the framework of the IGLO formalism and adding improved Malkin level shift operators, he obtained excellent results for ¹³C, ¹⁵N, ¹⁹F, and ²⁹Si shift values.^[24,25] Several pending structure problems could be successfully solved with this new method, such as the structure determination of the homotropylium cation,^[26,27] the description of solvated silylium cations,^[28–30] or the verification of an unusually stable carbonyl oxide,^[31,32] just to name a few.

3.2 | Spin-spin coupling constants

In 2002, Dieter Cremer and his group developed the first density functional theory (DFT) program for the routine calculation of NMR spin-spin coupling constants (SSCC) J within the Coupled Perturbed DFT (CPDFT) approach^[33,34] that considers all four Ramsey terms determining the SSCC mechanism, namely the Fermi contact (FC), the spin-dipole (SD), the paramagnetic spin-orbit (PSO), and the diamagnetic spin-orbit (DSO) term.^[35] Many of the calculated J values, which were published before 2000, were flawed by the fact that they considered just the FC term and neglected the other three (more expensive) Ramsey terms, which become important as soon as hetero atoms with electron lone pairs get involved (eg, in the case of NX, OX, FX coupling constants, with X = H, C, N, O, F).^[33]

Dieter Cremer was convinced that it should be possible to get more out of an SSCC calculation than just a number and a sign. Magnetic properties should embed electronic structure information, ready to be decoded. Therefore, he developed a detailed analysis of the four Ramsey terms by dissecting contributions into orbital terms and density terms leading to the J-OC-PSP (Decomposition of J into Orbital Contributions using Orbital Currents and Partial Spin Polarization) analysis.^[36–39] The J-OC-PSP analysis utilizes five decomposition criteria,^[36] spanning the five-dimensional analysis space. Figure 3 shows the three most important of these criteria.

The J-OC-PSP analysis provided for first time the possibility of assessing electronic structure features in a systematic way directly from routinely computed SSCCs, elucidating which orbitals are actively or just passively transferring spin information between the coupling nuclei.^[39,40] Using localized molecular orbitals (LMOs) as suitable descriptive tools, Dieter Cremer studied the contribution of the bond LMOs in dependence of atom electronegativity and bond polarizability, the influence of lone pair LMOs on the coupling mechanism, the passive but nevertheless important role of p -orbitals for spin transport, the description of multiple bonding and p -delocalization by the noncontact terms, or rear lobe interactions of bond LMOs in saturated molecules.^[40,41] J-OC-PSP was successfully applied to assess for the first time in a quantitative way the σ and π

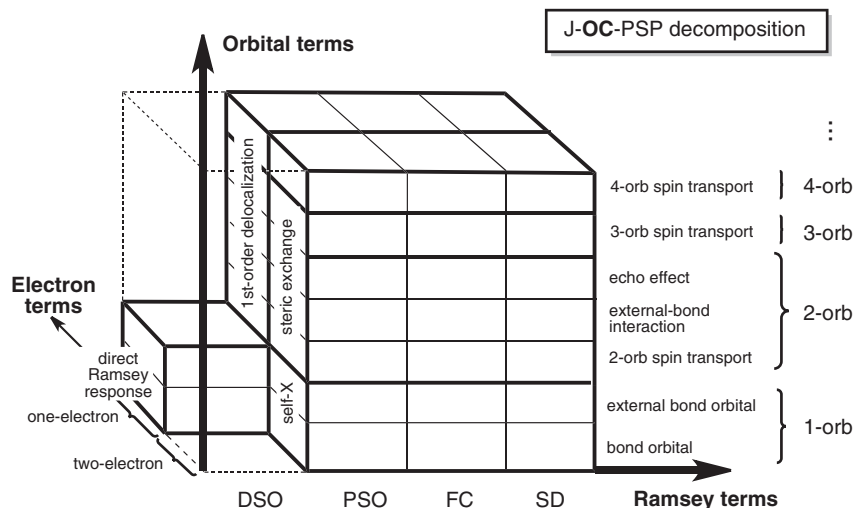


FIGURE 3 J-OC-PSP decomposition criteria I (Ramsey terms), II (orbital terms), and III (electron terms) of the SSCC shown in 3D space. The abbreviation “orb” denotes the term orbital. Reproduced with permission from the Royal Society of Chemistry^[36]

character of CC bonds based on SSCCs, questioning frequently used empirical relationship^[42-44] and to analyze mechanistic features such as through-bond and through-space coupling,^[45] across-H-bond coupling as for example in ubiquitin,^[40] and multi-path coupling.^[46] The first systematic study on H-bonding in a DNA hairpin molecule was carried out using a combination of calculated and measured SSCCs.^[47] These examples clearly show that Dieter Cremer advanced the analysis of SSCCs to a point where the information content of SSCCs can substantially aid to the understanding of the spin-spin coupling mechanism, and thereby increasing the value of SSCCs as structural and conformational descriptors of molecules.

3.3 | Generalized Karplus curves

Based on the Cremer-Pople puckering coordinates, NMR investigations of pseudorotating rings became feasible and a new type of SSCC documentation was established by sweeping through a molecule to calculate all possible SSCCs as well as their Ramsey terms.^[48-50] Dieter Cremer derived the concept of the generalized Karplus relationship for pseudorotating rings by expanding calculated NMR SSCCs J as functions of the puckering coordinates (puckering amplitudes q and pseudorotational phase angles ϕ) of the ring molecule. In this way, geometrical parameters of a pseudorotating ring molecule can be determined with the help of measured and calculated SSCCs.^[48] Via the calculation of so-called J -hypersurfaces conformational and geometrical features of biochemically interesting molecules can be obtained. As an example, the conformational energy surface $V(q, \phi)$ of tetrahydrofuran (THF) is shown in Figure 4A. The maximum value of $V(q, \phi)$ is located at $q = 0$, for example, the planar form. The corresponding $J(q, \phi)$ surface, shown in Figure 4B reveals that $3J(\text{HCCH}, \text{cis})$ coupling is large for the planar and for the envelope forms.^[48]

Another important analysis tool, determination of ring conformations (DORCO) was derived, which determines via the conformational probability function $\rho(\phi)$ the most stable conformations of a pseudorotating ring molecule combining measured and calculated SSCCs.^[49]

In summary, Dieter Cremer and his group created a powerful instrument using magnetic properties, both measured and calculated, as hyper-sensitive tools for determining electronic structure features of molecules not amenable to structural analysis, such as molecules in solution, molecules on surfaces, macromolecules, or drug-receptor complexes.

4 | RELATIVISTIC METHODS

Relativistic corrections are important for any atom with an atomic number larger than 18. As a consequence, more than 80% of the elements of the periodic table require a relativistic quantum chemical description to obtain reliable results, as for example discussed in the pioneering work of Desclaux,^[51] Grant,^[52] and Pyykkö.^[53,54] However, the inclusion of relativistic corrections into a quantum chemical calculation has to be done with care in order to avoid a significant increase of the computational efforts. Dirac-exact relativistic methods, that is, two- or one-component methods, which exactly reproduce the one-electron energies of the original four-component Dirac method have established a standard for reliable relativistic quantum chemical calculations targeting medium- and large-sized molecules.^[55] This work was initiated and facilitated in the late 1990s by Dyall's development of the Normalized Elimination of the Small Component (NESC) method.^[56,57]

Inspired by Dyall's work, Dieter Cremer and Michael Filatov started in 2000 the development of a hierarchy of Dirac-exact relativistic methods systematically approximating the solution of the Dirac equation as accurately as possible. They targeted methods that could easily be implemented in standard quantum chemistry codes at computational costs only slightly higher than those of nonrelativistic methods. In addition, these methods should be able to calculate relativistic energies, first-order, and second-order response properties. Special focus was on the inclusion of relativistic effects at the all-electron level, which is needed for the relativistic calculation of NMR chemical shifts, nuclear spin-spin coupling constants, and other magnetic properties, which depend on the inner (core) electrons.

Cremer and Filatov demonstrated that the regular approximation to the relativistic Hamiltonian provides the best starting point to achieve these goals leading from Zeroth Order Regular Approximation (ZORA) via an Infinite Order Approach (IORA) directly to the unnormalized and non-normalized NESC method, and by increasing the orders of the perturbational description within NESC to the exact solutions of the Dirac equation.^[58] An important milestone was the solution of three major problems typical of the regular approximation: (1) The gauge-dependence problem was solved by inventing methods such as IORAm (IORA with Modified Metric), scaled IORA and finally ZORA-GI and IORA-GI (GI: gauge independent) suppressing gauge-dependence errors.^[59] (2) The difficulties of applying the regular approximation to correlation-corrected wavefunction methods were fixed by a clever matrix formulation of the key equations that opens a route to correlation-corrected wavefunction methods of increasing sophistication.^[60,61] (3) The positioning of the regular approximation within a hierarchy of relativistic methods was solved by showing for the first time the close relationship between the regular approximation and the NESC equations.^[58,62] The NESC-SORA (second-order regular approximation) turned out to achieve a level of accuracy, which easily could beat rival methods such as the Douglas-Kroll approach^[63,64] in fifth order at much lower cost.^[58] A new generally applicable method for relativistic NMR chemical shifts^[65,66] and SSCCs for heavy atoms^[67] was developed, and in this way, the importance of relativistic corrections of the magnetic properties of heavy-atom compounds could be systematically demonstrated for the first time.

In particular, two pending problems that could be solved with the new relativistic NESC methods deserve mentioning: (1) *The mercury story*:^[68] Mercury chalcogenides (HgE; E = O, S, Se, etc.) are described in the literature to possess rather stable bonds with bond dissociation

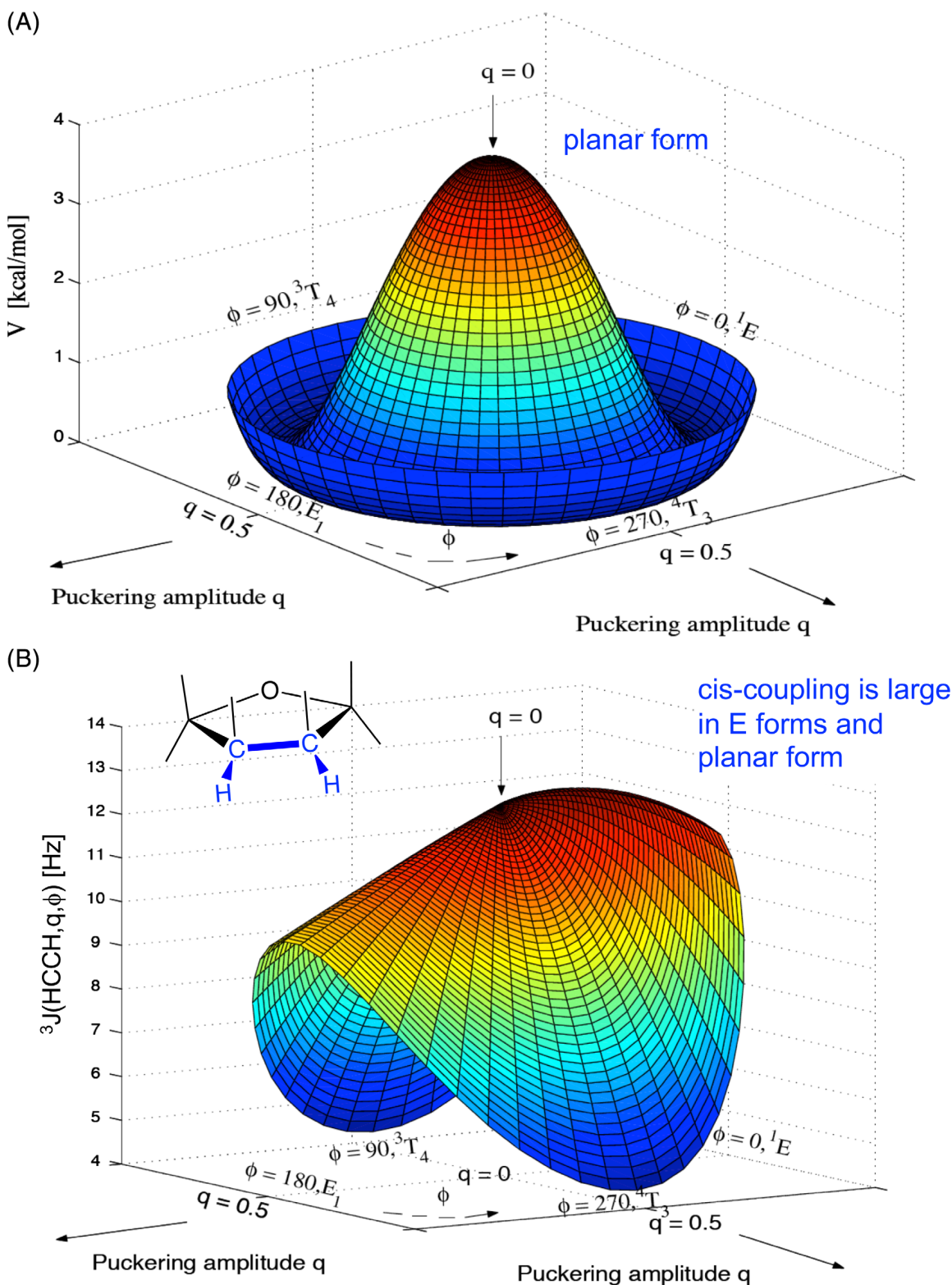


FIGURE 4 A, Perspective drawing of the three-dimensional conformational energy surface $V(q, \phi)$ of tetrahydrofuran (THF). The planar form with $q = 0$ is located at the maximum. T denotes twist forms and E denotes envelope forms. The direction of the radial coordinate q and the angular coordinate ϕ is indicated. B, Perspective drawing of the three-dimensional SSCC surface ${}^3J(\text{HCCH}, q, \phi)$ of THF. The SSCC has a maximum value for the planar form with $q = 0$. The direction of the radial coordinate q and the angular coordinate ϕ is indicated. Reproduced with permission from the International Journal of Molecular Sciences^[48]

energies between 30 and 53 kcal/mol, which is actually difficult to understand in view of the closed shell electron configuration of the Hg atom in its ground state. Based on relativistically corrected many-body perturbation theory and coupled cluster theory, Cremer and Filatov demonstrated that the covalent HgE bond is rather weak (2–7 kcal/mol), the ground state of HgE is a triplet rather than a singlet, and that the experimental bond dissociation energies had been obviously obtained for the dimers Hg_2E_2 (or mixtures of monomers, dimers, and even trimers) rather than

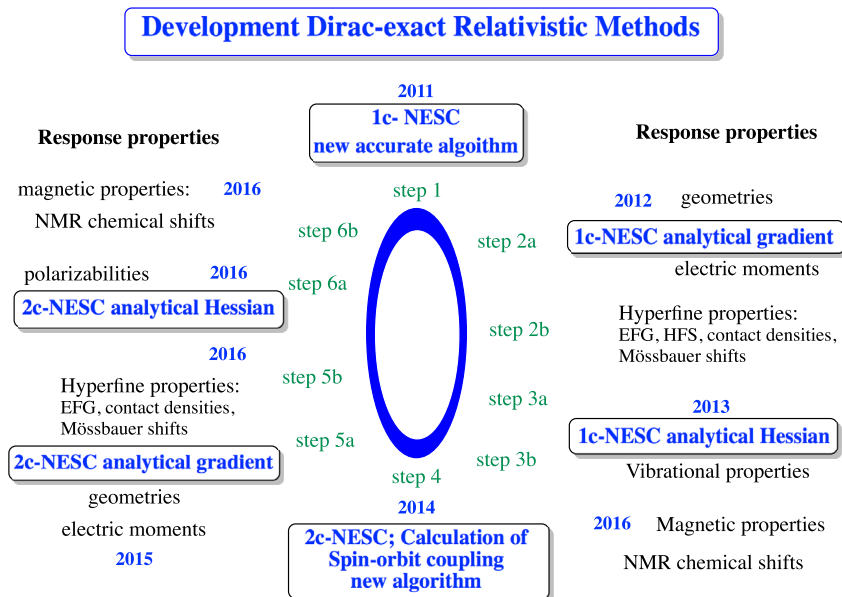


FIGURE 5 Schematic overview of the Dirac-exact relativistic methods developed in the Cremer laboratory during 2011 to 2016

for true monomers. The results for the mercury chalcogenides suggested that all experimental dissociation energies for group 12 chalcogenides should be revised. (2) *The Radonhexafluoride story*.^[69] Based on correlation corrected relativistic NESC calculations Cremer and Filatov proved that radonhexafluoride is a bound species (bond length Rn-F: 2.008 Å, atomization energy: 226.9 kcal/mol). The relativistic effect for the atomization energy is -10.8 kcal/mol rather than $+27.7$ kcal/mol as erroneously predicted based on Dirac-Hartree-Fock calculations,^[70] showing the importance of correlation corrected relativistic calculations.

During that time Kutzelnigg and Liu established the basic requirements for exact two-component relativistic methods, for which the term X2C was coined.^[71–73] As pointed out by Filatov and Dyall, Dyall's 2-component NESC method^[56] fulfills the criteria of an exact X2C method and therefore, can be considered as practical and efficient realization, accomplished in 2007 by introducing a new iterative algorithm for solving the NESC equations.^[74]

Between 2009 and 2017, Dieter Cremer took the NESC program package to the next level of sophistication by adding higher derivatives, new response properties, and spin-orbit coupling (SOC). In 2011, the computational difficulties still accompanying the solution of the NESC equations were finally solved by Zou, Filatov, and Cremer^[75] leading to a generally applicable NESC method that can be used for the routine calculation of first-order response properties^[76,77] (eg, molecular geometries,^[78–80] electric field gradients,^[81] hyperfine structure constants,^[82–84] contact densities, and Mössbauer shifts^[85]) and second-order response properties^[86] (eg, vibrational frequencies,^[86,87] electric polarizabilities,^[86,88] and infrared intensities^[86]). Special features of this new, effective NESC program are (1) the use of IORA as a convenient starting point for an iterative solution of the NESC equations, (2) a finite nucleus model based on a Gaussian charge distribution, and (3) a first-diagonalize-then-contract strategy for the solution of the NESC equations.^[75] Parallel and independently, Gauss and Cheng developed spin-free exact two-component Dirac-exact methods to calculate molecular geometries, vibrational frequencies, and magnetic properties.^[89–91]

Filatov, Zou, and Cremer extended the spin-free one-component NESC method to a two-component method that can be used for the calculation of spin-orbit coupling (SOC) effects, which are often neglected.^[92] However, SOC changes (1) molecular spectra by making spin symmetry-forbidden transitions possible, (2) has an impact on molecular reactions by enabling intersystem crossings, and (3) is relevant for the calculation of dissociation energies and reaction energies in general when heavy atoms with an atomic number $Z > 36$ are involved.^[80] Relativistic methods including SOC provide in general a deeper, more consistent insight into bonding patterns of molecules containing heavy atoms that can be achieved with the use of spin-free relativistic or nonrelativistic methods.^[93] For example, for the series of HgX_2 molecules ($X = \text{F, Cl, Br, I}$), the interplay between SOC and ligand field effects leads to a change of the character of low-lying valence spinors from predominantly σ -type to π -type.^[92] Recently, analytical first derivatives were developed^[94] for the two-component NESC method as well as for the calculation of electric dipole moments and static dipole polarizabilities^[95] and atomic magnetic nuclear shielding constants.^[96]

The Dirac-exact NESC program package in its current form is sketched in Figure 5, reflecting Dieter Cremer's emphasis on developing codes, which are easy to implement and to use, and which provide a broad spectrum of tools for solving pending chemical problems.

5 | POST-SCF METHODS

During his time in the Pople laboratory, Dieter Cremer followed John Pople's efforts to program efficient and affordable post-SCF methods. It was clear that Hartree Fock theory could not provide the desired chemical accuracy because of the missing electron correlation. Pople and his group pioneered the development of an easy to use program package which performs all ab initio calculations in one sequence, for example,

MP6 spaces: Single(S) Double(D) Quadruple (Q) SDQ; Triple (T); Pentuple (P) Hextuple (H)

	SDQ Space for MP5 (7/5)							T Space for MP5 (7/4)									
	SS	SD	DS	DD	DQ	QD	QQ	ST	TS	DT	TD	TT	TQ	QT	pt	pq	hq
MP4	SDQ Space for MP6 (17/12)							T Space for MP6 (33/20)							PH Space for MP6 (5/4)		
S	SSS	SSD	SDS	SDD	SDQ			SST	STS	SDT	STD	STT	STQ				
D	DSS	DSD	DDS	DDD	DDQ	DQD	DQQ	DST	DTS	DDT	DTD	DTT	DTQ	DQT			
Q			QDS	QDD	QDQ	QQD	QQQ		QTS	QDT	QTD	QTT	QTQ	QQT	QPT	QPQ	QHQ
T	TSS	TSD	TDS	TDD	TDQ	TQD	TQQ	TST	TTS	TDT	TTD	TTT	TTQ	TQT	TPT	TPQ	

Of a total of 55 terms, there are 36 unique terms ABC in the MP6 space:

SDQ: 12; T: 20; PH: 4; M^9 terms: QQQ, QQT, TQT

FIGURE 6 Schematic representation of the terms included in the MP6 space; unique MP6 terms as well as terms already included in the MP4 and MP5 terms are given

carrying out post-SCF methods after a routine Hartree-Fock calculation by simply using certain keywords. Pople's major focus was on Møller-Plesset (MP) perturbation theory, which leads to a hierarchy of well-defined and size-extensive methods MP_n (with $n = 2, 3, 4, \dots$).^[97] In addition, the calculation of MP4 energies for medium-sized molecules was still feasible with the computer hardware of the late 1970s. Using an algebraic approach, the Pople group programmed MP2,^[98] MP3,^[99] MP4,^[100] and later MP5^[101] while in competition with the Barlett group in Florida, using a somewhat more formal diagram and linked cluster approach.^[102,103] Over the next years, MP_n methods became the most popular correlation corrected methods in quantum chemistry for calculating dynamic electron correlation effects.^[104]

5.1 | Sixth-order perturbation theory

However, starting in the late 1980s, frequent reports on the oscillatory behavior of MP_n energies and other properties appeared.^[105,106] In the direct comparison with coupled cluster (CC) theory,^[107-109] MP_n proved to be inaccurate, in the direct comparison with density functional theory (DFT),^[110,111] which started to become more and more popular, MP2 proved to be too expensive. Dieter Cremer decided to inspect these deficiencies in more details. The obvious way to proceed was the development and programming of MP6. After MP2 and MP4, MP6 is the next even order method that introduces new correlation effects: connected quadruple excitations (Q), disconnected pentuple excitations (P) and hextuple excitations (H). He concluded that if programmed in an efficient way, MP6 should be still feasible for smaller molecules allowing a systematic investigation of the convergence behavior of the MP_n series (HF = MP1, MP3, MP5 vs MP2, MP4, MP6). Once the convergence behavior of the MP_n series was understood, prediction of full-CI energies should become possible as well as the development of approximate MP6 methods of lower cost. Dieter Cremer was convinced that the analysis of higher order correlation effects could also lead to a more general understanding of the electron correlation problem and to new insights on how to describe multi-reference systems within the framework of a single determinant approach.

Dieter Cremer and his co-worker Zhi He^[112-115] coded all 36 unique MP6 terms summarized in Figure 6 using 57 intermediate arrays and a new cluster operator technique combining Pople's algebraic and Bartlett's diagrammatic approaches to reduce the cost from original order $O(M^{12})$ to $O(M^9)$ with M being the number of basis functions. The TQT, QQQ, and TQQ terms of order (M^9) turned out to be most expensive in an MP6 calculation.^[115] Excluding these terms of higher costs from the MP6 calculation, Cremer and He programmed less costly $MP6(M^8)$ and $MP6(M^7)$ methods scaling with $O(M^8)$ and $O(M^7)$.^[114]

Besides mastering this tremendous programming task, the major achievement of this work has to be seen in the important insights provided. Testing a set of 29 molecules for which full configuration interaction (FCI) results were available, Cremer and He found two typical convergence scenarios for the MP_n energies ($n = 2, 3, 4, 5, 6$) shown in Figure 7: monotonic convergence for systems with well-separated electron pairs (which they called class A) and erratic convergence often coupled with initial oscillations for systems with electron clustering (which they called class B).^[116] As obvious from Figure 7, MP6 adds substantial correlation corrections to type B systems, such as difluoroperoxide (FOOF).^[117] The different convergence behavior of the MP_n series for molecules of classes A and B led to the important conclusion that one should determine first whether a given molecule belongs either to class A or class B and then to constrain the extensive MP6 calculations to molecules of class B. Other highlights of this

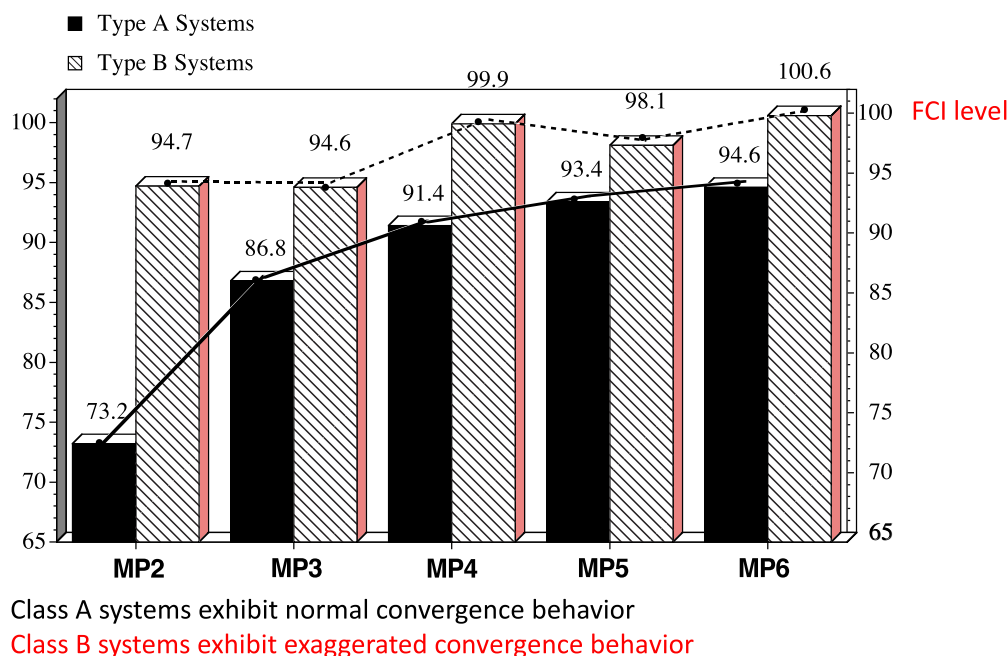


FIGURE 7 MP_n convergence behavior of class A and class B molecules. For a description of class A and class B molecules, see text

work were the development of new extrapolation procedures, such as second-order Feenberg scaling at no additional cost,^[118,119] a cost effective MP6(M⁷) variant for the routine calculations of larger molecules,^[120] and the prediction of reliable FCI correlation energies.^[121]

In 1996, John Pople and Dieter Cremer met in Jerusalem at the 4th World Association of Theoretically Oriented Chemists (WATOC) conference, where Dieter Cremer presented there his work on sixth-order Møller-Plesset perturbation theory. MP6 was at that time and is also today the limit of what can be done by traditional development work (eg, determining each term of a given MP_n method), considering the fact that MP7 has already 141 and MP8 has 583 unique terms. (In these cases, extracting MP_n energies from available higher order CC^[122] or FCI calculations is the only choice.)^[123] After his talk, Dieter Cremer and John Pople met at the dinner table. "I guess you said everything one can say about MP6." This was John Pople's comment and it was the strongest word of appreciation one could ever get from him.

5.2 | Size-extensive QCI methods

Besides Møller-Plesset perturbation theory, configuration interaction (CI) was the other post-SCF method used in the early days of quantum chemistry.^[124–126] In 1973, Pople pointed out that only full-CI (FCI) fulfill the requirements of size-extensivity and size-consistency, which hampered the use of truncated, but affordable CI methods considerably.^[127] Over the years, John Pople and Dieter Cremer saw each other frequently at conferences, and it was at one of these occasions that Dieter Cremer learned about John Pople's newly developed QCI (quadratic configuration interaction) method, which Pople classified as a size-extensive CI method having the nature of a simplified CC method^[128] and being a solid alternative to commonly used size-extensivity corrections of various kind for truncated CI methods.^[129] The QCI approach became very popular, especially, when it entered as basic tool for determining high-order correlation effects the *Gaussian-n* (*Gn*) composite methods.^[130] Dieter Cremer got interested in the QCI approach and the Cremer group provided additional proof for the usefulness of QCI. Gauss and Cremer developed in the years 1988 and 1989 analytical energy gradients of QCISD^[131] and QCISD(T)^[132] for the calculation of QCI response properties,^[133] electric field gradients and nuclear quadrupole coupling constants.^[134] These developments were based on their previous work on the gradients for third- and fourth-order Møller-Plesset perturbation theory.^[135] They further demonstrated that QCI could be used for obtaining suitable reference values when testing the accuracy and reliability of MP_n results for low values of order *n*.^[136]

Despite the success of Pople's new QCI method, criticism was raised with regard to the general usefulness of the QCI approach. Josef Paldus,^[137] Fritz Schaefer,^[138] and others pointed out that (1) QCI did not save much computer time compared to the more complete CC method, and (2) QCI in its extension to triple excitations was no longer size-extensive. This dispute inspired Dieter Cremer and Zhi He to investigate the general concept of QCI using the graphical analysis tools they had developed for MP6.^[139] They proved that QCI in its original form can be converted into a generally defined series of size-extensive methods by deleting certain disconnected terms of the CI equations and including just the connected part of appropriate quadratic correction terms. These QCI_c (c for connected) methods could be extended to triple, quadruple, and higher excitations without losing their size-extensive character.^[140,141] In particular, the QCISDTQc(6)^[136] qualified as a size-extensive method that is exact at the sixth-order perturbation theory and that leads to results which are better than those from CCSD(T), QCISDTc, or CCSDT calculations and close to CCSDTQ and FCI results at lower computational costs. Based on these findings Dieter Cremer suggested that the QCI methods have to be viewed as a series of simplified coupled cluster methods rather than a series of size-extensive CI methods. In 2013, Dieter

Cremer wrote a comprehensive review article about the QCI methods and the scientific dispute between QCI supporters and their opponents, and how his work contributed to solve this dispute.^[142]

5.3 | Spin-projected coupled cluster methods

Unrestricted Hartree-Fock (UHF) theory is a convenient starting point for single-determinant MP theory or CC methods for the description of open-shell molecules.^[143] However, one of the major shortcomings of the UHF method is that the wave function is not an eigenfunction of the spin operator \hat{S}^2 .^[144] Contaminations from higher spin states are mixed into the wave function and may lead to erroneous energies that affect the shape of a potential energy surface determined at the UHF or post-UHF levels of theory. Because of the growing interest of the Cremer group in radicals and singlet biradicals, Dieter Cremer analyzed the usefulness of UHF-CCSD and UHF-CCSD(T) in these cases. He showed that \hat{S}^2 is no longer a reliable indicator for the accuracy of calculated energies and he derived a method to split up \hat{S}^2 into several terms where an energy-related part of \hat{S}^2 was found to be a suitable indicator for the accuracy of calculated UHF-CCSD and UHF-CCSD(T) energies.^[145] Within this project, two new methods were developed, APCCSD-1 and APCCSD(T)-1 which project out of the UHF-CCSD wave function the major contaminations caused by higher spin states using annihilation operators.^[146] The advantage of these new methods is that they improve significantly UHF-CCSD and UHF-CCSD(T) energies at moderate additional cost when describing single bond dissociation or transition states characterized by the breaking/forming of a single bond. The regions, wherein dissociation processes spin decoupling (from a closed shell singlet electron pair to an open-shell singlet electron pair) occurs, could be identified.^[146]

In summary, Dieter Cremer's comprehensive work on the in-depth understanding of post-SCF methods paved the way for new post-SCF methodologies. He made the prognosis that CCSD(T) would become the quantum chemical gold standard and that the days of QCI methods would be counted, which indeed has turned into reality.

5.4 | Density functional methods

By the end of the 1980s, the development of correlation-corrected wave function (WFN) methods had come to a point where the computational limits were reached but complex chemical problems (such as the investigation of complex catalytic reactions, drug-receptor interactions in the human body or the folding of a protein) were waiting to be investigated. In this situation, DFT^[110,111] was introduced into the repertoire of standard quantum chemical methods. The Hohenberg-Kohn theorems^[147] and the Kohn-Sham equations^[148] formed the basis for modern DFT, which had for a long time been extensively used to determine the electronic structure of solids. From a practical point of view even more important was the integration of DFT program codes into standard quantum chemical packages for routine use, where John Pople took the lead. In 1998, the Nobel Prize in Chemistry was awarded to Walter Kohn, one of the founding fathers of DFT and to John Pople, who implemented DFT in computational chemistry. New density functionals leading to improved accuracy were introduced increasing the applicability of DFT to solve chemical problems. This work was connected with the names of Parr, Becke, Perdew, and many others.^[149,150] Quickly, DFT became one of the most popular quantum chemical methods^[151] connected with the fact that it often met the performance of MP2, even MP4 or CCSD(T) at a much lower computational cost.

5.5 | Analysis of correlation effects covered

However, while WFN methods systematically introduce correlation effects in a stepwise manner, DFT covers dynamic electron correlation in an unspecified way, which makes it difficult to predict the outcome of a DFT calculation unless DFT results for a closely related reference system are known. Clearly, a detailed knowledge about the correlation effects covered by the various exchange-correlation (XC) functionals in use was needed to assess its applicability to diverse molecular problems. This was the point where Dieter Cremer entered the DFT scene. He was in particular interested in the question, what does electron correlation actually mean at the DFT level? He decided to analyze electron density distributions and other molecular response properties^[133] to specify the correlation effects covered by the exchange (X) and the correlation (C) functionals of DFT, guided by his experience and knowledge of the coverage of electron correlation effects by post-SCF methods.^[115,132,133,136] The graphical method assessing correlation effects covered by CCSDT-n methods^[152] and the analytical energy derivatives for higher order correlation methods^[131,135,153] developed in the Cremer laboratory formed a unique tool for this purpose.

Following previous work, in which Dieter Cremer analyzed the correlation effects in WFN methods via the difference electron density distribution $\Delta\rho(r) = \rho(\text{method I}) - \rho(\text{method II})$ for a given molecule,^[133] he used the same approach for elucidating the correlation effects covered by DFT, based on the fact that a density-based theory is best analyzed via its density distribution $\rho(r)$, which provides a global impression and is more informative than single values of selected molecular properties such as energy or geometry.^[154] The analysis of $\Delta\rho(r) = \rho(\text{DFT}) - \rho(\text{WFN})$ for a variety of different X functionals revealed for the first time that X functionals contain correlation effects that are actually reminiscent of pair and three-electron correlation effects introduced by MP2 and MP4 in WFT, while hybrid exchange functionals lead to electron densities that often agree well with CCSD(T) densities.^[154]

For example, the difference electron density distribution Becke exchange,^[155] HF, $\Delta\rho(\text{B-only, HF})$ of the CO molecule, shown in Figure 8A strongly resembles the corresponding difference density distribution $\Delta\rho(\text{MP2, HF})$, shown in Figure 8B. Obviously, the Becke exchange functional includes correlation effects covered by MP2. Similar results were found for many other molecules.^[154]

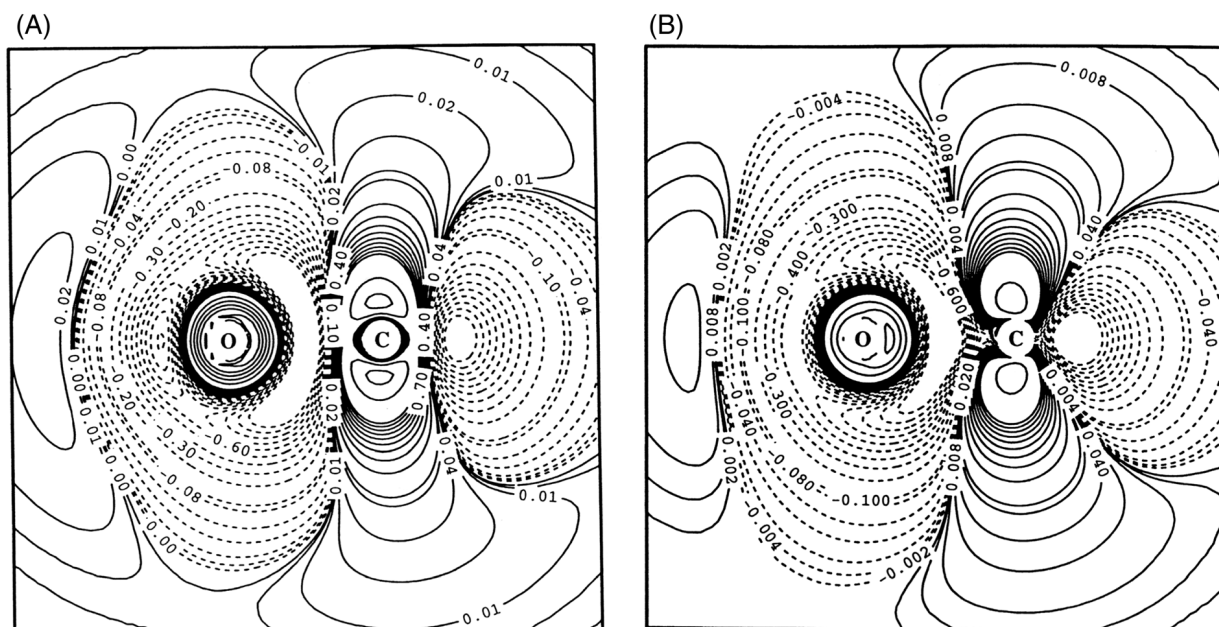


FIGURE 8 A, Contour line diagram of the difference electron density distribution $\Delta\rho(r) = \rho(\text{B-only}) - \rho(\text{HF})$ for the CO molecule calculated with Pople's 6-311+G(3df) basis set^[156–158] at a CO distance of 1.128 Å. B, Corresponding contour line diagram of the difference electron density distribution $\Delta\rho(r) = \rho(\text{MP2}) - \rho(\text{HF})$. Solid (dashed) contour lines are in regions of positive (negative) difference densities. The positions of the C and the O nucleus are indicated. The contour line levels have been multiplied by the scaling factor 0.01 and are given in $e a_0^{-3}$. Reproduced with permission from Taylor & Francis^[154]

Another interesting outcome of this work is that hybrid functionals, in particular, B3LYP,^[159] mimic higher-order pair and pair coupling correlation effects and a fairly large portion of three-electron correlation effects contained in CCSD(T), explaining why B3LYP results are often close to CCSD(T) results.^[154] The analysis of correlation functionals such as LYP^[160] revealed that they change the density distribution generally by contracting density from the van der Waals region to the bond region. They introduce corrections in the electron density distribution that are typical of the coupling between diagonal (2-, 3-, etc.) electron correlation effects included in higher order MPn and CC methods, that is, DFT correlation functionals contain by their construction correlation effects not or only partially covered by low order MPn methods. Overall, Dieter Cremer's in-depth investigations led to the unequivocal evidence that approximate exchange functionals do not only describe exchange-correlation, the purpose they were originally designed for, but also Coulomb correlation effects as found in post-WFN methods. The results of this work were summarized in a comprehensive article,^[161] which has served as a valuable source for DFT users and developers up to date.

5.6 | The role of the self-interaction error

Also, the self-interaction error (SIE) of approximate DFT attracted Dieter Cremer's attention. This error refers simply to the fact that DFT with the approximate functionals in use does not lead to an exact cancellation of self-repulsion and self-exchange for one electron as it should. The remaining difference is the SIE. A correct correlation functional should predict for a one-electron system a zero correlation energy, however, an approximate DFT correlation functional can lead to a finite value and accordingly to a self-interaction error for the correlation functional. This problem had been known and discussed since the early days of DFT,^[162–165] however, a systematic analysis of the SIE, in particular, its consequences was missing. Dieter Cremer speculated that there could be a connection between the SIE and his findings that approximate X functionals cover Coulomb (eg, dynamic) correlation. There was also a frequent discussion by Handy and Cohen,^[166] Becke,^[167] Baerends,^[168] and others that the SIE of approximate DFT exchange was responsible for long-range correlation effects (eg, nondynamic correlation). Therefore, a systematic analysis of the role of the SIE was more than overdue. Dieter Cremer combined his already established difference density tool with a new tool, the analysis of the DFT exchange hole,^[169] which helps to identify the type of correlation effects (eg, dynamic vs nondynamic) covered by a given exchange functional.^[170] In addition, the Cremer laboratory developed a self-consistent field, self-interaction error-free DFT program based on Perdew and Zunger's orbital-dependent self-interaction correction (SIC) formalism,^[171] for further detailed diagnostics of the SIE.^[82]

Dieter Cremer's investigations provided a clear picture of the important role of the SIE, when it adds to the performance of approximate DFT functionals, and when it may lead to erroneous results.^[82,169,172–177] Some of the highlights of this research are summarized in the following. Most important, the Cremer group could demonstrate via the analysis of DFT exchange holes that the SIE mimics indeed both, short-range and long-range correlation.^[82,161,169,172,174] The comparison of the exact HF delocalized exchange hole and the DFT localized exchange hole for the H₂ molecule shown in Figure 9 illustrates the two important roles of the SIE; (1) It compensates the delocalized structure of the SIC-DFT self-exchange hole to reproduce an unstructured, spherically symmetric localized DFT exchange hole, and (2) The SIE part of the exchange hole mimics left-right electron correlation.^[177] This explains the good performance of DFT in cases where HF and even HF-based correlation methods with

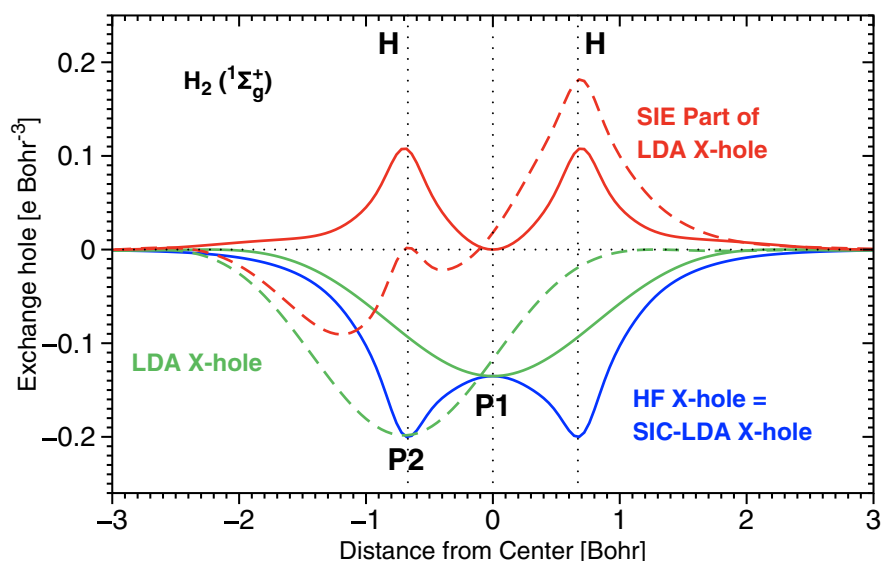


FIGURE 9 One-dimensional cut through the exchange (X)-hole calculated for H_2 in its ($1\Sigma_g^+$) ground state calculated with Dunning's cc-pVTZ basis set^[178,179] at an H-H distance of 0.742 Å along its bond axis; at the HF level (solid blue line), and the LDA level (X-only) for positions P1 (center of H_2 bond, solid green line) and P2 (position of left H nucleus, dashed green line) of the reference electron. The SIE part of the LDA X-hole is given by the red solid line for P1 and the red dashed line for P2. For the purpose of simplifying the comparison, HF orbitals were used in all calculations. Reproduced with permission from Springer^[177]

some low-order correlation effects drastically fail. Hybrid exchange functionals suppress the SIE largely and by this also the long-range correlation effects mimicked by DFT exchange.

On the other hand, exchange functionals leading to a larger SIE and by this to a larger amount of nondynamic and dynamic electron correlation do not necessarily imply a better description of a given electron system.^[161] The analysis of the intra-electronic (self-exchange) and inter-electron (Fermi correlation) part of the exchange hole revealed for the first time that the SIE reflects only features of the electronic structure as they are represented by the true intra-electronic exchange part of the exchange hole via the one-electron density distribution, while the inter-electronic exchange is poorly described by approximate DFT.^[161,169] Therefore, for systems with strong Fermi correlation an exchange functional leading to a larger SIE does not necessarily improve the overall description.^[169]

Another unsolved DFT curiosity was the puzzling fact that in contrast to the often astonishingly good performance of approximate DFT, it is not able to describe the dissociation of the simplest system, namely H_2^+ .^[180,181] In general, standard DFT was found to give a qualitatively incorrect picture for radical cations or odd electron systems, if the unpaired electron is delocalized over two or more atomic centers, and often energy barriers come out far too low.^[182] In particular, H-transfer reactions, important in biochemistry and catalysis seemed to suffer from this problem. However, this was often simply ignored because DFT was the only alternative to investigate systems such as proteins or complex transition metal catalysts. This obvious failure of DFT in these cases had been attributed to the SIE of approximate XC functionals.^[180,183,184]

Dieter Cremer decided to systematically analyze the special role of the SIE for these systems and to investigate if SIC-DFT could lead to a cure. He focused on one-electron bonds^[175] and on three-electron bonds^[176] as well. A comparison of SIC electron density distributions $\rho(\text{SIC-DFT})$ with standard DFT electron density distribution $\rho(\text{DFT})$ for dissociating one-electron and three-electron bonds confirmed that the SIE of the unpaired electron mimics nondynamic correlation effects that have no physical basis, and that these effects increase for an increasing separation distance R , leading to an artificial stabilization and as such to erroneous dissociation energies. Systematically increasing the exact exchange part (eg, by admixture of HF exchange) improves the dissociation curve and for SIC-DFT a qualitatively correct description of the dissociation is obtained.

Based on the analysis of the exact and DFT exchange holes, Dieter Cremer could show in addition for the first time that the DFT description of the dissociating radical cations does not only suffer from the SIE but also from the simplified description of interelectronic exchange.^[175,176] However, the use of SIC-DFT does not cure the interelectronic exchange problem and important long-range correlation effects simulated by the SIE are deleted. Therefore, he concluded that it would make little sense to focus on the development of SIC exchange functionals. SIC-DFT is much too expensive and in addition, suffers from the fact that interelectronic exchange is still wrongly described. Using a hybrid exchange functional should reduce the error, but he suggested as long term alternative to develop new exchange functionals, which are optimized with regard to the electron interaction effects they cover. As recent literature shows, the majority of DFT developers moves in this direction proving that Dieter Cremer's suggestion was right.^[185]

5.7 | DFT for open shell and multireference systems

Parallel to the DFT work, part of the applied research of the Cremer group moved into biochemistry and pharmaceutical chemistry, for example, computer-assisted drug design. DFT had opened this avenue by facilitating the quantum chemical calculation of large molecules relevant for these areas of chemistry. In particular, naturally occurring enediynes and related substances became a target, because of their potential as antibiotic and

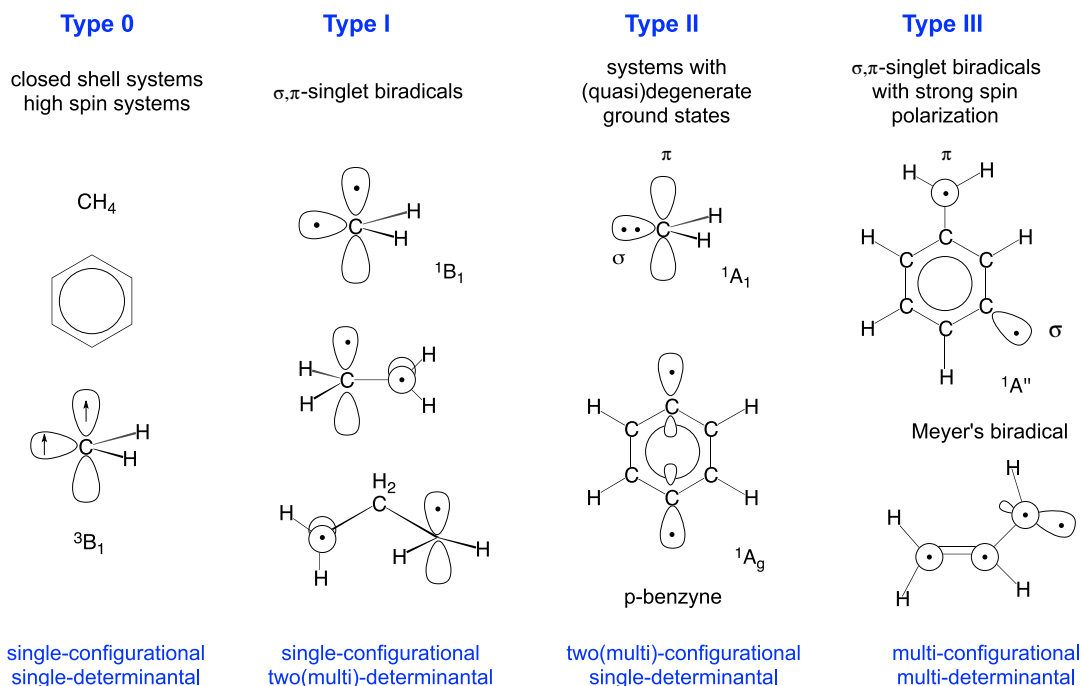


FIGURE 10 Some representative molecules with type-0, type-I, type-II, and type-III character (for a definition of the different types, see text). Electrons are denoted by dots or arrows if the spin has to be indicated. Reproduced with permission from Taylor & Francis^[161]

anti-tumor leads.^[186,187] These compounds dock into the minor groove of DNA where they transform via a Bergman cyclization into an aggressive benzyne biradical,^[188] which subtracts H-atoms from the sugar backbone of DNA leading to apoptosis.^[186] In the mid-1990s, Kraka and Cremer described the transformation of the enediyne part (eg, the warhead) into the biologically active *p*-benzyne singlet biradical at the CC level of the theory.^[189,190] However, the investigation of the complete natural compounds, for example, Calicheamicin or Dynemicin at the CC level, was out of reach and had to wait for the DFT methods.

However, before applying DFT to singlet biradicals, an important question had to be answered: to what extent can DFT describe open-shell systems, in particular, singlet biradicals, or more generally, systems with multi-reference character? Therefore, Dieter Cremer and his group thoroughly tested the performance of unrestricted DFT for the description of the Bergman reaction and in particular the *p*-benzyne biradical.^[191] They could prove that broken-symmetry unrestricted DFT description (BS-DFT) covers static correlation effects needed for the correct treatment of the *p*-benzyne biradical in its low-spin open-shell singlet ground state. They also solved the important question of how to estimate spin contamination in UDFT.^[191,192] \hat{S}^2 in DFT has no longer the same meaning as in wave function theory (WFT), because the Kohn-Sham wave function can only describe one-particle quantities correctly, while the expected value \hat{S}^2 is a two-particle quantity. Hence, an expectation value for \hat{S}^2 that deviates from $S(S + 1)$ does not necessarily indicate spin contamination.^[192] Dieter Cremer introduced the total and on-top pair density as an appropriate test tool, in line with the interpretation given by Perdew, Savin, and Burke.^[193] This work paved the way for the future enediyne research in the Cremer group and beyond^[194-196] and prompted Dieter Cremer to work out a general scheme for the description of open-shell molecules and multireference systems with DFT.

For this purpose, Dieter Cremer and his group followed a three-pronged approach:^[161,173] (1) they identified different types of open shell cases and designed a protocol for their appropriate description at the DFT level; (2) they investigated known DFT methods that extend standard Kohn-Sham theory to multi-reference problems including Restricted open-shell Kohn-Sham (ROKS),^[197] and Restricted Ensemble-referenced Kohn-Sham (REKS) DFT^[198] originally developed by Michael Filatov; and (3) They developed the ROSS-DFT method for open shell for singlet biradicals applying restricted open shell theory,^[199] followed by a generally applicable CAS-DFT method for both closed- and open-shell systems with high-spin or low-spin.^[200,201]

Cremer and Gräfenstein derived a general scheme of classifying multireference systems,^[200,202] which divides multireference systems into four different types, as shown in Figure 10. Type 0 systems include closed-shell molecules and high spin open shell cases. They are represented by a single configuration state function (CSF) and a single Slater determinant and can be described satisfactorily by standard DFT utilizing the available XC functionals. Type I systems are also represented by a single CFS type, which is however constructed from two or more Slater determinants. Therefore, conventional KS-DFT has to be replaced by ROSS-DFT or ROKS-DFT. Type II systems are multireference systems possessing a wave function that has to be constructed from two or more CSFs, each of which can be represented by a single determinant. Because of the two-configurational character of BS-UDFT, this method is suitable for type II systems. Most difficult is the description of type III systems, because they possess a multiconfigurational-multideterminantal wave function. PO (Perturbed orbital)-UDFT^[203] provides qualitatively correct energies but the method of choice is multireference DFT.

The development of a CAS-DFT method is the nontrivial unification of WFT and the DFT world; CAS-SCF operates in terms of configurations while DFT operates in terms of Kohn-Sham orbitals and local quantities. The key-idea of Dieter Cremer's CAS-DFT approach was to treat the exchange part exactly at the CAS-SCF level, while including dynamic correlation via a DFT correlation functional, as originally suggested by Miehlich, Stoll, and Savin^[204] and implemented for GVB-LSD by Elfi Kraka.^[205,206] Dieter Cremer and Jürgen Gräfenstein developed a CAS-DFT program that allows an economic treatment of static and dynamic correlation effects in molecules with multi-reference character and that master the basic CAS-DFT problems: It avoids a double-counting of correlation effects (a key problem in multi-reference DFT),^[207] uses a two-body rather than a one-body correlation functional, is size-consistent and free of any self-interaction errors, and adjusts the correlation part to a changing active space.^[161,173,200–202] This approach has inspired the multi-reference DFT developer community over the past decade.^[185,208,209]

In summary, Dieter Cremer's research on DFT provided a comprehensive overview of what one can expect from approximate DFT functionals and what not; how DFT calculations should be applied in an educated manner and how they can be improved. He always told his students and co-workers that DFT is a powerful tool, in particular for the investigation of large systems, however it cannot be used as a black box, results always have to be checked for a smaller test set against the CCSD(T) gold standard, which has always been a golden rule in his group.

6 | ELECTRON DENSITY PROPERTIES

In the early 1980s, Dieter Cremer visited Richard Bader's laboratory at the McMaster University in Hamilton, Ontario, where he first came in contact with Bader's seminal work on the topological analysis of the molecular electron density $\rho(\mathbf{r})$.^[210,211] Cremer and Bader had long discussions about the fact that although $\rho(\mathbf{r})$ is a measurable quantity that constitutes matter and that according to Hohenberg-Kohn^[147] determines all ground state properties of a molecule, the chemical community had not taken much notice of $\rho(\mathbf{r})$. The main reason was obviously that apart from difference density maps $\Delta\rho(\mathbf{r}) = \rho(\text{molecule}) - \rho(\text{promolecule})$, which depend on an artificial promolecular density, the appropriate tools had been missing to unravel finer details of $\rho(\mathbf{r})$ such as the location of lone pairs or bonding features. Bader provided for the first time these tools via the first derivative of $\rho(\mathbf{r})$, the gradient vector field $\nabla\rho(\mathbf{r})$ disclosing the topological network of bonds between the atoms in a molecule and separating the molecular space into atomic subspaces, and the second derivative of $\rho(\mathbf{r})$, the Laplacian $\nabla^2\rho(\mathbf{r})$ disclosing local concentration/depletion of charge. This formed the basis for Bader's Quantum Theory of Atoms in Molecules (QTAIM),^[210] which promised to provide a physical framework for commonly used chemical models and concepts.^[211] Although founded on a solid quantum mechanical basis, many colleagues met this fundamentally new approach with skepticism and resistance. However, Dieter Cremer saw a big potential in using Bader's new theory as an instrument for understanding and predicting chemistry, and to retrieve key physical information about the structure, bonding, and reactivity. Back home, he started to translate the molecular orbital language into the $\rho(\mathbf{r})$ language.^[212] He derived a $\rho(\mathbf{r})$ based description of hyperconjugation^[213] and aromaticity^[214] followed by a comprehensive study of three-membered rings visualizing bent bonds, ring strain, and surface delocalization with the topological analysis of $\rho(\mathbf{r})$,^[215,216] just to name a few.

6.1 | Cremer-Kraka criterion

An important milestone was the derivation of a necessary and sufficient condition for covalent bonding based on the topological analysis of $\rho(\mathbf{r})$, the *Cremer-Kraka criterion*, which is used today throughout the chemistry community.^[212,217–220] Bond formation is associated with a gain in molecular energy. This gain is a result of a complex interplay of changes in the potential and kinetic energy.^[221] Therefore, a focus on just the Laplacian describing local concentration or depletion of $\rho(\mathbf{r})$, or a bond discussion based on the electrostatic potential $V(\mathbf{r})$ ^[222] displaying electrostatic interactions lead only to an incomplete picture. According to the *Cremer-Kraka criterion*, a covalent bond between two atoms A and B is defined by (1) The existence of a zero-flux surface and bond critical point \mathbf{r}_b between the atoms in question (*necessary condition*) and (2) A negative and thereby stabilizing local energy density $H_{\mathbf{r}_b}$ (*sufficient condition*). $H_{\mathbf{r}_b}$ will be close to zero or positive if the interaction between A and B is non-covalent, that is, electrostatic or of dispersion type. Successful applications stretch over a wide range including the description of bonds between electronegative atoms, such as F–F or O–O, which according to difference density maps were labeled as noncovalent,^[217,218] nonclassical three-center-four-electron bonding,^[223] the quantitative characterization of hydrogen bonding, which can be either covalent or electrostatic in nature, or a mixture of both,^[224–226] or the characterization of weak chemical interactions in combination with vibrational spectroscopy (see, below).

6.2 | Description of helium compounds

In addition to translating Bader's theory into the language of a chemist, Dieter Cremer also explored its predictive power. One prominent example is Dieter Cremer's prediction of helium compounds, first strongly criticized but proved and accepted approximately 16 years later. In collaboration with Gernot Frenking, Marburg, he investigated under which conditions He, Ne, or Ar compounds may exist using the topological analysis of $\rho(\mathbf{r})$ as one of the key tools. A series of interesting results emerged. (1) Helium can form strong chemical bonds in ions such as HeCCH^+ and may even be bound in the ground state of a neutral molecule. (2) The analysis of the electronic structure of He compounds suggests a donor-acceptor model, which allows to predict if a molecule containing helium might exist.^[227,228] (3) The theoretical results predicted that HeBeO , NeBeO , and ArBeO should be stable toward dissociation of the noble-gas atom.^[229] (4) Covalent He bonding was predicted for first-row diatomic cations HeX^{m+}

($X = \text{Li-Ne}$, $n = 1,2$),^[230] covalent Ne and Ar bonding in first-row diatomic cations NeX^+ and ArX^+ ($X = \text{Li-Ne}$)^[231] and other light noble gas compounds.^[228,232] These results inspired other theoretical work^[233] and most important the experimentalists. Indeed some of the predicted compounds such as Na_2HeO , Na_2HeO were recently experimentally confirmed.^[234]

In summary, Dieter Cremer's work was instrumental to convince the chemistry community that Bader's QTAIM approach is a powerful tool for the analysis of molecular structure, bonding, and reactivity. QTAIM is now routinely used and has inspired the development of new tools, such as the electron localization functions (ELF) first advocated by Fuster and Silvi,^[235,236] and initiated new conceptual discussions about the link between DFT and the electron density $\rho(\mathbf{r})$.^[237]

7 | LOCAL VIBRATIONAL MODES

In the early 1990s, Dieter Cremer started a collaboration with Wolfram Sander, Bochum, a matrix-isolation specialist who focused during that time on the isolation of unstable species and their identification via IR-spectra taken in cryogenic matrices. They both had a common interest in arynes. These unstable compounds had already enjoyed a special status in mechanistic and preparative organic chemistry for a long time,^[188] however new attention was added from the discovery that derivatives of *p*-dehydrobenzene play an important role in the mechanism of action of the enediyne anticancer agents^[186] as discussed above. Being well equipped with analytical derivatives for wavefunction as well as DFT methods, Dieter Cremer was the ideal partner for Wolfram Sander, complementing and confirming the experimental IR-spectra by comparison with the calculated ones, and providing additional information about the structure and electronic properties. This fruitful collaboration led to a series of important discoveries, ranging from the first identification of meta-benzyne^[238,239] and related derivatives,^[240-242] para-benzyne,^[243] dimesityldioxirane,^[244,245] propinal O-oxide,^[32,246] and strained systems such as 1,3-bridged cyclopropenes.^[247,248]

Next, Dieter Cremer wanted to find out if one could do more with IR spectroscopy than just using it as an analytical tool. Detailed information on the electronic structure of a molecule and its chemical bonds is encoded in the molecular normal vibrational modes. He was sure that with the increasing number of available high precision measured and calculated spectra, vibrational spectroscopy could become an excellent tool for encoding the electronic structure of a molecule, and for providing a new measure bond strength. However, there was one big obstacle that had to be overcome before using vibrational properties as bond strength indicators. Normal vibrational modes are generally delocalized over the molecule caused by electronic and mass-coupling.^[249] Therefore, functional group frequencies for ketones, aldehydes, alkenes, alkanes, alcohols, etc. are always contaminated by coupling with other modes, and as such are far from providing any quantitative measure of the bond strength. Accurate bond strength descriptors are only obtained when referring to localized rather than delocalized vibrational modes. Spectroscopists had been searching since decades for these local vibrational modes without much success.^[250-252] Most of this work had led to information on local stretching modes in special cases such as the CH or NH bonds without any possibility of generalization. For example, McKean solved the problem of measuring local mode frequencies in the case of CH stretching modes by exploiting the dependence of the vibrational frequency on the reduced masses. He synthesized isotopomers of a given molecule, in which all CH bonds except the target bond were replaced by CD bonds.^[253] Henry demonstrated that the higher overtones of an XH stretching mode reveal increasingly local mode character.^[254]

In 1998, the physical basis for deriving local vibrational modes directly from normal vibrational modes was presented by Konkoli and Cremer.^[255-259] They made use of a mass-decoupled analog of the Wilson equation of vibrational spectroscopy^[249] to eliminate the electronic and mass coupling between normal vibrational modes, leading to local modes, associated local mode frequencies, and force constants that are free from any mode-mode coupling. These modes can be defined for any internal coordinate or coordinates describing molecular fragments, and they can be based on either calculated or experimentally determined vibrational frequencies. The local mode frequencies proved to be the theoretical counterparts of McKean's isolated CH stretching modes,^[260] and, even more important, the local stretching force constants turned out as a direct measure of the intrinsic strength of a chemical bond spectroscopists were looking for since decades.^[261] Contrary to normal mode force constants, local mode force constants are independent of the choice of the coordinates to describe the molecule in question and are independent on the masses of the atoms involved, therefore they directly reflect the electronic structure properties. A general Badger-type relationship was derived leading to a bond strength order BSO $n(\text{AB})$ for any covalent or weak chemical interaction based on the local mode frequencies $k^q(\text{AB})$.^[262] The indisputable proof of the failure of the commonly used bond dissociation energies (BDE)s as an intrinsic bond strength measure was delivered. BDEs contain both geometry relaxation and electron density reorganization of the molecular fragments upon dissociation.^[261,263] Therefore, it seemed that the Konkoli-Cremer local modes could become the most useful bond strength descriptors ever invented.

However, there was one important proof missing, which first slowed down the success local vibrational mode concept, namely the proof that each set of normal (delocalized) vibrational modes of a molecule is linked to just one set of local vibrational modes, and that these modes are the Konkoli-Cremer local vibrational modes. This proof was published in 2012 in a landmark paper.^[264] An adiabatic connection scheme (ACS) relates the local vibrational modes with the normal vibrational modes by slowly switching on the mass-coupling, and it provides a unique decomposition of each normal mode into local mode contributions. In this way, the coupling mechanism between normal vibrational modes could be quantitatively explored for the first time.

For example, the local H-bond stretching frequency of the water dimer is 520 cm^{-1} compared to a normal mode stretching frequency of just 143 cm^{-1} . The ACS between local and normal vibrational modes reveals that this lowering is due to mass coupling, a change in the anharmonicity,

TABLE 1 Local mode analysis and chemical bonding

Topic	References
<i>Covalent bonding</i>	
The strongest bond in chemistry	Ref. [273]
Long carbon-carbon bonds	Ref. [274]
Carbon-halogen bonds	Ref. [275–277]
Bonding in the C ₂ molecule	Ref. [272]
<i>Weak chemical interactions</i>	
Hydrogen bonding	Ref. [224,265,278–282]
Halogen bonding	Ref. [223,283,284]
Pnicogen bonding	Ref. [285–287]
Chalcogen bonding	Ref. [288,289]
BH... π Interaction	Ref. [290,291]
<i>New electronic parameters/rules</i>	
Aromaticity index	Ref. [292–294]
Generalized Tolman parameter	Ref. [295–297]
Generalized badger rule	Ref. [262,263]
Shorter but weaker bonds	Ref. [298,299]

and coupling with the local HOH bending modes. The local mode stretching force constant reflects the strength of the H-bond energy of 5 kcal/mol, whereas the normal mode stretching force constant and frequency lead to an erroneous underestimation of the H-bond strength, which could not be explained in the past.^[265] Dieter Cremer demonstrated that the so-called *Compliance Constants*, for example, the diagonal elements of the inverse normal mode force constant matrix in internal coordinate are nothing else but the reciprocals of the Konkoli-Cremer local mode force constants. When spectroscopists realized that the normal mode force constants are coordinate dependent (ie, change with the choice of internal coordinates) and reflect the coupling between vibrational modes Decius^[251,266] and others^[250,267] suggested to use the inverse of the force constant matrix, because the inverse force constants are invariant under coordinate transformations and they may represent meaningful molecular parameters. Later it was shown that bond compliance constants provide some measure of the bond strength, which is not contaminated by contributions from other bonds,^[268–270] however without presenting any physical rationale. Dieter Cremer's work created the important link relating the compliance constants to the physically based local vibrational modes, again showing that the Konkoli-Cremer local mode force constants are unique and currently the most useful bond strength descriptor.

The addition of local mode intensities,^[271] and the definite proof that local mode force constants reflect the intrinsic bond strength^[272] completed the Konkoli-Cremer local vibrational mode analysis to be used as a powerful tool for the investigation of both covalent and noncovalent interactions in molecules and molecular complexes, and for the derivation of new electronic parameters, as summarized in Table 1. Some highlights: (1) The intrinsic bond strength of C₂ in its $1\Sigma_g^+$ ground state could be determined by its local stretching force constant. In comparison with the local CC stretching force constants obtained for ethane, ethene, and acetylene, an intrinsic bond strength halfway between that of a double bond and a triple bond was derived. These results, based on both measured and calculated frequency data refute the verbose discussion of a CC quadruple bond.^[272] (2) The modeling of liquid water with 50-mers and 1000-mers using both quantum chemistry and molecular dynamics simulations at different temperatures led to a set of interesting results. The local mode analysis revealed that there are 36 hydrogen bonds in water clusters of different strength. In warm water, the weaker H-bonds with predominantly electrostatic contributions are broken, and smaller water clusters with strong H-bonding arrangements remain that accelerate the nucleation process leading to the hexagonal lattice of solid ice. Therefore, warm water freezes faster than cold water in which the transformation from randomly arranged water clusters costs time and energy.^[278] This effect known in the literature as the Mpemba effect according to its first discovery by Mpemba,^[300] could not be explained so far. (3) For the first time, nonclassical hydrogen-bonding involving a BH... π interaction was described utilizing both quantum chemical predictions and the experimental realization. According to the *Cremer-Kraka criterion*, this interaction is electrostatic in nature and the local BH... π stretching force constant is as large as the H-bond stretching force constant in the water dimer.^[290,291] (4) The local mode analysis revealed that the Tolman electronic parameter (TEP)^[301] commonly used to indirectly characterize the metal-ligand bond does not generally correlate with the intrinsic strength of the metal-ligand bond as assumed so far. A new electronic parameter was introduced that is directly based on the metal-ligand local stretching force constant, the metal-ligand electronic parameter (MLEP), and successfully tested for 181 nickel complexes.^[295–297] This discovery will open new avenues for catalyst design.

Future application possibilities are numerous, including for example the development of molecular mechanics force field parameters based on local mode force constants and the derivation of effective bond charges from local mode intensities, which are no longer contaminated by mass- or mode-coupling.

8 | UNIFIED REACTION VALLEY APPROACH

In their seminal paper, Miller, Handy, and Adams^[302] introduced in 1980, a classical *Reaction Path Hamiltonian* (RPH) for a reacting molecular system (eg, the reaction complex RC). In the same year, Kato and Morokuma introduced a simplified theoretical model being defined in terms of a reaction path (RP) and the normal coordinates perpendicular to the motion along the path.^[303] In the RPH approach, the (3N-6)-dimensional configuration space of an RC with N atoms is partitioned into the one-dimensional reaction coordinate s (describing the translational motion along a reaction path usually the intrinsic reaction coordinate [IRC] path of Fukui^[304]) and the (3N-7)-dimensional reaction valley being spanned the (3N-7) generalized normal vibrational modes (describing the vibrational motions perpendicular to the reaction path). In this way, the RPH forms the basis for the description of a reacting system via vibrational spectroscopy, with the coupling elements $B_{\mu s(s)}$ between translational and vibrational motions, and the coupling elements $B_{\mu\nu(s)}$ between the vibrational modes themselves playing as key features for the reaction dynamics and mechanism.^[305-307]

The main focus of the RPH was and still is to use it as a tool for the calculation of the dynamics of a chemical reaction, in particular, the calculation of rate constants and tunneling coefficients,^[308,309] or as a valuable resource for laser spectroscopists working in the field of vibrationally driven reactions, which includes both enhancement of reaction rates, manipulation of energy disposal, and promotion of a certain product channel by mode-selective excitation.^[305-307,310-312] However, the depth of mechanistic information provided by the RPH was not fully exploited in a systematic way, until Elfi Kraka and Dieter Cremer started to transform the RPH approach into an advanced mechanistic tool, the Unified Reaction Valley Approach (URVA).^[305,313-315]

The reaction path is a curved line $\tilde{\mathbf{x}}(s)$ where the 3N-dimensional vectors is composed of mass-weighted Cartesian coordinates $\tilde{x}_i(s)$ (the tilde indicates mass-weighting) and the parameter s is the arc length of the reaction path according to^[302,316]

$$ds^2 = d\mathbf{x}^\dagger \mathbf{M} d\mathbf{x} = d\tilde{\mathbf{x}}^\dagger d\tilde{\mathbf{x}} \quad (4)$$

with \mathbf{M} being the diagonal matrix of nuclear masses.

It can be described at each path point s by its direction and curvature. The reaction path direction is given by the unit vector $\boldsymbol{\eta}(s)$:^[314,316]

$$\boldsymbol{\eta}(s) = \frac{d\tilde{\mathbf{x}}(s)}{ds} = \frac{\tilde{\mathbf{g}}(\tilde{\mathbf{x}}(s))}{c(s)} \quad (5)$$

where the derivative of the mass-weighted reaction coordinate $\tilde{\mathbf{x}}(s)$ with regard to s is the normalized mass-weighted gradient vector $\tilde{\mathbf{g}}(s)/c(s)$ with the normalization constant $c(s)$ being equal to the length $\|\tilde{\mathbf{g}}(s)\|$ of the gradient vector.

The curvature vector $\boldsymbol{\kappa}(s)$ is given by^[314,316]

$$\boldsymbol{\kappa}(s) = \frac{d^2\tilde{\mathbf{x}}(s)}{ds^2} = \frac{d\boldsymbol{\eta}(s)}{ds} = -\frac{1}{\|\tilde{\mathbf{g}}(s)\|} \left(\tilde{\mathbf{f}}^\times(s)\boldsymbol{\eta}(s) - \left[\boldsymbol{\eta}(s)^\dagger \tilde{\mathbf{f}}^\times(s)\boldsymbol{\eta}(s) \right] \boldsymbol{\eta}(s) \right). \quad (6)$$

Matrix $\tilde{\mathbf{f}}^\times(s)$ is the mass-weighted force constants matrix expressed in Cartesian coordinates. All vibrational properties have to be expressed with the help of mass-weighted generalized normal vibrational modes $\tilde{\mathbf{e}}^\beta(s)$ defined in the 3N-7 dimensional subspace.^[316]

The curvature coupling coefficients $B_{\mu s(s)}$ are related to the curvature vector by Equation (7):

$$B_{\mu s(s)} = \boldsymbol{\kappa}(s)^\dagger \tilde{\mathbf{e}}_\mu^\beta(s) \quad (7)$$

and the scalar curvature $\kappa(s) = \|\boldsymbol{\kappa}(s)\|$ is given by^[302]

$$\kappa(s) = \left[\sum_{\mu}^{3N-7} B_{\mu s}^2(s) \right]^{1/2}. \quad (8)$$

Any electronic structure change leads to a change in the normal vibrational modes of the RC, and this in turn leads to a change in the coupling with the RC along the path as reflected by the coupling coefficients $B_{\mu s(s)}$. Hence, exploration of the scalar reaction path curvature $\kappa(s)$ (as defined in Equation (8)) along s detects the locations on the reaction path where the chemical changes of the RC take place. Each chemical event (eg, bond breakage/formation, rehybridization, etc.) corresponds to a local curvature maximum flanked by two curvature minima, for example, locations with minimal change of the RC, which often can be classified as "Hidden Intermediates."^[317,318] Therefore, Kraka and Cremer^[313,317] defined a reaction phase as the reaction path region from one curvature minimum to the next, characterized by a curvature maximum. Different chemical reactions possess different curvature patterns with a different number of reaction phases, which can be used as their *fingerprints*.

Further insight into the mechanism requires a decomposition of the reaction path curvature. In the original RPH of Miller, Handy, and Adams, the decomposition is done in terms of the coupling coefficients $B_{\mu s(s)}$. However, for the mechanistic analysis, the coupling coefficients $B_{\mu s(s)}$ are of limited use because they refer to delocalized vibrational normal modes. Therefore, the first milestone of the URVA analysis was to introduce the curvature decomposition into local curvature coupling coefficients $A_{n s}$ based on local vibrational modes that are associated with the internal coordinates $q_{n(s)}$ used to describe the RC.^[314] In this way, each curvature peak can be associated with a particular chemical event. Often, only a few vibrational modes at a given path position s contribute to the curving of the reaction path, which makes the analysis of larger chemical reactions feasible.^[80,314,319-326] The second important milestone was the improvement of the path following procedure by Hratchian and Kraka,^[327] which allows to follow a chemical reaction far into the entrance and exit channel, where often decisive events happen. A typical example is the Diels-Alder reaction between 1,3-butadiene and ethylene, shown in Figure 11. According to the URVA analysis,^[322,328] the important events preparing

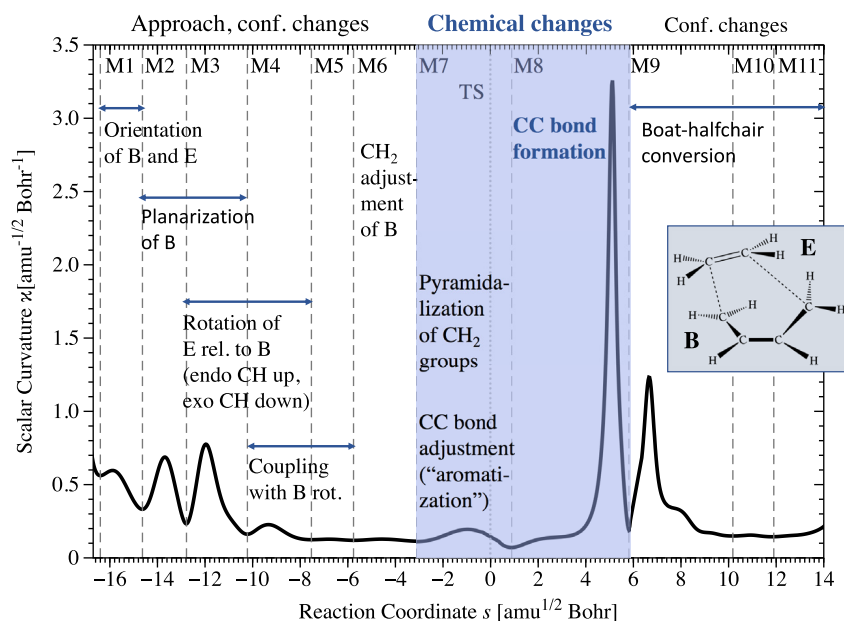


FIGURE 11 Curvature diagram of the Diels-Alder reaction between butadiene and ethylene. The colored region from -3.1 to 5.9 seconds-units is the region of chemical changes. The transition state TS is located at $s = 0$ $\text{amu}^{1/2}$ Bohr. Reproduced with permission from the American Chemical Society^[328]

the reactants for the cycloaddition occur already in the prechemical phases. A first, smaller charge transfer to the dienophile facilitates the rotation of gauche butadiene into its *cis* form. The actual chemical processes are initiated by a second larger charge transfer to the dienophile that facilitates pyramidalization of the reacting carbon centers, bond equalization, and biradicaloid formation of the reactants. The new CC bond formation occurs after the transition state followed by the pseudorotation of the boat form into the half-chair of cyclohexene. Noteworthy is that the transition state (TS) does not play an essential role (eg, there is no curvature at the TS), questioning the general belief that chemically important changes occur always at the TS.

URVA is not restricted to the IRC. It can be applied to any representative path. For example, in the case of barrier-less reactions without TS for which an IRC does not exist, a representative path based on Newton trajectories can be used.^[329] This led to the surprising result that barrier-less reactions such as the chelotropic reaction between methylene and ethene^[318] or the spontaneous cycloaddition between vinylidene and acetylene reaction often possess a complex reaction mechanism.^[330]

The next important milestone leading to a major breakthrough for the analysis of homogeneous catalysis reaction was the development and programming of the direct decomposition of the reaction path curvature into internal coordinate components.^[326,328,331] In this way, the reaction path analysis is no longer sensitive to path instabilities frequently encountered in reactions involving transition metals.

The URVA study of a multitude of catalyzed reactions in comparison with their noncatalyzed counterparts led to a number of interesting mechanistic insights: (1) nearly all chemical reactions are initiated according to the *Charge-transfer/Charge-polarization principle*: in a collision of the reactants, charge is transferred from one reactant to an anti-bonding orbital of the other, which leads to both labilization and charge-polarization of the second reactant that, as an acting partner with radicaloid character, that drives the reaction. (2) The simplest form of catalysis is the *Electrostatically-driven Catalysis*: Mechanistic features of the noncatalyzed reaction are enhanced by the presence of Lewis acids/Lewis bases, polar solvents, solid surfaces, etc. However, the lowering of the energy barrier of the catalyzed reaction is often limited. (3) The *Coordination-sphere-driven Catalysis* is typical of transition metal complexes that catalyze a chemical reaction by extending the coordination sphere of the transition metal to facilitate a specific charge-transfer/charge-polarization effect. (4) The *Space-confinement-driven Catalysis* requires that the catalyst generates a compartment that guides the reactants to each other. It is obvious that the space-confinement-driven catalysis requires a larger catalyst that is able to generate a suitable compartment. (5) While in noncatalyzed reactions chemical events (eg, bond breakage/formation) often occur rather abruptly, in catalysis bond breaking may stretch over several reaction phases, thus transforming this event into an energy saving process, as shown in Figure 12 for the Rh–H cleavage during the first step (ethylene insertion into the Rh–H bond) of the rhodium catalyzed hydroformylation.^[332] The Rh–H bond transforms first into agostic, then into anagostic bonding, and far out in the exit channel, the actual bond breakage happens. As revealed by Figure 12B showing the Rh–B bond length as a function of s , the bond length changes do not occur smoothly but in “quantum steps”, which Kraka and Cremer coined the *quantization* of H-bond breakage.

Basic differences between catalyzed and noncatalyzed reactions can be determined in this way, but also the limitations of man-made catalysts. A first roadmap for catalyst design has been formulated.^[326] (1) First study the noncatalyzed reaction; identify energy-consuming events before the TS, identify hidden intermediates to be used to break up the reaction into several steps. (2) Then identify a catalyst which can (a) transform the hidden intermediates into real intermediates and (b) change the sequence of steps and/or moves the energy consuming steps into the exit channel.

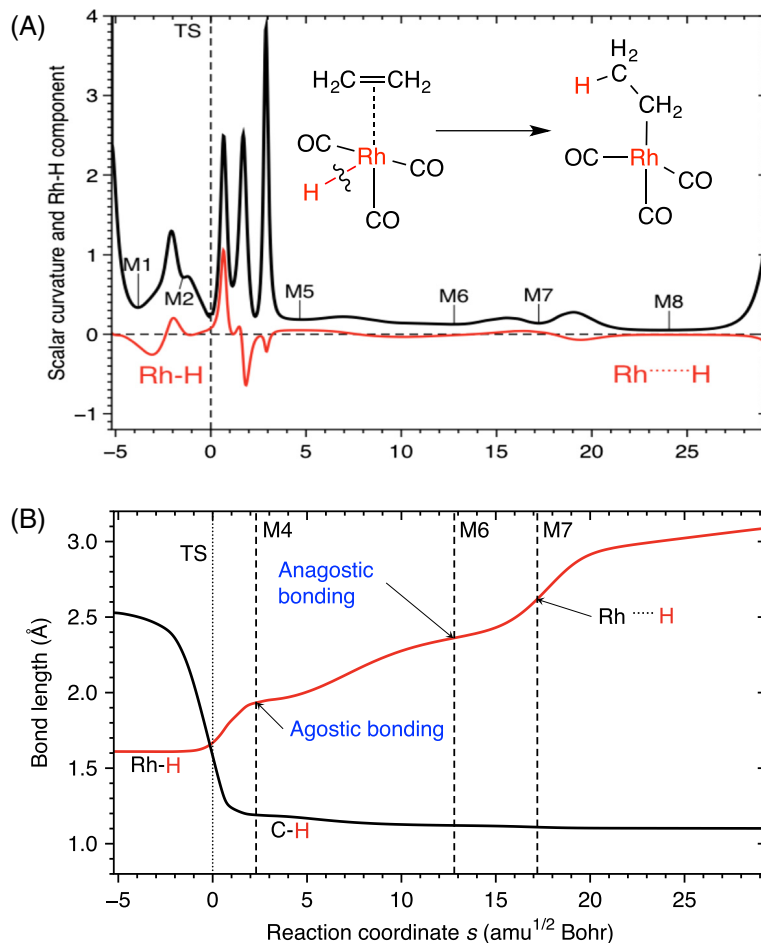


FIGURE 12 Quantized changes of the Rh–H bond length (red) along the reaction path. A, Scalar curvature along the reaction path (bold black line), Rh–H contribution (red line). The transition state TS is located at $s = 0 \text{ amu}^{1/2} \text{ Bohr}$. B, Corresponding changes of the Rh–H and the C–H distance along the reaction path

In summary, URVA has turned into a powerful quantum chemical tool to study the mechanism of chemical reactions in a detail never seen before. URVA unravels the interplay between the vibrations and the electronic structure changes of the reaction complex. It records all events when the reaction complex follows the energy valley from the entrance channel (van der Waals region) up to the energy pass point and then down through the exit valley to the products. Important and less-important events are differentiated by analyzing the direction and curvature of the reaction path rather than analyzing features of the reaction complex itself. This makes URVA feasible also for large molecular systems with many degrees of freedom. Just recently, the first URVA study of a chemical reaction in an enzyme was completed.^[333]

9 | PROTEIN STRUCTURE ANALYSIS

A fortunate stroke of serendipity happened during the work on URVA which led to a breakthrough in the analysis of protein structure, similarity, and folding. One of Dieter Cremer's graduate student wanted to work on the challenging question of how to describe protein structure, similarity, and folding. Dieter Cremer was skeptical because this would imply to correctly describe global and local features of the protein structure without getting lost in atomistic details, in addition too many groups were already working on this topic. However, he got an idea inspired by the URVA work, visualizing the protein backbone as a "reaction path". As discussed in the previous section the reaction path is a multidimensional curve being characterized by its arc length s , tangent vector \mathbf{t} and scalar curvature $\kappa(s)$. Including the next higher derivative, the torsion $\tau(s)$, these parameters define the *Frenet-Serret Frames*, which are used in differential geometry to describe the movement of a particle along a curved line in 3D space.^[334] This could be also useful for the description of the protein backbone "curve" leading to characteristic patterns for given structural features of a protein. Furthermore, such a description could be easy to program and could lead to an automated and mathematically based description of protein structure.^[335]

Along these lines and applying the techniques used for the presentation of the reaction path, the Cremer group developed a generally applicable Automated Protein Structure Analysis (APSA) program.

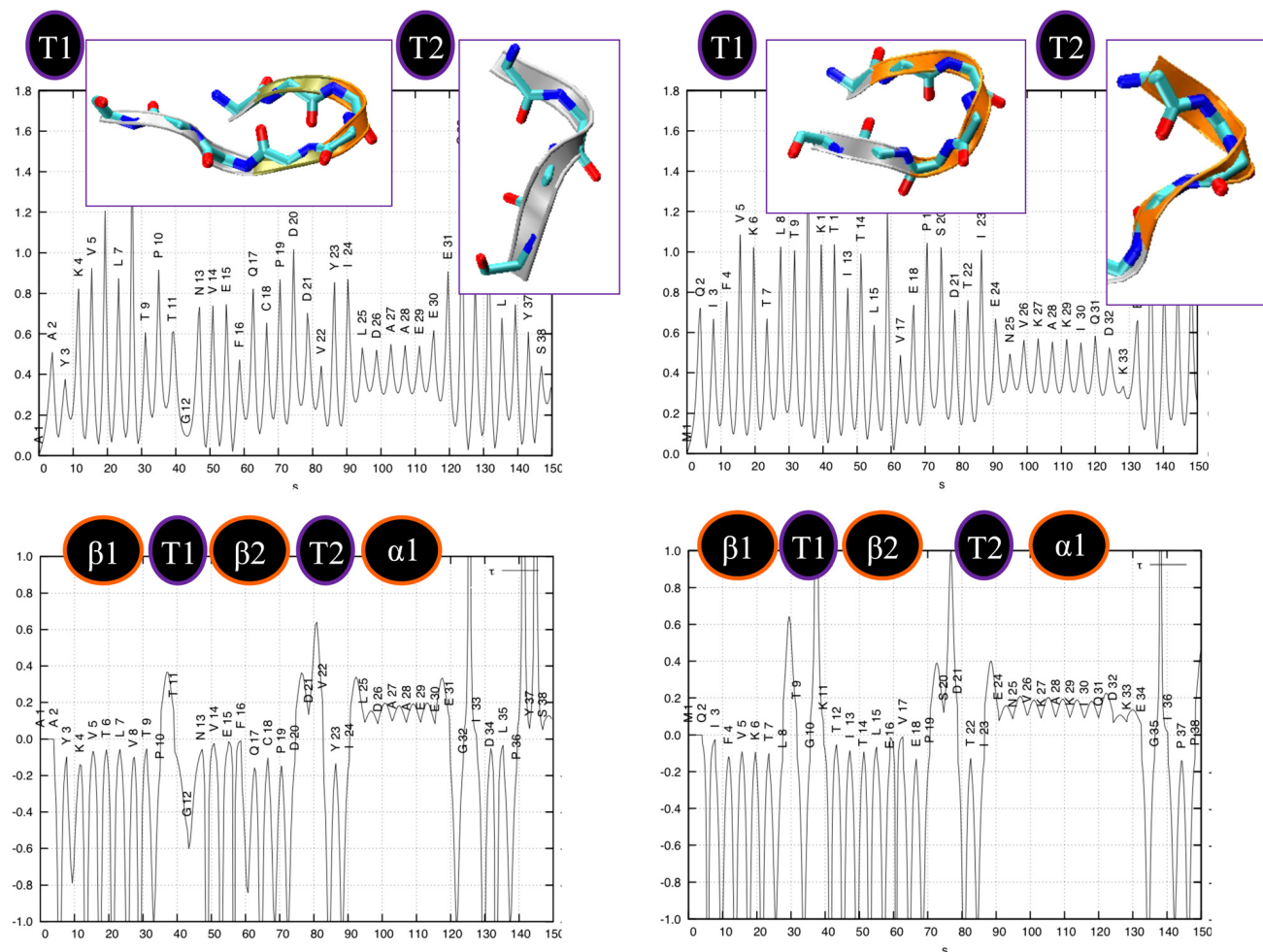


FIGURE 13 Comparison of curvature (above) and torsion diagrams (below) of the first 38 residues of ferredoxin (1A70) on the left and ubiquitin (1UBQ) on the right. The first five secondary structure units ($\beta 1$ T1 $\beta 2$ T2 $\alpha 1$) corresponding to the $\beta\beta\alpha$ motif) are indicated. Ribbon diagrams for T1 and T2 are shown as insets for each protein above the curvature diagrams. Reproduced from Ref. [337]

APSA represents the protein backbone via coarse-graining and spline-fitting, using the C_{α} atoms as anchor points. The backbone structure of proteins is converted into a 26-letter code based on the curvature and torsion of the backbone assessing protein similarity in a rapid fashion as tested so far for more than 2000 proteins.^[335–337] As an example, in Figure 13, a comparison of the first 38 residues of ferredoxin and ubiquitin is shown.^[337] Another important feature, to be mentioned is that APSA offers for the first time an exact way of describing protein helices. The exact description of helices (where does a helix start, where does it end?) was an unsolved problem, which hampered protein structure analysis, in particular, the distinction between α -, (3-10), and π -helices. According to accepted theories, the number of (3-10) helices is related to the evolutionary changes of a protein. However, APSA reveals that the number of (3-10) helices (determined for 14 000 secondary structural units) is much lower than previously claimed.^[336,337] APSA offers also the possibility of monitoring the protein folding process, as shown in Figure 14 for the folding of a 13 residue polypeptide.^[337]

In summary, APSA turned out to be a powerful multipurpose tool for describing protein structure and flexibility, motif detection, protein similarity, or protein folding. Since it describes global and local structure and is very fast, it is an ideal basis for future investigations of the relationship between protein sequence, conformation, and functionality, the search for binding pockets in drug design, the compression of protein structure data from 3D to 1D for effective storage and retrieval from 1D to 3D.

10 | DIETER CREMER'S LEGACY

Dieter Cremer left behind a wealth of research topics and unfinished ideas, concerning both method development and applications, some of which are summarized in Figure 15. The current members of the Computational and Theoretical Chemistry Group (CATCO) continue working on these topics in Dieter Cremer's spirit and we hope that also other groups are inspired by Dieter Cremer's shining example how to develop and apply theoretical chemistry to the benefit of our scientific community.

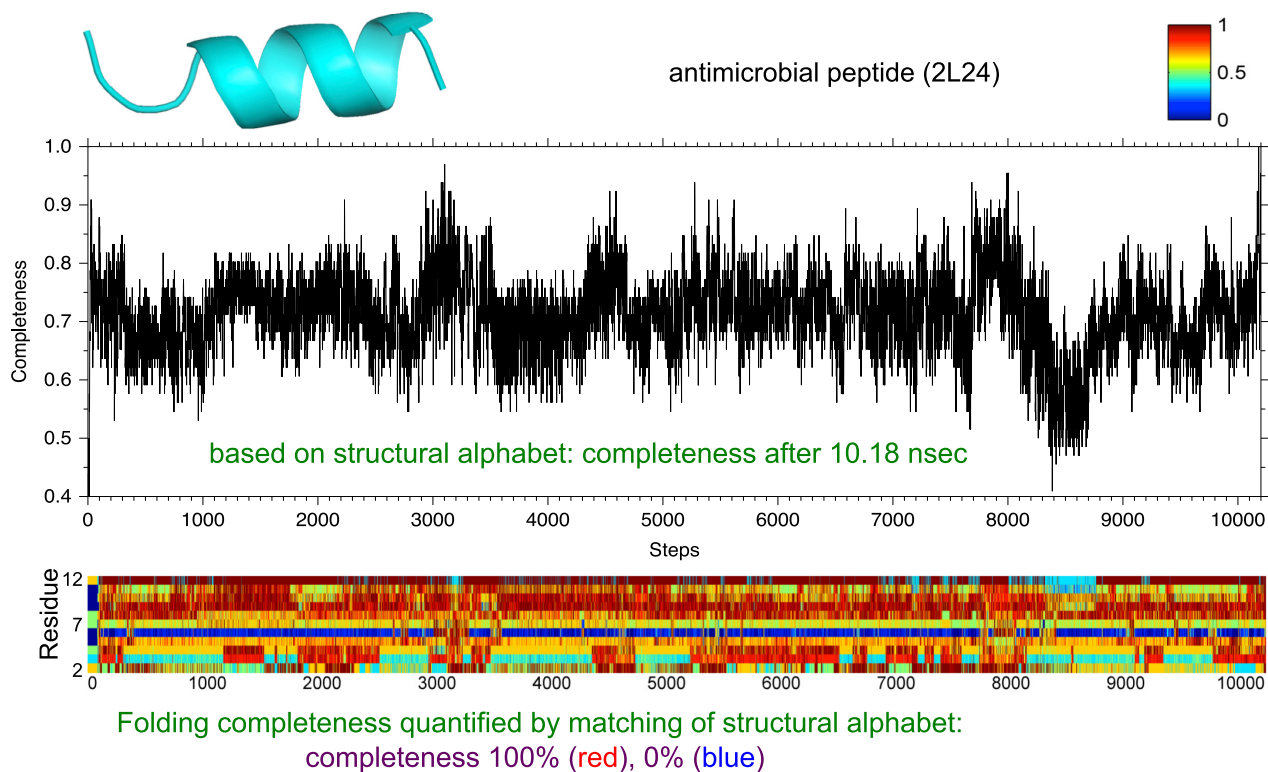


FIGURE 14 Upper part: folding trajectory of the antimicrobial peptide 2L24 (shown as ribbon diagram in the upper left corner) obtained from a 10.18 nanoseconds MD simulation. For each picosecond-step, the folding completeness is given as derived from a similarity analysis. Lower diagram: folding spectrum in form of a color-coded similarity test for each of the residues analyzed (vertical axis) at the 10 180 time steps (horizontal axis). The color code is given in the upper right: dark blue—unfolded; dark red—folded. Reproduced from Ref. [337]

Reaction Mechanism	Relativistic Theory	Local Modes	Protein Structure	CADD	Curvilinear Coordinates
Unified Reaction Valley Approach (URVA) for Chemical Reactions Study of Ti, Cr, Mo, Mn, Fe, Ru, Co, Rh, Ir, Ni, Pd, Pt, Cu, Ag, Au, Zn Catalysis Economic replacements for gold catalysts Study of metal free catalysis Study of Enzyme Catalysis Study of Metalloenzymes <i>De novo</i> catalyst design	Dirac-exact Relativistic 1c- and 2c-Methods First and second order response properties Properties of actinides and trans-actinides Calculation of Mossbauer Shifts Removal of heavy metals from wastewaters Cleaning waters from arsenic Cleaning of fracking water from radioactive compounds	Local Vibrational Mode Analysis Covalent Bonding Hydrogen Bonding Halogen Bonding Pnicogen Bonding Chalcogen Bonding Tetrel Bonding BH- π interactions Pancake bonding Metal-ligand Bonding Agostic Bonding Origin of Chirality	Automated Protein Structure Analysis (APSA) Investigation of Protein Similarity Investigation of Protein Folding Generation of Protein Structure Library Analysis of H-bonding with NMR and vibrational properties	Computer-Assisted Drug Design and QM/MM protocols QM/MM for large systems Design of anti-tumor leads based on the enediyne principle Accurate pKa calculations Investigation of cis-platin compounds Chemical similarity and mutation paths	Quantum Chemistry in terms of curvilinear coordinates Jahn-Teller surfaces Pseudo-Jahn-Teller surfaces Ringpseudorotation and Ringpseudolibration Berry pseudorotation Bartell pseudorotation Ray-Dutt twists DNA/RNA conformation and function

FIGURE 15 Some highlights of Dieter Cremer's Legacy. Method and program development topics are given in blueprint and applications in physics, chemistry, and biochemistry are given in black print

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