Why an integrated approach between search algorithms and chemical intuition is necessary?

Journal:	*Physical Chemistry Chemical Physics*
Manuscript ID	CP-ART-01-2022-000315.R1
Article Type:	Paper
Date Submitted by the Author:	23-Mar-2022
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Journal Name

ARTICLE TYPE

Cite this: DOI: 00.0000/xxxxxxxxxx

Why an integrated approach between search algorithms and chemical intuition is necessary?[†]

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Received Date
Accepted Date

DOI: 00.0000/xxxxxxxxxx

Though search algorithms are appropriate tools for identifying low-energy isomers, fixing several constraints seems to be a fundamental prerequisite to successfully running any structural search program. This causes some potential setbacks as far as identifying all possible isomers, close to the lowest-energy isomer, for any elemental composition. The number of explored candidates, the choice of method, basis set, and availability of CPU time needed to analyze the various initial test structures become necessary restrictions in resolving the issues of structural isomerism reasonably. While one could arrive at new structures through chemical intuition, reproducing or achieving those exact same structures requires increasing the number of variables in any given program, which causes further constraints in exploring the potential energy surface in a reasonable amount of time. Thus, it is emphasized here that an integrated approach between search algorithms and chemical intuition is necessary by taking the $C_{12}O_2Mg_2$ system as an example. Our initial search through the AUTOMATON program yielded 1450 different geometries. However, through chemical intuition, we found eighteen new geometries within 40.0 kcal mol^{-1} at the PBE0-D3/def2-TZVP level. These results indirectly emphasize that an integrated approach between search algorithms and chemical intuition is necessary to further our knowledge in chemical space for any given elemental composition.

1 Introduction

Structural isomerism is one of the most fundamental concepts in general chemistry, being addressed from the most basic chem-

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[†] Electronic Supplementary Information (ESI) available: [Total electronic energies, Zero-point vibrational energies (ZPVEs), ZPVE corrected total energies (E + ZPVE), relative energies without ZPVE corrections (ΔE_e), with ZPVE corrections (ΔE_0), thermally corrected free energies (ΔG), Cartesian coordinates of the optimized geometries, and the number of imaginary frequencies (NImag) obtained for all isomers of $C_{12}O_2Mg_2$ calculated at the PBE0-D3/def2-TZVP level of theory are given. Valence structures and IUPAC names of the first 36 isomers are also given]. See DOI: 00.0000/00000000.

istry courses in the high school itself. Isomers are molecules that have the same molecular formula but have a different arrangement of atoms in space. Predicting all the isomers for a given formula is a problem that becomes more complex as the size of the system increases. This is basically because the number of possible isomers grows exponentially as c^N (N being the number of atoms in the system and c a constant that depends on the system's nature).[1–3] The c parameter can be small, as in the case of alkanes,[4] or very large when there are clusters composed of different types of atoms.[5–14] That is, while one could use chemical intuition when the total number of atoms is less than or equal to six,[15–17] it is quite hard to imagine the permutations and combinations of all various possibilities if all the six atoms are different.[18]

Different approaches, such as simulated annealing,[19] genetic algorithm (GA),[20–22] gradient-embedded GA (GEGA),[23,24] artificial bee colony algorithm,[25,26] stochastic search,[18,27–29] basin-hopping approach,[30–32] grid-based comprehensive isomeric search,[33,34] tabu-search,[35–39] particle-swarm optimization,[40] etc., were developed or are continuously being developed over the last two decades to specifically address the issue of structural isomerism.[18,41] Although automation is a significant development, due to limitations in the search algorithms themselves, it is practically not possible to get all the structural isomers possible for a given elemental composition. Though automated methods provide unusual and low-lying energy structures for a given elemental composition, one question arises. Is there an algorithm that can identify with certainty all possible structural isomers? The answer is an emphatic "no", unfortunately. As pointed out elsewhere,[18] no algorithm to date guarantees one hundred percent recovery of all possible geometries for a given elemental composition. Nevertheless, using search algorithms are unavoidable for two key reasons: 1) manual handling of several permutations and combinations is extremely time-consuming and not at all a manageable task; 2) intuitively arriving at the most stable geometry for any random elemental composition is also not possible because intuition has the limit from existing empirical knowledge. Therefore, automated searches through various search algorithms will remain an integral part in this endeavor.

As an illustrative example of the latter, we refer to the $Be_6B_{11}^-$ cluster.[42] Guo et al. using two independent methods in their structural search, the coalescence kick (CK) method[29,43] and the Bilatu code,[27,28] reported as candidates for global minima two structures of similar energy, one composed of three stacked rings [$Be_3Bi_{11}Be_3$] and the other of a helix-shaped B_{11} chain interspersed with 6 Be atoms.[42] However, two of the authors of the present work, using confined search spaces within the AUTOMATON program, managed to identify better minima with less striking structures than those initially proposed.[44] Based on genetic algorithms, an independent search has recently confirmed the latter results.[45]

In this work, various structural isomers of $C_{12}O_2Mg_2$ are studied to emphasize the fact that an integrated approach between search algorithms and human chemical intuition is highly necessary. Thirty-four low-lying isomers eventually obtained for $C_{12}O_2Mg_2$ at the PBE0-D3/def2-TZVP level using a combination of these two approaches are shown in Figs. 1 and 2. The present theoretical work done here is certainly not an exhaustive study of all isomers of $C_{12}O_2Mg_2$. On the contrary, what the present work emphasizes is the fact that search algorithms and chemical intuition have to go hand in hand to identify new molecules for any random elemental composition. Retrospectively, it is believed that chemical intuition may help to improve or create better checkpoints for search algorithms, which would be beneficial to all. To the best of the authors' knowledge, all isomers of $C_{12}O_2Mg_2$ remain elusive in the laboratory to date including the putative global minimum, (1,7-dimagnesacyclododeca-3,5,9,11-tetrayne-2,8-diylidene)dimethanone (**1**), which is an organomagnesium ketene derivative.

2 Computational details

The initial search for all $C_{12}O_2Mg_2$ isomers is carried out using AUTOMATON[41] at the PBE0[46]/SDDALL[47,48] level. It is important to note that AUTOMATON is a program that uses a probabilistic cellular automated method to generate the initial population, which then evolves through genetic operations. This method has been designed to identify the global minimum, assessing its efficiency in different systems,[41] with recent application to design global minima with planar hypercoordinate carbons,[49–52] organic dications,[53] deltahedral Zintl clusters,[54] among others.[55,56] Our initial search yielded 1450 different geometries. It is noted here that this initial search was carried out with a limited population of 5n (where, n = total number of atoms in a given elemental composition, for $C_{12}O_2Mg_2$ it is 16). The first one hundred stationary points that span from 0 to 63.52 kcal mol^{-1} are reoptimized at the PBE0-D3[57]/def2-TZVP[58] level to reach a reasonable conclusion on the energetics. It is noted here that relative energy discussions refer to the latter level unless otherwise stated. For brevity, all isomers that lie below 40 kcal mol^{-1} are shown here and all other geometries are given in the ESI.†Similar exercises were done for all geometries that were arrived at based on chemical intuition. A third search was performed, using the best 80 isomers of the first AUTOMATON search as the initial population. This procedure forces the program to run at least nine more cycles (the minimal number of cycles that the exact best minimum must be repeated to converge the search). No low-energy isomers additional to those identified in the initial search are found. This result validate the relevance of using alternative methods (or strategies) to test candidates that the automatic search process has missed. Triplet geometry optimization and frequency calculations were done with the unrestricted HF (UHF) wavefunctions, that is, at the UPBE0-D3/def2-TZVP level. All these density functional theory calculations have been carried out with the Gaussian suite of programs.[59]

3 Results and discussion

Isomers of $C_{12}O_2Mg_2$ that lie under 25 kcal mol^{-1} are shown in Fig. 1 whereas those that lie between 25 to 40 kcal mol^{-1} are shown in Fig. 2. Relative energies without ZPVE corrections (ΔE_e), with ZPVE corrections (ΔE_0), and thermally corrected free energies (ΔG) of the first thirty-six isomers of $C_{12}O_2Mg_2$ in their singlet and triplet ground electronic states are given in Table 1.

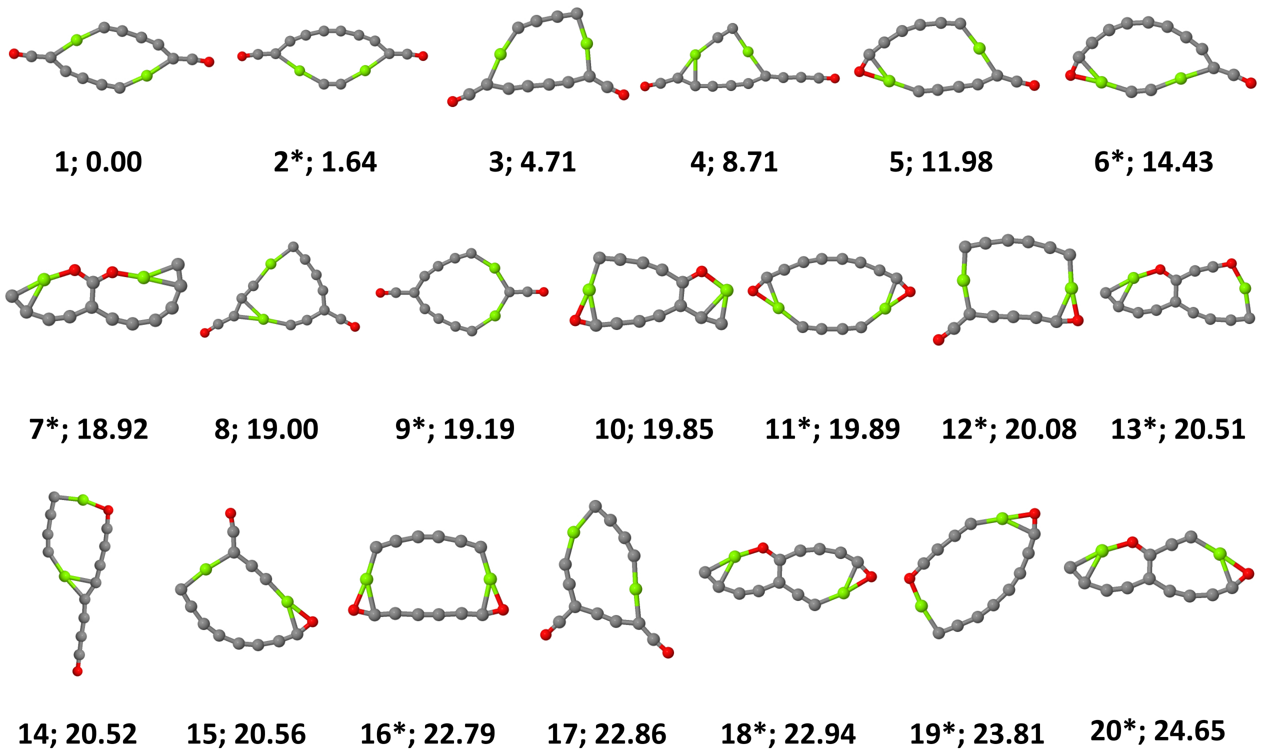


Fig. 1 Isomers of $C_{12}O_2Mg_2$ considered on the singlet PES within 25 kcal mol^{-1}. Relative energies including ZPVE corrections (in kcal mol^{-1}) are calculated at the PBE0-D3/def2-TZVP level. Isomers identified by chemical intuition are marked with an asterisk whereas unmarked ones are from AUTOMATON. All isomers are minima.

3.1 Why search algorithms are inevitable?

For small elemental compositions such as C_6,[29,60] for example, it is easy to apply our chemical intuition and try various possibilities as the total number of isomers itself will be less. However, on the contrary, when we have two or more than two different atoms, and the total number of atoms are greater than ten, it is undoubtedly impossible to discern intuitively in advance about what would be the most stable geometry.[61–63] Therefore, search algorithms are inevitable to find out the most stable geometry in a reasonable amount of time. Moreover, as a byproduct, we get some of the low-lying minima.

All these different structures that we get through search algorithms initially improve our chemical intuition instantaneously about that particular elemental composition. For example, in the case of $C_{12}O_2Mg_2$, when we initially finished our search through AUTOMATON at the PBE0/SDDALL level, isomer **21** was the most stable geometry. This structure gave us an idea to think about similar structures such as **7**, **13**, **18**, **20**, **22**, **23**, and **26** in which some fell on the low-lying side that lie within 25 kcal mol^{-1} whereas others fell on the high-energy side between 25–40 kcal mol^{-1}. The only difference is that isomer **21** consists of a bicycle with a six-membered and a twelve-membered ring, while the others consist of a bicycle with eight- and ten-membered rings. Note that in all cases, the rings are connected through two carbons. Nevertheless, the point is, we wouldn't have thought about such possibilities without carrying out our initial search through AUTOMATON. Importantly, our initial search at the PBE0/SDDALL level yielded 1450 different geometries. Then, we re-optimized the first one hundred geometries at the PBE0-D3/def2-TZVP level to identify the possible global minimum geometry with certain reliability. Once re-optimization with a higher basis set plus empirical dispersion corrections were done, we identified that isomer **1** is the putative global minimum and not isomer **21**. This highlights the role of the level used concerning the quality of PES scanning. However, performing an AUTOMATON search at the PBE0-D3/def2-TZVP level from the beginning would be very time-consuming with our computational resources. For example, our PBE0/SDDALL search required two weeks, using 80 cores in total, with the specification to use eight cores for each structural optimization. Note that the search benefits from parallel computations. It would be faster if more cores were used in the process.

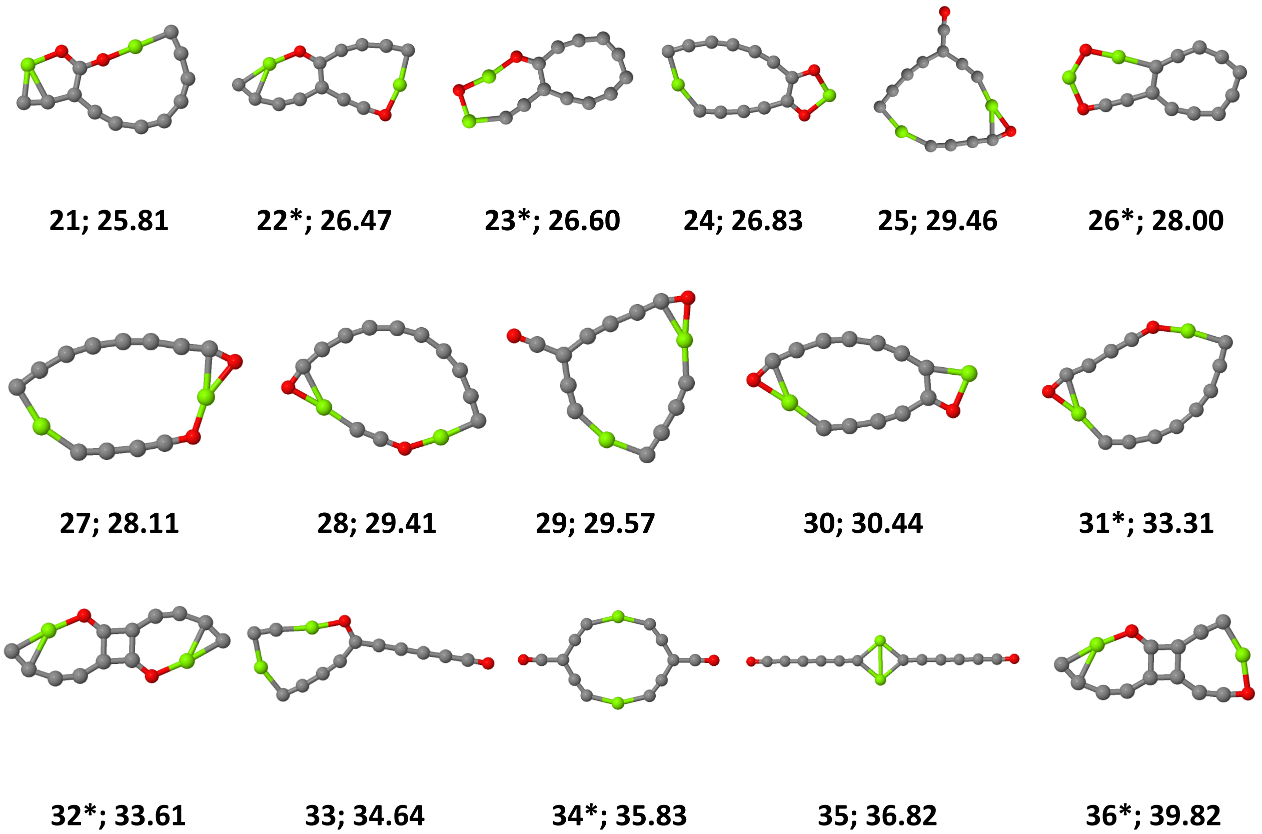


Fig. 2 Isomers of $C_{12}O_2Mg_2$ considered on the singlet PES between 25 to 40 kcal mol^{-1}. Relative energies including ZPVE corrections (in kcal mol^{-1}) are calculated at the PBE0-D3/def2-TZVP level. Isomers identified by chemical intuition are marked with an asterisk whereas unmarked ones are from AUTOMATON. All isomers are minima.

3.2 Why chemical intuition is necessary?

Through chemical intuition, we found eighteen new isomers within 40 kcal mol^{-1} (see the structures indicated with asterisk marks in Figures 1 and 2) for $C_{12}O_2Mg_2$. The purpose of GA is to identify the lowest-energy isomer for any given elemental composition. While some low-lying isomers can be obtained as a byproduct, all possible low-lying isomers are not guaranteed as the prime purpose of GA is to find the global minimum. Another strategy developed by some of the authors is to build the molecules bottom-up starting from a single atom by adding the remaining atoms sequentially searching for local minima at each stage and using those minima to grow the molecule up to the desired composition.[39] However, this approach is computationally quite expensive for larger elemental compositions like $C_{12}O_2Mg_2$. Of course, from our previous studies of small clusters such as $CAl_4Mg^{-/0}$[64] and $BAl_4Mg^{-/0/+}$,[65] we realized that it does not guarantee all possible low-lying isomers although global minimum can be found unequivocally.

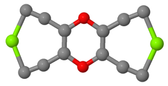
In an earlier theoretical work related to $Si_2C_5H_2$ isomers, we suggested a systematic approach to arrive at all possible geometries, starting from reported and related structures.[62,66] However, such an approach is a very tedious exercise for elemental composition of this size. Because the initial search through AUTOMATON itself yields 1450 different geometries. If we try implementing a systematic approach here by considering each geometry as a base structure, then we may have to work out as much as 29000 geometries even if we assume that only 20 different geometries are possible for each base structure. Therefore, the best alternative that is practically possible in cases like this is to use chemical intuition to reasonably extend our knowledge about the chemical space of $C_{12}O_2Mg_2$.

Out of curiosity, some of us in our earlier theoretical work designed an organomagnesium crown ether molecule called 6,14-dimagnesa-2,10-dioxatricyclo[9.5.0.0^{3,9}]hexadeca-1(11),3(9)-dien-4,7,12,15-tetrayne (**112**; see Fig. 3) using the elemental composition $C_{12}O_2Mg_2$.[67] The motivation behind the organomagnesium crown ether work is to design flat crown ether molecules that could effectively be synthesized in the laboratory.[68] From the current theoretical work, it is evident that the organomagnesium crown ether is not the global minimum geometry for $C_{12}O_2Mg_2$. However, it is noted here that the synthetic viability of molecules are largely driven by kinetic factors instead of thermodynamic factors alone.

Table 1 Relative energies without (ΔE_e) and with ZPVE corrections (ΔE_0), thermally corrected free-energies (ΔG) of singlet and triplet electronic states of $C_{12}O_2Mg_2$ isomers. Singlet-triplet energy gaps (ΔE^{S-T}) are also given. All values are in kcal mol^{-1}.

isomer	PBE0-D3/def2-TZVP (singlet)			UPBE0-D3/def2-TZVP (triplet)			(U)PBE0-D3/def2-TZVP^a		
	ΔE_e (0 K)	ΔE_0 (0 K)	ΔG (298.15 K)	ΔE_e (0 K)	ΔE_0 (0 K)	ΔG (298.15 K)	ΔE_e^{S-T} (0 K)	ΔE_0^{S-T} (0 K)	ΔG^{S-T} (298.15 K)
1	0.00	0.00	0.00	24.97	22.89	20.73	47.04	45.63	44.93
2	2.04	1.64	1.51	15.80	12.88	10.38	37.87	35.62	34.58
3	4.95	4.71	4.03	21.27	19.26	16.94	43.34	42.00	41.14
4	9.42	8.71	7.87	20.49	17.34	14.73	42.56	40.08	38.93
5	12.29	11.98	12.04	26.91	24.36	21.94	48.98	47.10	46.14
6	15.08	14.43	14.74	29.08	25.90	24.10	51.15	48.64	48.30
7	18.20	18.92	21.01	22.26	21.30	21.86	44.33	44.04	46.06
8	19.04	19.00	18.84	28.98	26.88	24.56	51.05	49.62	48.76
9	19.05	19.19	18.58	27.53	25.55	22.87	49.60	48.29	47.07
10	18.66	19.85	22.29	22.13	21.62	21.14	44.20	44.36	45.34
11	20.37	19.89	20.58	31.16	28.42	26.87	53.23	51.15	51.07
12	20.72	20.08	18.63	32.72	30.29	28.50	54.79	53.03	52.69
13	19.32	20.51	23.04	28.76	28.11	27.51	50.83	50.85	51.71
14	21.17	20.52	19.85	37.07	34.15	31.42	59.14	56.89	55.61
15	21.02	20.56	20.31	32.02	29.36	26.87	54.09	52.10	51.07
16	23.49	22.79	22.43	55.13	52.17	49.84	77.20	74.91	74.04
17	23.17	22.86	21.72	28.56	26.46	24.15	50.63	49.19	48.34
18	21.82	22.94	25.46	36.29	34.35	35.02	58.36	57.09	59.22
19	24.33	23.81	23.66	37.11	34.06	31.90	59.18	56.80	56.10
20	23.59	24.65	27.26	36.19	34.67	35.35	58.26	57.41	59.55
21	24.83	25.81	27.67	21.68	20.74	20.03	43.75	43.48	44.23
22	25.56	26.47	28.80	32.47	31.11	30.90	54.54	53.85	55.10
23	25.49	26.60	29.58	23.89	23.24	24.18	45.96	45.98	48.38
24	26.07	26.83	29.13	0.00	0.00	0.00	22.07	22.74	24.20
25	29.80	29.46	29.41	39.51	37.06	34.90	61.58	59.80	59.10
26	27.17	28.00	30.76	33.19	31.98	32.41	55.26	54.72	56.61
27	28.66	28.11	28.28	34.79	32.15	30.25	56.86	54.89	54.45
28	30.00	29.41	29.33	42.30	39.10	36.77	64.37	61.84	60.97
29	29.98	29.57	29.31	37.82	35.43	33.08	59.89	58.17	57.27
30	29.77	30.44	32.63	15.36	14.59	14.22	37.43	37.32	38.42
31	34.01	33.31	33.44	57.59	54.34	51.48	79.66	77.08	75.68
32	32.72	33.61	36.13	31.47	30.89	30.55	53.54	53.63	54.75
33	35.61	34.64	34.23	25.15	22.44	19.66	47.22	45.18	43.86
34	36.08	35.83	34.42	46.59	44.41	41.05	68.66	67.15	65.24
35	36.92	36.82	34.33	38.78	36.57	31.47	60.85	59.31	55.67
36	38.77	39.82	42.35	28.66	27.87	28.17	50.73	50.61	52.36

[a] Positive value indicates that singlet electronic state is more stable.



MgC$_6$-6-crown-2
112*; 73.71

Fig. 3 Organomagnesium crown ether structure that we initially considered on the singlet PES of $C_{12}O_2Mg_2$. Relative energies including ZPVE corrections (in kcal mol^{-1}) are calculated at the PBE0-D3/def2-TZVP level.

4 Conclusions

Various structural isomers of $C_{12}O_2Mg_2$ are identified using an automated search (AUTOMATON program) and chemical intuition. After analyzing 1450 different geometries (obtained through the search algorithm), we could still arrive at sixteen new geometries through chemical intuition within 40 kcal mol^{-1} at the PBE0-D3/def2-TZVP level. Perhaps, this is not a drawback of the search algorithm as one restricts some variables, i.e., a reduced number of candidate structures. Other practical factors such as CPU time available, method, and basis-set used to analyze the PES indirectly restrict our search further. Besides, the chemical intuition is enriched with the knowledge provided by the automatic search, i.e., the sixteen new structures are obtained by permuting atoms in structures identified by AUTOMATON. It is virtually impossible to glimpse the global minimum geometry intuitively without using search strategies as genetic algorithms. It is also virtually impossible to identify all local minima by search algorithms when the variables used in the search, for practical reasons, are tightly constrained. Therefore, an integrated approach such as finding various isomers through search algorithms and then using chemical intuition is the best alternative to increase the chemical knowledge of such large elemental compositions. On the contrary, bottom-up cluster building algorithms and chemical intuition alone are not practically viable to identify the lowest-energy isomers.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

Computational support provided at the SDSU by DURIP Grant W911NF-10-1-0157 from the U.S. Department of Defense and by NSF CRIF Grant CHE-0947087 is gratefully acknowledged. The work in Chile is supported by Fondecyt grant 1211128 and Powered@NLHPC: This research was partially supported by the super-computing infrastructure of the NLHPC (ECM-02). The work in Chile is also supported by National Agency for Research and Development (ANID)/Scholarship Program/BECAS DOCTORADO NACIONAL/2019-21190427. This work in part used the Super-computing facility of IIT Kharagpur established under National Super-computing Mission (NSM), Government of India and supported by Centre for Development of Advanced Computing (CDAC), Pune. Additional computational support provided at VIT, Vellore, India, to KT is also gratefully acknowledged. VST thanks Dr. Ganesh Venkataraman (IIT Kharagpur) for helpful discussions on the synthetic viability of ketene derivatives.

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