

Application of molecular mechanics to natural product chemistry

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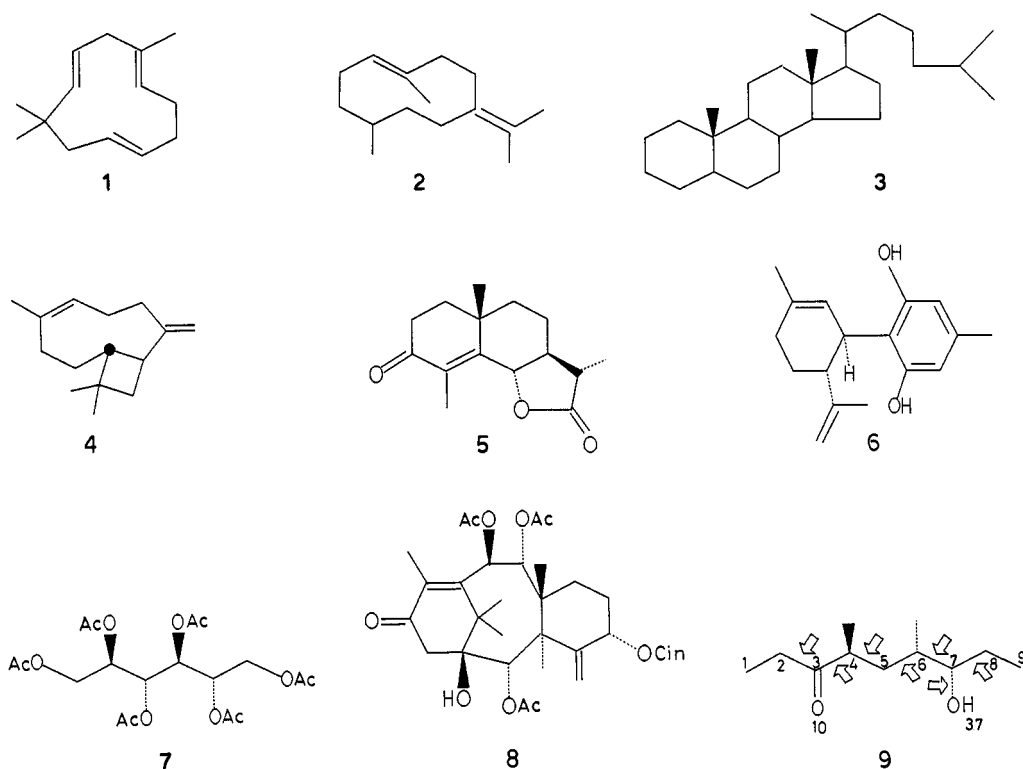
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Abstract—The past contribution to the application of molecular mechanics calculation to natural product chemistry by the authors are briefly reviewed. Two major problems of molecular mechanics, insufficient parameters for heteroatoms and available algorithms for covering the torsional energy of flexible molecules are addressed. Progress on the calculations of two flexible molecules, tricyclic taxine **8** and linear serricornine **9**, is reported.

INTRODUCTION

Molecular mechanics method of calculating submolecular properties on the empirical theoretical basis has been extensively applied to various problems of natural product chemistry (ref. 1). Since our early entry in this field, which fortunately demonstrated clear cases for conformational control in the biosynthetic route of illudoid sesquiterpenes (ref. 2), we have calculated a number of natural products, starting with hydrocarbons having rather rigid skeletons such as humulene **1**, germacrene B **2** (ref. 3), cholestanol **3** (ref. 4) and caryophyllene **4** (ref. 5). Then the target molecules were expanded to simply substituted molecules like santonin **5** (ref. 6) and cannabidiol **6** (ref. 7), and more recently to heavily substituted and flexible molecules like hexitol peracetate **7** (ref. 8), taxine **8** (ref. 9) and serricornine **9** (ref. 10). In view of increasing interests among natural product chemists to utilize this powerful computational technique themselves, we illustrate below some of our latest results.



HETEROATOM PARAMETERS

Before mentioning applications, a few words seem appropriate on the most acute problem in the molecular mechanics which has discouraged many potential users. The problem is insufficient supply of reliable heteroatom parameters for potential functions used in molecular mechanics and arises from the lack of experimental data that can be used as the standard in the parameterization. The lacking data have so far been supplemented by molecular orbital calculations. Still better and more consistent than the temporary supplementing will be to switch from the current experiment-based force field to the one based entirely on *ab initio* computations. Construction of an *ab initio* molecular mechanics force field is in progress in our laboratories (ref. 11). It may be noted, however, that most of the medium-sized molecules can be readily processed on ever-faster, low-priced workstations or on recently appearing 32-bit type personal computers using semi-empirical molecular orbital methods like AM1 (ref. 12)

FLEXIBLE MOLECULES

Even if the daily needs for calculating medium-sized molecules may be eventually met with semi-empirical molecular orbital calculations in the nearest future, medium-to-large flexible molecules and polymers must be handled with molecular mechanics. The first task in the calculation of flexible molecule is to find the global energy minimum conformation. Table 1 summarizes available algorithms for such purpose.

Table 1. Available algorithms for covering torsional energy surfaces of flexible molecules

Category	Algorithm
Intuitive	Multiple-bond driver (ref. 1, 13), Lagrange's undetermined multipliers method (ref. 14)
Random search	Energy-embedded distance geometry (ref. 15), Stochastic kick (ref. 16)
Exhaustive	Systematic rotation ^a (ref. 8), 'RINGMAKER' ^b (ref. 17), Corner flapping ^b (ref. 9)

^a For acyclic systems. ^b For cyclic systems.

For relatively small molecules such as 7 to 9, complete coverage of the torsional energy surface is possible. However, the computer time for the exhaustive coverage increases exponentially with the size of molecule, hence one must rely on the random search methods for larger molecules. Among the methods given in Tab. 1, the corner flapping method for cyclic system is the newest, wherein the ring carbon atoms are systematically flapped and energy-minimized. All the known conformers of small cycloalkanes could be generated by this method (ref. 9). When this method was applied, using MM2 (ref. 18), to *trans*-tricyclo[9.3.1.0(3,8)]pentadecane, the skeletal carbon ring system of 8, 41 energy minima could be obtained after flapping all of the corner carbons of 595 starting conformations. The global energy minimum thus found had a chair-twist boat-chair conformation in accordance with the x-ray structure of a substituted derivative (ref. 19) and its steric energy was 4.8 kcal/mol lower than the lowest energy conformation found previously by driving only the central eight-membered ring. This illustrates the danger of relying on the intuitive bond driver method.

Conformational study of 9, a sex pheromone of cigarette beetle (ref. 10), is by no means trivial, since this molecule contains seven single bonds (marked with open arrows), for each of which three staggered rotamers are expected. This means that 2,187 conformations must be optimized. It is a straightforward matter to implement routines that allow the existing molecular mechanics programs like MM2 to perform all these energy-minimization automatically. The calculations took a few hours of CPU time on a mainframe computer and a few days on a workstation. About one half of the starting conformations had merged into other conformers during structure-optimization, and 1,204 unique conformers were finally obtained. Table 2 (next page) presents the 20 lowest-energy conformers. As can be anticipated, the global energy minimum conformer, populating 10.4%, has a folded shape due to hydrogen bonding between hydroxyl proton at C7 and carbonyl oxygen at C3. All-anti conformers regarding the skeletal C-C bonds appear in this Table only at the 15th and 17th positions. These suffer not only from small dipole interactions but also from meager van der Waals attraction energies. When Altona's empirical modification of Karplus equation (ref. 20) was applied to the 1,204 conformers, the average vicinal H/H coupling constants thus obtained compared rather well with the observed with regard to the patterns and magnitudes (Table 3).

Table 2. Low-energy conformers of **9** according to MM2 calculation

No. (File)	Conformation								Rel SE kcal	POP %	Dist 10/37 Å	-----Component of steric energy, kcal/mol-----						
												Stretch	Bond	St.-Bd	Van der Waals	Tors	Dipol	
	2-3	3-4	4-5	5-6	6-7	7-8	7-13	1,4				Others						
1	0889	A	A	G	G	G	A	-G	0.00	10.40	3.30	1.05	2.89	0.37	7.81	-2.55	2.21	-1.49
2	0088	A	-G	-G	G	A	A	A	0.23	7.07	3.37	1.06	3.31	0.40	7.93	-2.82	2.02	-1.38
3	0080	A	A	G	G	G	A	A	0.44	4.92	4.67	1.04	2.58	0.36	7.88	-2.83	2.62	-0.91
4	0143	A	G	G	G	A	A	A	0.53	4.20	4.89	1.01	2.26	0.34	7.85	-2.67	2.71	-0.47
5	0106	A	-G	-G	G	A	G	A	0.54	4.13	3.38	1.11	3.74	0.44	7.93	-3.15	2.20	-1.43
6	0183	A	G	G	G	A	G	A	0.63	3.54	4.88	1.01	2.51	0.36	7.91	-3.20	2.84	-0.49
7	1184	A	A	G	-G	A	A	-G	0.79	2.75	2.64	1.09	3.05	0.38	8.14	-2.49	3.23	-2.30
8	0005	A	-G	A	A	A	A	A	0.81	2.65	6.93	1.13	2.34	0.34	7.73	-1.77	1.63	-0.29
9	0044	A	A	G	G	A	A	A	0.82	2.59	5.70	1.06	2.29	0.34	7.65	-2.21	2.04	-0.05
10	0082	A	A	G	G	A	G	A	0.95	2.10	5.68	1.06	2.56	0.36	7.72	-2.46	2.12	-0.11
11	0471	A	A	G	G	A	A	G	1.09	1.66	5.60	1.05	2.44	0.36	7.65	-2.29	2.60	-0.42
12	1102	G	A	G	G	G	A	-G	1.14	1.47	3.38	1.07	3.08	0.38	7.82	-2.99	3.45	-1.36
13	0072	A	-G	A	A	A	G	A	1.17	1.44	6.97	1.12	2.64	0.36	7.80	-1.92	1.77	-0.30
14	0864	A	A	-G	G	A	A	-G	1.19	1.39	2.25	1.15	3.55	0.43	7.84	-1.79	2.13	-1.80
15	0846	A	A	A	A	A	A	-G	1.20	1.38	4.54	1.17	2.51	0.36	7.63	-1.42	1.52	-0.26
16	0981	A	G	G	G	A	A	-G	1.20	1.36	4.47	1.03	2.32	0.35	7.91	-2.98	2.74	0.13
17	0001	A	A	A	A	A	A	A	1.29	1.18	5.72	1.16	2.37	0.35	7.66	-1.54	1.62	-0.04
18	0489	A	A	G	G	A	G	G	1.33	1.10	5.56	1.06	2.74	0.38	7.70	-2.51	2.70	-0.44
19	0070	A	-G	A	A	G	A	A	1.37	1.02	6.80	1.12	2.54	0.36	7.97	-1.97	1.78	-0.07
20	0970	A	G	G	G	G	A	-G	1.38	1.01	2.45	1.07	2.84	0.38	7.92	-2.73	3.17	-0.98

Table 3. Comparison of observed vicinal H/H coupling constants (Hz) of **9** with the calculated (weight-averaged over 1,204 unique conformers)

	Obs	Calc	Diff
H-C4-C5-H	6.2	5.3	-0.9
H-C4-C5-H'	7.6	8.5	0.9
H-C5-C6-H	8.1	8.8	0.7
H'-C5-C6-H	5.4	6.0	0.6
H-C6-C7-H	3.8	2.7	-1.1
H-C7-C8-H	8.5	8.9	0.4
H-C7-C8-H'	5.0	4.0	-1.0

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