Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2021, **31**, 612–614

Mendeleev Communications

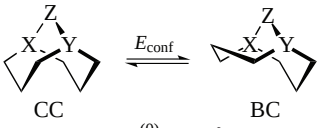
Conformational effects of 1,5,9-substitution in symmetric bicyclo[3.3.1]nonane analogues

Sergey A. Pisarev and Vladimir A. Palyulin*

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: vap@qsar.chem.msu.ru

DOI: 10.1016/j.mencom.2021.09.007

The high-level *ab initio* calculations on several derivatives of bicyclo[3.3.1]nonane, 1-aza- and 1,5-diazabicyclo[3.3.1]-nonanes show the 'double chair' (CC) conformer as optimal for all of them, dominating over the 'boat–chair' (BC) form. Conformational effects of several substitution types involving positions 1, 5 and 9 are quantified, and their values are found rather transferable.



$E_{conf} - E^{(0)}_{conf} = \Sigma_i \delta E(i)$

Keywords: conformational behaviour, bicyclo[3.3.1]nonanes, conformational effects, *ab initio* computations.

Dedicated to the memory of our teacher Academician Nikolay Serafimovich Zefirov

The bicyclo[3.3.1]nonane system is generally considered as two six-membered rings sharing a three-atom, two-bond chain, so that the conformation of the bicycle is completely defined by those of constituent cycles thereof, and is named accordingly.[1] The conformational behaviour of the bicyclic system under the study is furthermore restricted to the only equilibrium between the 'boat–chair' (BC) and the 'double chair' (CC) conformers due to the sufficient energy excess of the next possible 'double twist' (TT) form, that usually vanishes its ratio in the equilibrium mixture (Figure 1).

The state of the BC–CC equilibrium is governed by the conformational energy E_{conf} defined as the relaxation energy *via* the strain energies E_s of the individual conformers, BC *vs.* CC.

$$E_{conf} = E_s[BC] - E_s[CC] = E_{\varpi}[BC] - E_{\varpi}[CC] \quad (1)$$

It is also simply obtained from the total energy values of these structures (E_{ϖ}) calculated by an appropriate theoretical method (1).

Due to the unequivocally greater stability of the 'chair' (C) structure for a certain saturated six-membered ring, it is the CC structure that assumed to be optimal for the saturated bicyclo[3.3.1]nonane moiety (*i.e.*, $E_{conf} > 0$). However, the CC is often strongly destabilized by repulsion of *endo*-substituents in positions 3 and 7. On the other hand, the BC form should suffer from the endocyclic torsion (Pitzer) strain around the eclipsed bond pairs in the same 'wing' of the system: either (1–2) and (4–5) or (1–8) and (5–6). This is exactly the same strain type that is generally recognised to make the 'boat' (B) form of the saturated six-membered cyclic compounds to be the transition state (saddle point) rather than the conformer (*i.e.*, a local minimum of energy).[2] Additionally, the BC structures correspond to the 'chair–boat' (CB) conformations of the enveloping eight-membered ring, close to that of the optimal cyclooctane conformer,[3] whereas the CC bicyclic structure appears to be based on the higher energy 'double boat' (BB) cyclooctane conformation in this context. The overall picture of the conformational predominance is even more complex for derivatives, unsaturated and hetero analogues of bicyclo[3.3.1]-nonanes.[1,4] Therefore, the influence of 1-, 5- and 9-positioned substituents on the conformational behaviour of the bicycle could not be simply deduced from the basic statements of structural organic chemistry.[2,3]

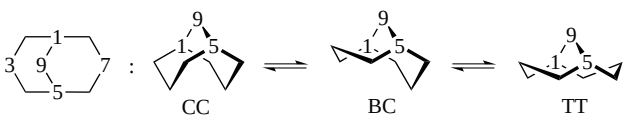


Figure 1 Conformational equilibria in 1,5,9-substituted bicyclo[3.3.1]-nonanes.

We have calculated the strain energy values E_s (Table 1) for the individual conformers using the hyperhomodesmotic bond separation reactions (BSRs)[5] that comprised a class of formal schemes for the improved accuracy of thermodynamic properties estimation (Figure 2).[6] Introduced initially for hydrocarbons, this class was later extended to cover amines,[7] ketones,[8] *etc*. All the E_s and E_{conf} values given in Table 1 are approximated from first-principles calculations using equation (1), where the total

Table 1 Conformational and strain energy of BC and CC conformers for the investigated bicyclo[3.3.1]nonane derivatives.

Structure	X	Y	Z	E_s/kcal mol^{-1}		E_{conf}/kcal mol^{-1}
				BC	CC	
1	CH	CH	CH_2	8.92	6.81	2.11
2	C–Me	CH	CH_2	5.78	3.51	2.27
3	C–Me	C–Me	CH_2	2.63	0.22	2.41
4	CH	CH	C=O	8.02	7.18	0.83
5	C–Me	CH	C=O	4.57	3.65	0.92
6	C–Me	C–Me	C=O	1.21	0.21	1.00
7	N	CH	CH_2	10.58	7.42	3.16
8	N	C–Me	CH_2	7.19	3.94	3.25
9	N	CH	CH_2	9.86	5.87	4.00

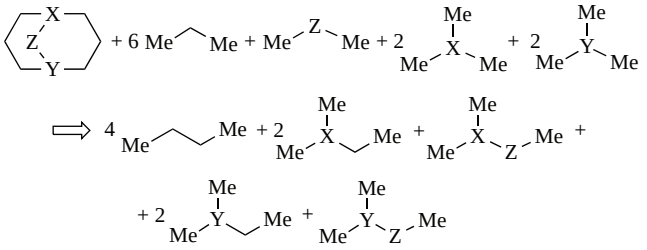


Figure 2 General scheme of bond separation reactions for the investigated bicyclo[3.3.1]nonane derivatives.

molecular energy E_{ϖ} is obtained using an additive *ab initio* scheme:[9]

$$E_{\varpi} = E_{tot} + E_{ZPE}. \quad (2)$$

An expression (2) for the molecular energy unites the total energy E_{tot} and zero-point vibrational correction E_{ZPE}, where the latter value is resulted from the unconstrained geometry optimization followed by the finite difference Hessian calculations at the 'resolution of identity' (RI) MP2[10,11] level of theory using the cc-pVTZ orbital basis set.[12] The optimal MP2 energy values are reported below as E_{MP2}. We used the results of the explicitly F12(D) formulated domain-based (DLPNO) CCSD(T) calculations for optimized structures extrapolated to the orbital basis set limit starting from cc-pVTZ-F12 using a CABS for E_{tot} in equation (2). All *ab initio* calculations were performed using version 4.2.1 of the ORCA program system.[13]

Unless otherwise noted, the conformational energy E_{conf} and strain energy E_s values are given in kcal mol^{-1}, while any other energy quantity is in atomic units (hartrees, E_h); interatomic distances (*e.g.*, bond lengths) are in angstroms (Å). Wherever the structure formula represents the BC form here, its convex hexagon corresponds to the 'chair' (C) cycle.

The notion of 'conformational effect'[14] has been recently adopted as the difference in conformational behaviour for a compound under investigation as compared to a certain prototypical hydrocarbon structure in both qualitative features and quantitative characteristics, as shown in Figure 3, according to the chosen theoretical model of chemistry.[8] Thus defined, it could be easily quantified as the difference between the conformational energy of the appropriately substituted compound and that of the unsubstituted one:

$$\delta E(X) = E_{conf}(X) - E^{(0)}_{conf}. \quad (3)$$

The results for the compounds of different classes such as hydrocarbons, bicyclic ketones, and amines are summarized in Figure 4. The present set of structures represents three types of substitution, and mean values of their conformational effects could be easily found:

$\langle \delta E^{(1,5)}(C–Me) \rangle = 0.11$ kcal mol^{-1} for the methyl group introduction in positions 1 and 5;

$\langle \delta E^{(9)}(C=O) \rangle = -1.34$ kcal mol^{-1} for the carbonyl group introduction in position 9;

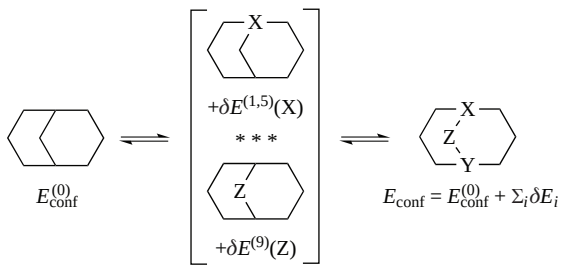


Figure 3 Conformational effects of 1,5,9-substitution in bicyclo[3.3.1]-nonane derivatives.

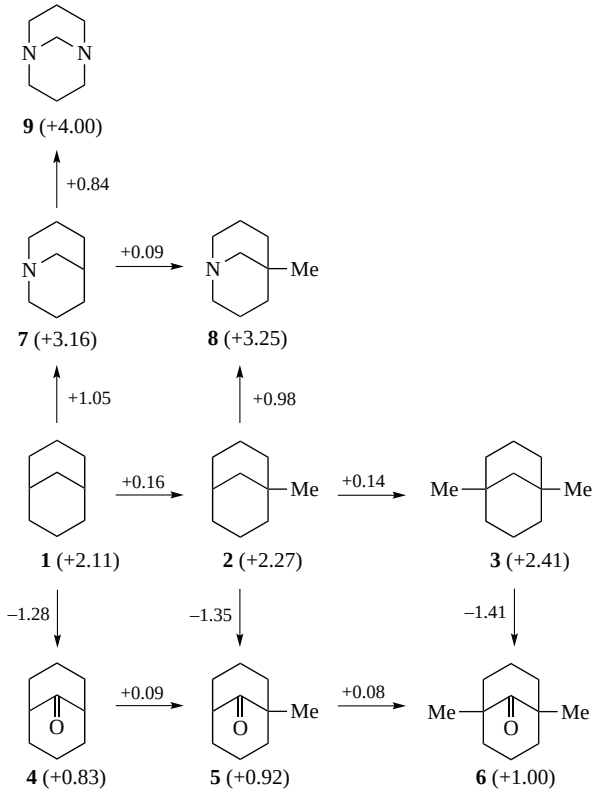


Figure 4 Conformation energy effects for various types of substitution in bicyclo[3.3.1]nonanes including 1-methylation, 1,5-dimethylation (from left to right), 9-carbonyl introduction (down), and 1-aza and 1,5-diaza hetero analogy (up); all energy values are in kcal mol^{-1}: values of δE are each near a corresponding arrow, values of E_{conf} are bracketed below the corresponding structures. Positive signs show the CC stabilization, while negative ones indicate the decrease in the energy of BC forms.

$\langle \delta E^{(1,5)}(N) \rangle = 0.96$ kcal mol^{-1} for the nitrogen hetero atom in positions 1 and 5.

The introduction of a methyl substituent in position 1 and further in position 5 slightly increases the relative stability of the CC form in spite of the conclusions from the earlier force field calculations.[15,16] The introduction of N hetero atom in the same positions makes the CC even more favourable. On the opposite, the carbonyl group substitution in position 9 decreases the E_{conf} and stabilizes the BC form *vs.* the CC one though the latter still remains preferable. Deviations of the values in Figure 4 from the corresponding mean values are small enough to conclude that the latter are transferable so that the presented additive conformation effect approach could succeed in some preliminary E_{conf} estimation.

In conclusion, the vibrationally corrected strain and conformational energy values were calculated for least-energy conformer pairs of several 1,5,9-substituted bicyclo[3.3.1]nonanes using high level correlated *ab initio* methods. All calculated molecules exhibit the CC form predominance in their conformational behaviour. Conformational effects for three formal substitution types, *i.e.*, 1-methyl, 1,5-dimethyl, 9-oxo, 1-aza and 1,5-diaza substitution, were numerically characterized. Both types of 1,5-substitution make the CC form even more favourable, while introduction of a carbonyl group in position 9 sufficiently stabilizes the BC conformer *vs.* the CC one, though the latter still remains optimal.

This work was supported by the state assignment of the Department of Chemistry, Lomonosov Moscow State University (project no. 121021000105-7).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.007.

References

1 N. S. Zefirov and V. A. Palyulin, *Top. Stereochem.*, 1991, **20**, 171.
2 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
3 E. L. Eliel, S. H. Wilen and M. P. Doyle, *Basic Organic Stereochemistry*, Wiley-Interscience, New York, 2001.
4 I. S. Bushmarinov, I. V. Fedyanin, K. A. Lyssenko, V. L. Lapteva, S. A. Pisarev, V. A. Palyulin, N. S. Zefirov and M. Yu. Antipin, *J. Phys. Chem. A*, 2011, **115**, 12738.
5 S. E. Wheeler, K. N. Houk, P. von R. Schleyer and W. D. Allen, *J. Am. Chem. Soc.*, 2009, **131**, 2547.
6 S. E. Wheeler, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, **2**, 204.
7 S. A. Pisarev, V. A. Palyulin and N. S. Zefirov, *Dokl. Chem.*, 2013, **450**, 131 (*Dokl. Akad. Nauk*, 2013, **450**, 185).
8 S. A. Pisarev, D. A. Shulga, V. A. Palyulin and N. S. Zefirov, *Struct. Chem.*, 2019, **30**, 509.
9 A. Tajti, P. G. Szálay, A. G. Császár, M. Kállay, J. Gauss, E. F. Valeev, B. A. Flowers, J. Vázquez and J. F. Stanton, *J. Chem. Phys.*, 2004, **121**, 11599.
10 C. Møller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618.
11 F. Weigend and M. Häser, *Theor. Chem. Acc.*, 1997, **97**, 331.
12 T. H. Dunning, Jr., *J. Chem. Phys.*, 1989, **90**, 1007.
13 F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2018, **8**, e1327.
14 N. S. Zefirov, *Tetrahedron*, 1977, **33**, 3192.
15 M. J. Bovill, P. J. Cox, H. P. Flitman, M. H. P. Giu, A. D. U. Hardy, P. H. McCabe, M. A. Macdonald, G. A. Sim and D. N. J. White, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1979, **35**, 669.
16 G. A. Sim, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1979, **35**, 2455.

Received: 28th April 2021; Com. 21/6547