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Ab Initio Conformational Analysis of 3,7-Diacetyl-3,7-Diazabicyclo[3.3.1]Nonanes*

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Abstract

Introduction: The importance of the conformational behavior comprehension for proper prediction of properties for a certain compound or for a class of compounds is indisputable. For 3,7-diacylbispidines (3,7-diacyl-3,7-diazabicyclo[3.3.1]nonanes), only "double chair" (**CC**) conformers were prior found experimentally in the condensed phase, which differ only in the acyl groups relative orientation, "parallel," **pa** or "antiparallel," **ap**. However, 2 other conformer families, "boat-chair," **BC** and "double twist," **TT**, are known for other bicyclo[3.3.1]nonane derivatives. Features of these conformers would be useful for the accurate prediction of properties and activities of the compounds. **Methods:** Second-order perturbation theory *ab initio* techniques (MP2) in the triple-zeta correlation-consistent orbital basis set cc-pVTZ was employed to optimize the electronic energy for structures, to characterize the optimized structures as potential energy surface minima by energy hessian eigenvalue calculations and to calculate zero-point energy corrections for the minima using the "rigid rotor-harmonic oscillator" approximation to model the molecular ensemble thermodynamics. Additionally, the computational chemical thermodynamics benefits much from the concept of the molecular strain and its energy assessed successfully through the bond separation energy formalism. We combine both approaches in our investigation to find and consistently characterize the conformers previously unknown for the compounds under the studies. **Results:** Six possible conformers were found for the investigated 3,7-diacetyl-3,7-diazabicyclo[3.3.1]nonanes **1-4**, formed by combining the skeletal conformation changes with the internal rotation of acyl substituents. The conformational behavior is quite similar for all investigated molecules. In all cases, the **CC** conformation is optimal for the bicyclic skeleton and **ap** orientation prevails over **pa** for 2 acetyl groups. This prevalence is 4-5 kcal mol^{-1} in **CC** and less than 1 kcal mol^{-1} in other skeletal forms, making rotation of 2 acyl groups in **BC** and **TT** almost independent. Concerning the skeletal conformations, the common energy sequence **CC < BC < TT** is found. While the relative **BC** energy is 6-7 kcal mol^{-1} over the optimal **CC** structure, **TT** forms are all strained by more than 12 kcal mol^{-1}. **Conclusions:** For the first time, both **BC** and **TT** conformers of 3,7-diacetylbispidines were characterized by their strain and conformation energies together with known less strained **CC** forms. On the basis of our calculations, the relative energies of **BC** conformers are expected to be close to those of the **CC** acetyl amide bond rotamers found previously in experiment, therefore, their exclusion from the conformational behavior would look unjustified. On the contrary, **TT** conformers are found to be much more strained enough to be neglected in the conformational ensemble modeling.

Keywords

bispidines, amides, conformational analysis, internal rotation, amide resonance, nonempirical calculations, molecular modeling

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Introduction

Derivatives of 3,7-diazabicyclo[3.3.1]nonane (bispidines[1]) are similar to several classes of biologically active alkaloids, for example, lupanine and anagyrine, and considered as potential antiviral agents.[2,3] These tertiary amides are known to be strongly dependent upon the conformation in their manifold properties,[4] including diverse aspects of their biological activity.[5,6] However, after more than a century of structural investigations of bicyclo[3.3.1]nonane derivatives,[7] the principal

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*The paper is dedicated to Professor Hans-Jörg Schneider (University of Saarlandes, Saarbrücken, Germany) on the occasion of his 88th birthday.

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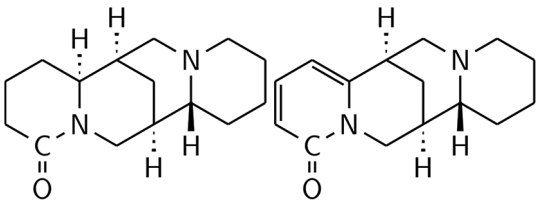
factors governing their conformational behavior are not yet completely clear despite the relative simplicity of the underlying transformations.[8]



(–)-lupanine (–)-anagyrine

Four skeletal conformers are commonly postulated for these molecules (Figure 1), named according to the forms of two 6-membered rings that comprised the bicyclic structure: "double chair," or **CC**, "boat-chair" (**BC**) / "chair-boat" (**CB**), and "double twist" (**TT**). All the length of time of studies the bicyclo[3.3.1]nonane moiety is considered mainly as the *seco*-adamantane structure,[7] so that in all cases the **CC** conformer is considered as the most stable as it is comprised from the least-energy forms of saturated 6-membered rings. For the compounds with equivalent substituents in positions 3 and 7, a case of conformational degeneracy (**BC** ≡ **CB**) reduces the number of conformers to 3, but the total ratio of **BC** / **CB** family in an equilibrium ensemble of structures is increased.

Recent theoretical investigations[8] characterized the **CC** predominance in bispidines as weakened, compared to that of corresponding bicyclo[3.3.1]nonane derivatives. The **BC** / **CB** conformational family is thus lower in their relative energy and even becomes optimal for some classes of bispidine derivatives, including 3,7-dialkylbispidinones (properly substituted 3,7-diazabicyclo[3.3.1]nonan-9-ones; Z=CO). The X-ray structure elucidation experiments reveal the "boat-chair" conformation for several bispidines in solid state.[9,10] The substituents in positions 3 and 7 have little steric effect on it, for they are shown to prefer the less crowded (pseudo)equatorial conformations in all cases, as presented in Figure 1. The repulsive interaction between substituents in positions 3 and 7, destructively increasing energy for **CC** conformers, is reportedly minimized in this substituent orientation.[11]

Some of the 3,7-diacyl bispidine derivatives are known to possess useful properties, tightly bound to the state of internal rotation for the acyl substituents.[12,13] The **CC** is assumed to be the only possible skeletal conformation for 3,7-diacylbispidines based upon several X-ray diffraction studies.[14,15] The 3,7-repulsion is presumably reduced in these compounds[16] due to the polarizational conjugation of a nitrogen atom with a carbonyl group ("amide resonance"[17]). The most important stereochemical consequence of the amide resonance is the nitrogen atom planarization, increasing valency angles centered on it.[18] Concerning puckered azacyclic compounds it would suggest the tendency for cycle flattening in *N*-acyl derivatives compared to the corresponding unsubstituted or *N*-methyl (generally *N*-alkyl) compounds. This also means the perturbed relation and extended concurrency between Baeyer and Pitzer strain determining the optimal spatial structure, with participation of van der Waals transannular interaction for the medium rings, if any found for the investigated structures.

Considering the skeleton conformation to be invariant, the change in the relative acyl substituent orientation—parallel (**pa**) versus antiparallel (**ap**)—is found to be the principal conformational process in 3,7-diacylbispidines (Figure 2). Its state is believed to be governed by the long-range nonvalency (presumably electrostatic) interactions between C=O dipoles, and its energy is therefore minimized in the **ap** conformations.[12] Actually the **pa** orientation is nevertheless found in the solid state by the X-ray diffraction analysis for several related compounds with additional strain sources.[19,20] The ratio of **pa** conformation is greater in polar media due to its more polar character or in the presence of metal cations, that are able to form chelate complexes with 2 carbonyl groups.[12]

The most common research techniques of the conformational analysis so far remain the experimental assessment of the state of conformational equilibria using the indirect observations of the conformational ratios from the NMR spectra

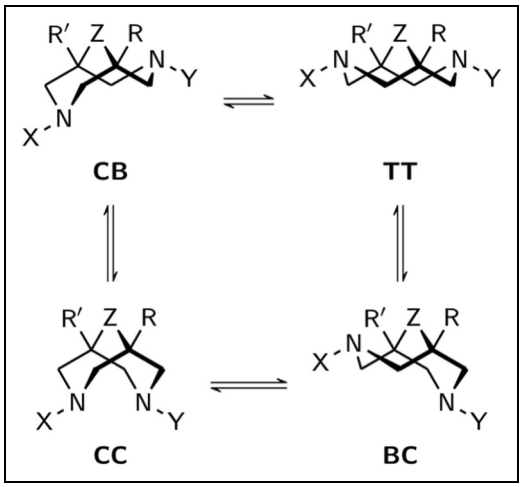


Figure 1. 3,7-dialkylbispidine skeletal conformations.

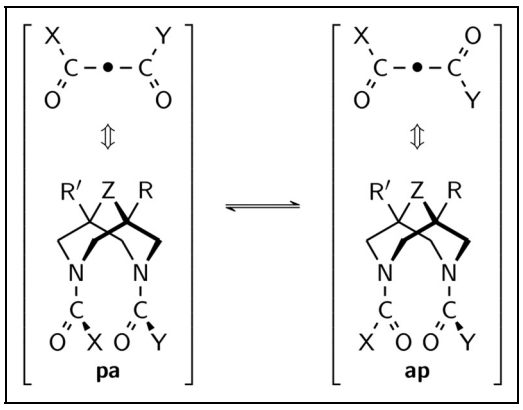


Figure 2. The "rigid double chair" pseudoatomic viewpoint on the internal rotation in 3,7-diacylbispidines.

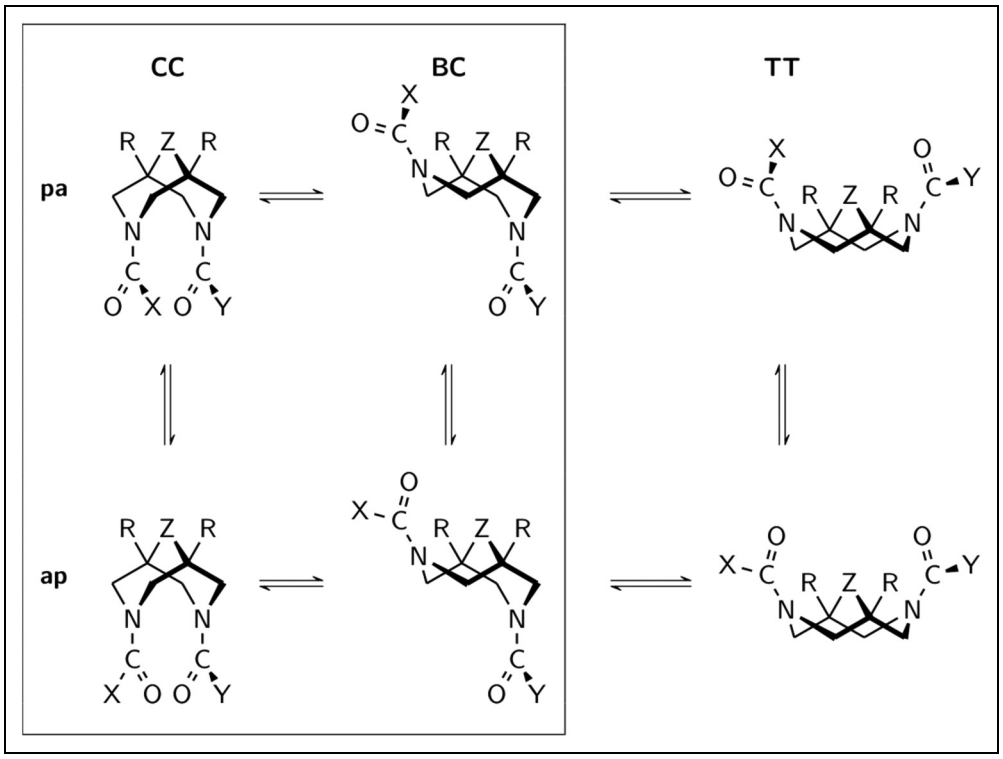
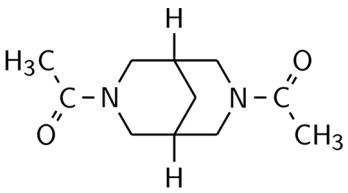


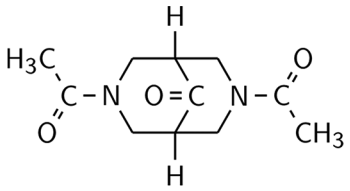
Figure 3. The complete conformation coupling diagram for 3,7-diacylbispidines.

and single-crystal X-ray diffraction structure determinations, that most often supplies us with the solid state conformer optimal structure. On the other hand, the whole conformation ensemble could be approximated using the structure and energy of forms obtained from the results of molecular modeling from first principles, using initially the minimal amount of the available experimental observations.

The present paper contains the detailed studies of potential energy surface (PES) minima of 3,7-diacylbispidines using the reliable high-level nonempirical correlated computational chemistry methods. Their possible changes in skeletal conformation were completely out of the scope of any computational studies due to the previous experimental findings. Actually, the coupling between the skeletal conformational interconversion and the carbonyl groups reorientation shall form the whole picture of the conformational behavior of the entitled compounds as in Figure 3, somewhat more complicated than reviewed above as based upon the experimental data. Here, we try to assess in greater detail (including all 6 possible spatial forms) the conformational behavior for 4 simplest 3,7-diacetylbispidines **1–4**.



1



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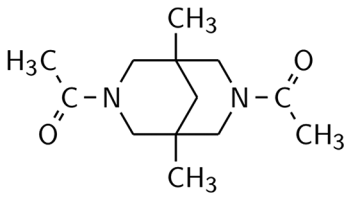

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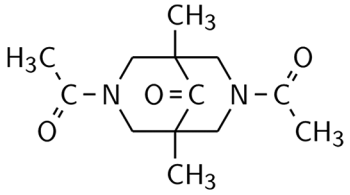

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Methods

Conformational energy E_{conf}(S) of a certain conformation of the molecular structure S is computed as the difference of the

energy value for the investigated conformation versus that of the lowest energy (optimal) conformer of the molecule (S_0) using either the absolute (optimized total, probably zero-point energy [ZPE]-corrected) energy E obtained from any kind of nonempirical calculations (1) or, similarly, using the molecular strain energy E_ς (2):

$$E_{conf}(S) = E(S) - E(S_0) \quad (1)$$

$$E_{conf}(S) = E_\varsigma(S) - E_\varsigma(S_0) \quad (2)$$

The latter is more consistent with the chemical concept of a conformational equilibrium as a form of the molecular potential energy relaxation and redistribution.[21] When making use of the decent means to quantify the molecular strain, the strain energy analysis allows to predict reliably the principal conformation features of molecule series including the investigated derivatives.

Hereafter, we apply the bond separation reaction (BSR) formalism to estimate the strain of a molecular structure. Following the implicit axiom of chemistry that the molecule is a union of chemical bonds between atoms, we evaluate the strain energy of a structure as the energy effect of the formation reaction of the target structure S from strainless fragments. The formal chemical reaction (3) of bond separation in S contains 2 types of reagents:

$$\sum_j b_j \cdot B_j \rightarrow S + \sum_i a_i \cdot A_i \quad (3)$$

Here, each B_j is a *bond prototype*, that is, a simplest molecule containing a chemical bond of a certain type found in S, and b_j stands for a number of bonds of this type. Each A_i is an *atomic reagent*, representing a type of atoms and a_i are stoichiometric numbers to equalize (3). An expression (4) is the form of the Hess' Law for the reaction (3). It allows to quantify the strain in any instant conformation of S, if its absolute energy E(S) is available, through the energy effect E_ς(S) of this reaction:

$$E_\varsigma(S) = E(S) - \underbrace{\left[\sum_j b_j \cdot E(B_j) - \sum_i a_i \cdot E(A_i)\right]}_{E_{(0)}(S)} \quad (4)$$

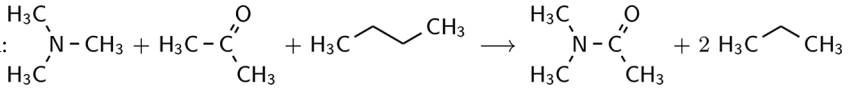
The proper choice of the bond set for the further separation and corresponding reagents allows for rather accurate strain estimation even when the electronic correlation treatment within the chemical theory level chosen for E is moderate and systematically incomplete (but the method should be dimension-consistent, eg, MP2). It is the simplicity of B_j, that allows one to suggest their being free of strain, for instance, in the course of internal rotation around the typed bonds (one of the fundamental conformational concepts), that could be attained by proper structure optimization, while A_i are free of such strain by definition due to the lack of rotatable bonds. So, the quantity $E_{(0)}(S) = \sum_j b_j \cdot E(B_j) - \sum_i a_i \cdot E(A_i)$ as defined in (4) is the energy of a given molecule as the composition of its unstrained bonds, hereafter referred to as the *off-strain molecular structure energy*. Therefore, the $E_\varsigma(S) = E(S) - E_{(0)}(S)$ value, which is not necessarily positive, could consistently measure both molecular strain and additional electronic stabilization for rather loosely related spatial structures of a certain molecule.

Structures were optimized at the (RI)MP2[22,23] / cc-pVTZ[24] level of theory using the 5.0.4 version of the ORCA quantum chemistry package.[25] Models were initially prepared using the OpenBabel[26] and Avogadro[27] software. None constraints were applied either in the course of geometry/energy optimization resulted in E_2 energy values or in the following finite difference Hessian computations supplied the optimized PES points with the quantum ZPE correction value E_{ZPE}. All optimized structures are herewith characterized as PES minima by all eigenvalues of molecular Hessian being positive.

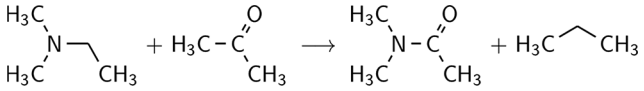
Results and Discussion

First, it should be mentioned that elementary paths of conformational conversion in bicyclo[3.3.1]nonane derivatives drawn here by arrows are hypothetical. Here, they are based upon the known least energy paths of conformational change for 6-membered rings. Each arrow should be assigned to an elementary transformation, characterized by a transition state, but none of them is characterized by now.

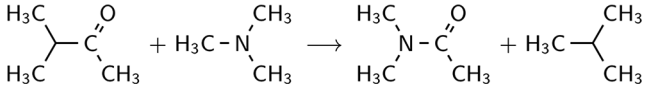
To "turn" an atomic or a bond type into a corresponding reagent molecule is to fill the free valency of the corresponding molecular subgraph—for example, N → −N< or CO → >C=O—by an appropriate univalent "ending" group. The simplest way is their formal "hydrogenaton": N → NH_3, CO → H_2CO, N−CO → H_2N−CHO. There are no special restrictions to use any other compliant group, other than the context in which the BSR approach is applied. Here, we use "methylation": N → $N(CH_3)_3$, CO → $(H_3C)_2CO$, N−CO → $(H_3C)_2N$−$COCH_3$ that is shown to be both practical and accurate in the general context of computational organic thermochemistry. The absolute energy values for reagents at this level of theory are published elsewhere for most of molecules to be used hereafter[8,21,28] (summarized in the "Supporting Information" section; Table S1 for prototypes, Table S2 for atomic reagents) with a valuable exception of *N*, *N*-dimethylacetamide required to estimate the strain in molecules containing the tertiary amide fragment: >N−C(=O)−. From our calculations, we found $E_2 = -287.26163$ au; $E_{ZPE} = 0.13141$ au for this molecule. The energy of "tertiary amide resonance" could be estimated as −17.85 kcal mol^{-1} through the energy effect of the

following reaction: 

changing both π and σ-character of the N atom binding environment, and −16.85 kcal mol^{-1} from the reaction:

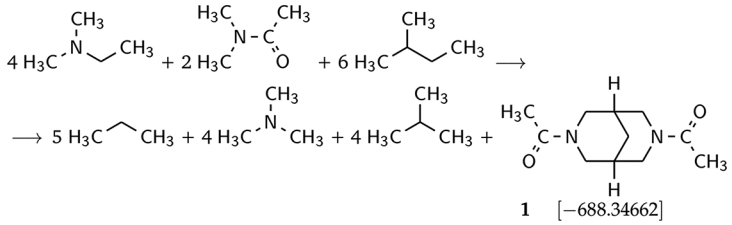


where π-conjugation with carbonyl group is introduced. Another related reaction of π-system extension:

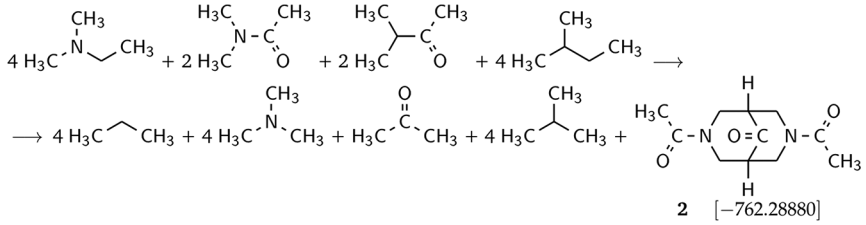


gives −18.71 kcal mol^{-1}. The small interval of ±1 kcal mol^{-1} that contains all these values reveals the small amount of σ-contribution to the amide bond stabilization, the π-effect to be sufficiently greater. It should be mentioned that these values are close to the energy of "primary amide resonance" calculated as −19.6(3) kcal mol^{-1} from the experimental thermochemistry, and −18.3 kcal mol^{-1} from high level *ab initio* calculations.[17] The intricate theoretical question of the amide groups equilibrium (non)planarity is left for further possible special publications.

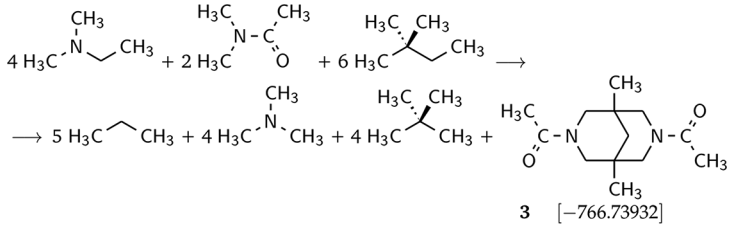
The general bond separation scheme for 3,7-acetylbispidines (Figure 4) includes both the skeletal bonds and the amide substituent attachments. The equations derived for the investigated structures **1–4** are shown below including the values of the off-strain molecular structure energy $E_{(0)}$ (in atomic units, bracketed).



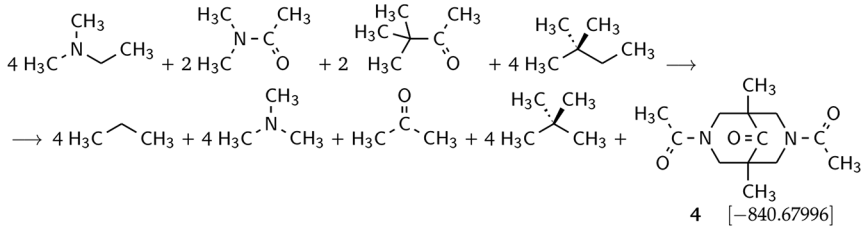
1 [−688.34662]



2 [−762.28880]



3 [−766.73932]



4 [−840.67996]

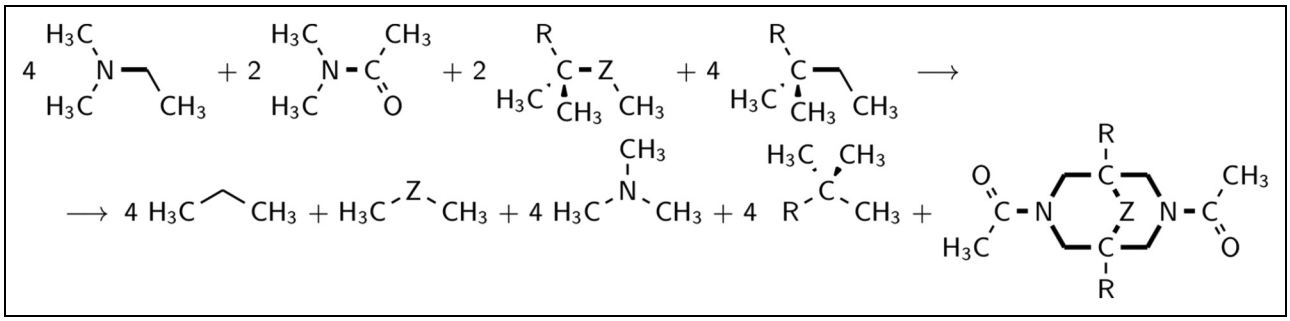


Figure 4. The general scheme of bond separation in 3,7-diacetylbispidines. Separated bonds are given in bold.

Table 1. Strain and Conformational Energies of 3,7-Diacetylbispidines **1–4**, kcal mol^{-1}.

Structure	Energy, kcal mol^{-1}	ap BC	ap CC	ap TT	pa BC	pa CC	pa TT
1	E_ς	–0.03	–6.38	6.44	0.52	–1.87	6.61
	E_{conf}	6.35	0	12.82	6.90	4.51	12.99
2	E_ς	3.35	–3.11	10.32	3.86	1.60	10.21
	E_{conf}	6.46	0	13.43	6.97	4.71	13.32
3	E_ς	–6.61	–13.61	0.52	–6.05	–8.90	0.61
	E_{conf}	7.00	0	14.12	7.55	4.70	14.21
4	E_ς	–4.82	–11.68	2.34	–4.31	–6.83	2.24
	E_{conf}	6.85	0	14.01	7.37	4.84	13.92

They all satisfy the criteria of hyperhomodesmotic reaction scheme (atom and bond types being equal in total numbers of corresponding atoms and bonds for both left and right parts of an equation) as extended consistently from that initially formulated for hydrocarbons[29,30] to cover heteroatomic molecules,[28] while the amide resonance schemes are homodesmotic. Here, the negative values of E_ς exhibit the successful realization of the double "amide resonance" conjugation phenomena as it is mentioned in literature.[17,31]

All conformers assumed from the scheme of skeleton / substituents conformation coupling in Figure 3 were optimized and characterized as PES minima by Hessian calculations. The results are collected in the "Supporting Information" section (Table S3). Corresponding strain and conformational energy values are presented in Table 1. In all investigated molecules, the "double chair" skeletal forms with antiparallel acetyl groups orientation (**ap**) are optimal, and **CC** with their parallel (**pa**) orientation is the next in energy. However, **BC** forms are not sufficient in their strain overhead to neglect them in the general conformational behavior description. The **pa–ap** energy gap in non-**CC** conformers is substantially lower, than that for **CC** ones. All "double twist" conformations are strained enough to be painlessly excluded from the overall ensemble.

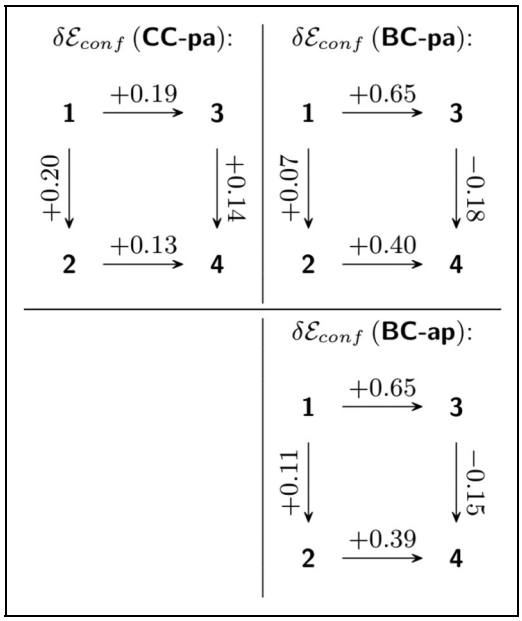


Figure 5. Substitution conformational effects in least-energy conformers, kcal mol^{-1}.

Their conformational energy is about a twice of that for **BC** / **CB** conformations: $E_{conf} > 12$ kcal mol^{-1}.

Bispidinones **2** and **4** are in general more strained than bispidines **1** and **3** with methylene group in position 9. Two methyl substituents in positions 1 and 5 reduce the strain in both 9-methylene compounds (**3** vs **1**) and in bispidinone **4** as compared to **2**. Figure 5 describes conformational effects[8,21] from both types of substitution—(H → CH_3) in both positions 1 and 5 and (CH_2 → C=O) in position 9 (from left to right and from up to down, respectively)—on 3 lowest conformational energies. Substitution of first type inevitably leads to the increase in **CC** predominance ($\delta E_{conf} > 0$), the second is rather contradictory: the **CC** relative stabilization for 1,5-unsubstituted compound **1**, and the **BC** stabilization with $\delta E_{conf} < 0$ for 1,5-dimethyl derivative **3**. This is valid for both **ap** and **pa** conformations.

Conclusions

Correlated *ab initio* calculations on the structures and energy of conformers of 4 bispidine (3,7-diazabicyclo[3.3.1]nonane) derivatives allow to add some points to the known picture of their conformational behavior. Conformations with antiparallel acyl group orientation in 3,7-diacetylbispidines are shown to be lowest in energy and thus dominating the parallel-oriented forms in the equilibrium ensemble. Studies of the conformational behavior show that **CC** conformations are optimal for 3,7-diacetylbispidines, where the only internal rotation restriction for the substituents is a so-called "amide flattening" of the nitrogen heteroatoms in positions 3 and 7 of the bicyclic moiety. However, an assumption on the bicyclo[3.3.1]nonane moiety being rigid in the acetyl internal rotation process, issued previously based upon the review of several X-ray diffraction structure determination experiments looks weak, since all the non-**CC** conformers (ie, **BC** and **TT**) are found stable for these compounds, and both energy gaps (**BC** vs **CC** and **TT** vs **BC**) are comparable in their absolute value (ca. 7 kcal mol^{-1}) with that of parallel–antiparallel forms in **CC** (around 5 kcal mol^{-1}). All these makes their previous exclusion from the overall picture of the conformational behavior unjustified, whereas all **TT** forms could easily be excluded owing to their high conformational energy values. Small energy differences between parallel and antiparallel conformations in non-**CC** forms reveal the independence in the remote acetyl group conformational (rotational) behavior in these structures. Molecular strain estimations show that introduction of a carbonyl group in position 9 leads to extra strain in the resulted bicyclic compounds compared to their unsubstituted counterparts while the introduction of 2 methyl groups in positions 1 and 5 leads to partial relaxation of strain.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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