

## Research Article

# An Investigation of the Enolization and Isomeric Products Distribution in the Water Promoted Aldol Reaction of Tropinone and Granatanone

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The *exo,anti/exo,syn*-diastereoselectivity of water promoted direct aldol reactions of tropinone and granatanone (pseudopelletierine) is strongly dependent on the amount of water added and aromatic aldehyde used. DFT methods were applied to calculate the free energies of tropinone and granatanone enols, transition states, and isomeric aldol products. A theoretical model was verified by comparison of results from several DFT methods and functionals with experiments. The 6-31g(d)/CPCM method proved most suited to the problem, although all methods tested predicted similar trends. Explicit inclusion of a water molecule bonded to the amino ketones resulted in increased stability of the enol forms. The dependence of the *anti/syn*-diastereoselectivity on the amount of water used may be rationalized on the basis of change in the polarity of the reaction medium. The predicted stabilities of competing products agreed with experimental results supporting the notion of thermodynamic control. The isomeric products distributions for the aldol reaction of several aromatic aldehydes in solventless (neat) conditions were accurately calculated from free energies of the aldol addition step in the gas phase using B3LYP/6-31g(d) method and in aqueous conditions using the CPCM-B3LYP/6-31g(d) model. Our methodology can be useful for predicting the outcome of this type of aldol reactions.

## 1. Introduction

The organocatalytic aldol reaction [1] is one of the most powerful methods for forming C-C bonds in a highly stereocontrolled manner. Since the pioneering work of List's group [2] concerning the application of (L)-proline as a catalyst, a variety of amines have been designed as organocatalysts for aldol reactions [3] aiming at high efficiency, wide applicability, relatively low cost, and availability from the chiral pool. Primary and secondary amines are the most popular NH-functionalised organocatalysts [3, 4]. The typical mechanism of catalysis of a direct aldol reaction based on the formation of (Z)- or (E)-enamine intermediates is well known [4, 5]. The use of tertiary amines as catalysts is rather underrepresented. However, tertiary amine catalysts involving, for example, DBU [6], DIPEA [6], cinchona alkaloid derivatives [6, 7], or pyridine [8, 9], have been applied in direct aldol reactions, typically under anhydrous

conditions. The role of nonenamine catalysts often remains unclear, but it has been assumed that these amines often act as general base catalysts. After Pihko and coworkers [10] demonstrated that water increases efficiency of (L)-proline catalysed aldol addition, the study of reactions in the presence of water had intensified, including those catalysed by tertiary amines, for example, DABCO [11]. Investigations involved a combination of computational and experimental methods or computational studies (especially based on DFT methods) [12]. However, these studies have not involved reactions contingent on the presence of water and promoting role of tertiary amine functionality present in the substrate/product itself.

Chiral lithium amide promoted aldol reaction of tropinone (**1**, 8-methyl-8-azabicyclo[3.2.1]octan-3-one) has been used by us [13, 14] and others [15, 16] as a diastereoselective and enantioselective key step in several syntheses of tropane derivatives, mostly natural tropane alkaloids.

Before our preliminary communication on aldol addition of tropinone and granatanone (pseudopelletierine, **2**, 9-methyl-9-azabicyclo[3.3.1]nonan-3-one) to aldehydes (Scheme 1) in the presence of water [17], the only method for accessing these *exo,anti*-aldols [18, 19] or related nor-analogues [20, 21] was reactions promoted by lithium amide bases under anhydrous conditions. Moreover, our solventless reaction in the presence of small (ca. equimolar) amounts of water [17] is the only practical method for preparation of the *exo, syn* isomers [18, 22]. Because no chiral additives are present in the reacting mixture, the reaction is diastereoselective but not enantioselective and provides products in the racemic form.

Herein, we disclose in full our theoretical investigations on stereoselectivity of tropinone and granatanone aldol reactions, computations of reaction parameters, and isomer stability, as well as suitability of computational methods at different levels of theory for rationalization of the results of these “green” reactions.

## 2. Results and Discussion

We proved that water and a tertiary nitrogen atom built into substrate are necessary for the effective, direct, and spontaneous aldol reaction of cyclic ketones with aromatic aldehydes [23]. In a preliminary communication, we proposed that in the reactions of tropinone and granatanone with benzaldehyde the origins of the stereoselectivity may be found in thermodynamic equilibration of the internal hydrogen bond stabilized conformers [17, 24] of the competing isomeric products (Scheme 1), unless preferential crystallization of solid products is involved. We found that calculated stabilities of the isomers and their distributions could accurately reproduce experimental results for reactions without solid product deposition. Interestingly, gas-phase calculations best approximated solventless (neat) reaction conditions [24].

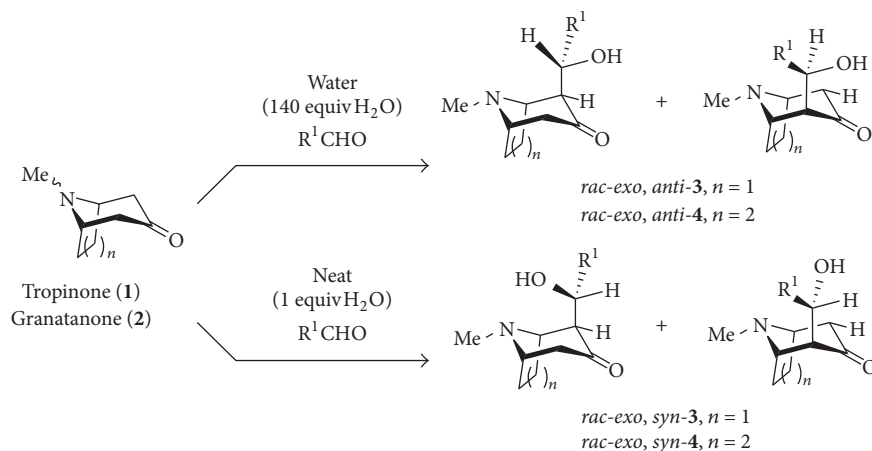
Therefore, with hopes of possibly tuning and expanding the scope of the method on prediction of reactions feasibilities with new reactants, we found it worthwhile to further study the theoretical methods for description of the processes. A good correlation of DFT results and experiments could possibly allow for prediction of outcomes of such reactions.

**2.1. Enolization and Hydration of Cyclic  $\beta$ -Amino Ketones in the Presence of Water.** As such reactions had no precedents in the literature, we approached the problem by comparing experimental results with data obtained in a theoretical manner, analogous to the one used by Houk for acetone reaction and invoking ketone enol [26]. Water catalysed tautomerization has been studied by experimental [27] and computational methods [28, 29]. In our case one could assume involvement of the general base catalysis in tropinone and granatanone enolization [30]. However, the success of the reactions is dependent on the presence of the amine nitrogen in the substrate and pH of the reaction medium (see Supplementary Material available online at

<http://dx.doi.org/10.1155/2016/4674901>) (optimized geometries and frequencies of the invertomers in methanol). This suggests involvement of hydroxide ion (specific base). Ketone enolization needs base or acid catalysis [31] and enolization in the presence of tertiary amines in water is commonly known [32, 33]. Aqueous tropinone (**1**) and granatanone (**2**) solutions (0.1 M) show pH ca. 10 and 9.2, respectively. This corresponds to calculated  $pK_b$ , 7.0 and 8.6 for these bases; thus, granatanone is a slightly weaker base than tropinone (both amino ketones are weaker than closely related amino alcohol, tropine (estimated  $pK_b$ , ca. 3.8) or triethylamine ( $pK_b$ , ca. 3.4)). Nonetheless, both amino ketones are basic enough and sufficiently soluble to give considerable concentration of hydroxide ions (strong specific base) and, as a result, effect relatively rapid ketone enolization in water. This is experimentally indirectly observable through spontaneous  $\alpha$ -deuteration in  $D_2O$  solution (see supporting information) (exchange of the axial hydrogens in the  $\alpha$ -position in granatanone is faster (ca. 90% exchange for deuterium in 2 h), then in tropinone (ca. 70% deuteration in 2 h) as observed by  $^1H$ -NMR spectroscopy). The spontaneous deuteration is faster than aldol reaction, the rate of which depends also on reactivity of the aldehyde used, indicating that the rate limiting step of the whole process is not the enolization. Thus, addition of water results in a relatively fast self-enolization of **1** and **2**, in the observed aldol reaction time frame [17]. The question whether the presence of water influences the ketone-enol preequilibrium, changing enol concentration in these reactions, needs to be addressed, for example, by computations (*vide infra*).

Negative results obtained under the same aqueous conditions with other reactive electrophiles (see supporting information), including electrophiles known to give products in reaction with tropinone enolates (e.g., cyanofornate and chlorofornates [19, 34]), suggest that aldehydes are privileged reagents in this context.

The appreciation of the configurational preferences of N-methyl group in tropinone and granatanone is vital for understanding dissimilarities in their reactivity. Considering enolization of the  $\beta$ -amino ketones in the presence of water one could assume involvement of hydrated forms. The studies on the hydration of tropinone have been conducted in Cocinero's group. They applied Fourier-transform microwave spectroscopy and theoretical calculation to show that the tropinone  $\cdots H_2O$  monohydrated complex is stabilized by a hydrogen bond formed between one molecule of water and the tertiary amine group [35]. Furthermore, their results agree with our findings that an equatorial N-invertomer of tropinone predominates in aqueous solution [36]. We found also that other N-alkyl substituted nortropinones have a tendency to appear in equatorial conformation [37, 38]. However, the opposite axial configuration of the N-methyl group was observed in a crystal of tropinone without a molecule of water [39]. Our previous NMR study on equatorial/axial position of the N-methyl group indicated axial preference in granatanone (pseudopelletierine) in water [36]. The same axial position of N-methyl substituent in the crystal of granatanone with and without a molecule of water was observed by us in this study. We observed for the first



SCHEME 1: Water dependent stereoselective formation of either *exo,anti* or *exo,syn*-aldols of tropinone and granatanone [17].

time that granatanone has a tendency to crystalize from *n*-hexane/diethyl ether mixture, without exclusion of moisture, as a hemihydrate ( $2 \cdot (1/2)\text{H}_2\text{O}$ ); thus, the granatanone crystal without a molecule of water was obtained from dried solvents.

Two crystal structures of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one (2) and its hemihydrate ( $2 \cdot (1/2)\text{H}_2\text{O}$ ) have been experimentally determined by single crystal X-ray diffraction. The crystal structure of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one (Figure 1) contains two granatanone molecules in the asymmetric unit, which suggests a classical hydrogen bond network within a crystal lattice. The crystal structure of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one hemihydrate (Figure 2) contains two granatanone units and one water molecule in the asymmetric unit. A water molecule is involved in intermolecular interactions with two symmetry independent molecules and two hydrogen bonds:  $\text{O1} \cdots \text{N9}$  with  $\text{O1} \cdots \text{N9} = 2.934(2) \text{ \AA}$  and  $\text{O1} - \text{H1B} \cdots \text{N9} = 168(3)^\circ$  and  $\text{O1} - \text{H1A} \cdots \text{N19}$  with  $\text{O1} \cdots \text{N19} = 2.862(2) \text{ \AA}$  and  $\text{O1} - \text{H1A} \cdots \text{N9} = 174(3)^\circ$  are generated between a water molecule and heterocyclic nitrogen atoms. In both crystal structures, granatanone molecules show a very similar conformation. In all cases, piperidine and piperidinone rings adopt a chair conformation with very similar puckering parameters [40], shown in Table 1 in Supplementary Material.

The question arises how the bonding of the nitrogen to water, observed in the crystals, or an alternative bonding of the carbonyl oxygen to water may influence the enolization equilibrium of the bicyclic amino ketones.

**2.2. Evaluation of Computational Methods.** To assess the accuracy of different basis sets/DFT functionals combinations in relation to our systems, we performed systematic benchmark calculations. Previously [24], we found the B3LYP/6-31G(d) [41, 42] method as a good tool for investigating the stereoselectivity in the aldol reaction of the bicyclic amino ketones in the presence of water. The B3LYP method with larger basis set (6-311++G(3d,3p) [43]) and the BH&HLYP/cc-pVDZ [44, 45] method were also successfully validated in investigating tropinone and granatanone N-invertomers equilibria [36]. Recently, a  $\text{M0n}$  ( $n = 5, 6$ )

[46] family of functionals was introduced and widely used in different areas of chemistry [46]. Therefore, because of the excellent performance with respect to the prediction of relative energies for gas-phase monosaccharide isomers [47], we also included this method in our assessment. Overall, we employed six different DFT functional/basis set combinations, including one tested for organocatalytic reactions, B3LYP/6-31(d,p) [48]. Considering the relative stability of four H-bond stabilized forms of product, shown in Figure 3, has been found successful for rationalization of stereochemical outcome of this reaction [24]. Using the same approach, the results of the current method evaluation are presented in Table 1 (including deviation from experimental data) and are plotted in Figures 4 and 5. It is evident that in the gas phase all the methods pointed out to significant dominance of the HB-N form of *exo,syn*-aldols (Figures 4 and 5). For the water phase, the calculated ratios differ fairly significantly depending on the method used, although both HB-N forms dominate in all cases (see Figures 4 and 5). To assess the influence of increasing the basis set used, the B3LYP/6-311++g(3d,3p) method was also used to compare with the lower level calculations. Surprisingly, the simplest and the least demanding B3LYP/6-31g(d) can be credited with highest confidence in the quantitative respects of the issue investigated, whereas the worst agreement was observed for the reportedly highly accurate M062X functional. It may also be concluded that larger than 6-31g(d) basis sets with diffuse functions (e.g., 6-31G(d,p) and 6-311++G(3d,3p)) do not improve results.

Satisfactory (but worse than for B3LYP) accuracy was also noted for the BH&HLYP functional. Comparison of calculated MAD of the B3LYP for the simplest 6-31g(d) (A) and the most computationally demanding 6-311++G(3d,3p) (B) basis sets is shown in Tables 2 and 3. In general, the data (Tables 2 and 3) show that the structure of the aldehyde used should not affect the conclusions of method evaluation. The agreement of the B3LYP/6-31g(d) results with experimental results confirmed this functional/basis set combination as

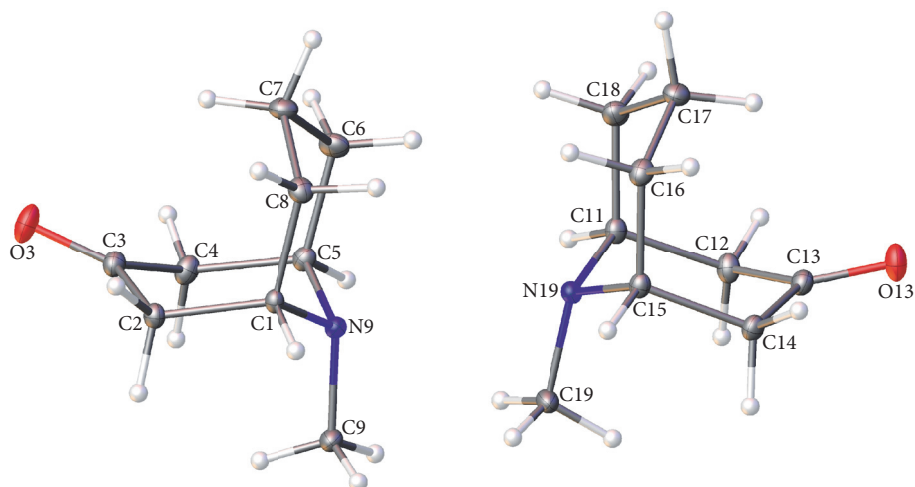


FIGURE 1: The view of the asymmetric unit of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one. Displacement ellipsoids are drawn at the 30% probability level. The figure was prepared with OLEX2 [25].

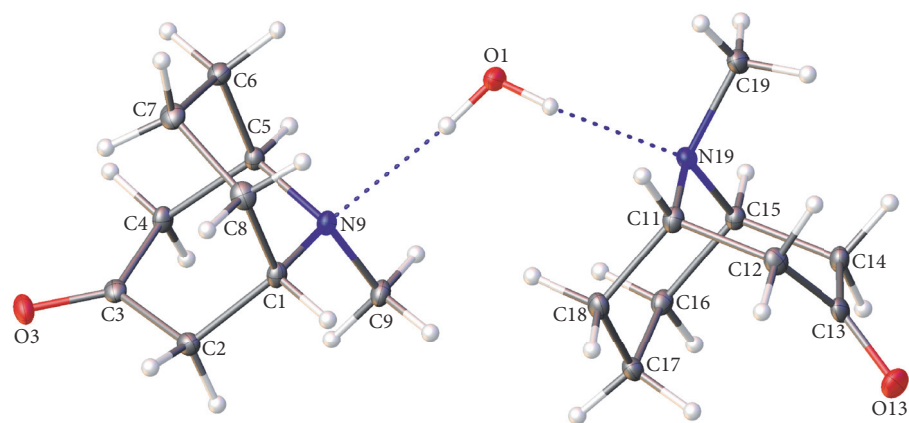


FIGURE 2: The view of the asymmetric unit of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one hemihydrate. Displacement ellipsoids are drawn at the 30% probability level. Dashed lines represent hydrogen bonds. The figure was prepared with OLEX2 [25].

the most adequate for modelling the progress of these aldol reactions; thus, this method was used in the discussion through this study.

**2.3. Computational Study of the Reaction.** To consider all the possible forms of reacting donor species (Figure 6), we calculated the  $\Delta G$  of the enol forms **5** and **6**, the zwitterionic forms (protonated enolates, **7** and **8**), a dimer of protonated tropinone and tropinone enolate (**9**), and the hydrated zwitterionic forms (**10** and **11**). At the B3LYP/6-31g(d) level the zwitterionic forms were estimated to be much higher in energy than the enol forms, by 11.2 and 13.2 in water for tropinone and granatanone. At the B3LYP/6-311++g(3d,3p) level, zwitterions were higher by 7.2 and 10.7 kcal/mol (Table 4). The dimer of enolate and protonated tropinone was even less stable than the zwitterion: in the gas-phase 44.7 and in water 26.0 kcal/mol above the enol form at the B3LYP/6-31g(d) level. According to our calculations in water, the hydrated zwitterionic forms (**10** and **11**, Figure 6)

have higher energies compared to nonhydrated species (**7** and **8**) by ca. 3 and ca. 6 kcal/mol at the B3LYP/6-31g(d) and B3LYP/6-311++g(3d,3p) levels, respectively. Thus, such enolate species, although imaginable, are highly unlikely to play a significant role in these reactions, which are run in an aqueous environment.

Calculated at the 6-311++g(3d,3p) level of theory, free energy differences between ketone and enol forms (Figure 6, predominating N-invertomers shown) suggest that, in water, granatanone should have a higher enol form contribution than tropinone (Table 4). Both tropinone (**1**) and granatanone (**2**) should exhibit a higher percentage of the enol forms (lower  $\Delta G$  of enolization) than typical ketones, for example, cyclohexanone (7.36 kcal/mol and  $\text{p}K_{\text{enol}} = 5.4$  [49]) or acetone (9 kcal/mol [26] or 11.2 kcal/mol and  $\text{p}K_{\text{enol}} = 8.22$  [50]). The result at 6-31g(d) level suggests also a higher degree of enolization for granatanone (**2**) than for tropinone (**1**), thus properly reproducing the higher level results (Table 4). With this method, the free energies of enolization for **1** and

TABLE 1: Distributions of the products of the aldol reaction of tropinone and granatanone with benzaldehyde at 25 °C calculated with different methods.

Method [lit. ref.]	Reaction medium	Tropinone (exp. dr <sup>a</sup> neat 10 : 90, water 41 : 59)			Granatanone (exp. dr <sup>a</sup> neat 11 : 89, water 39 : 61)		
		Calculated dr <sup>b</sup> <i>anti</i> : <i>syn</i>	Deviation of calculated from experimental dr <sup>c</sup> [%]	MAD	Calculated dr <sup>b</sup> <i>anti</i> : <i>syn</i>	Deviation of calculated from experimental dr <sup>c</sup> [%]	MAD
M062X/6-31g(d)	Gas/neat	3 : 97	72	70	5 : 95	57	46.5
	Water	18 : 82	68		29 : 71	36	
BH&HLYP/6-31g(d)	Gas/neat	11 : 89	11	20	10 : 90	10	9
	Water	33 : 67	29		37 : 63	8	
B3LYP/6-31G(d)	Gas/neat	11 : 89	11	5.5	11 : 89	0	2
	Water	41 : 59	0		38 : 62	4	
B3LYP/6-31G(d,p)	Gas/neat	10 : 90	0	9.5	9 : 91	20	18
	Water	36 : 64	19		35 : 65	16	
B3LYP/6-311++G(3d,3p)	Gas/neat	17 : 83	84	56	16 : 84	54	33
	Water	47 : 53	28		36 : 64	12	
BH&HLYP/cc-pVDZ	Gas/neat	11 : 89	11	17	9 : 91	20	12
	Water	35 : 65	23		40 : 60	4	

<sup>a</sup>Diastereoisomer ratio of *anti* to *syn* isomers as indicated by NMR analysis. <sup>b</sup>Diastereoisomer ratio given as a ratio of the sum of both *anti* forms (HB-O, HB-N) to both *syn* forms (HB-O, HB-N). <sup>c</sup>Calculated as  $100\% \cdot |\text{dr}_{\text{expt}} - \text{dr}_{\text{calcd}}| / \text{dr}_{\text{expt}}$ . MAD: mean average deviations to experimental results.

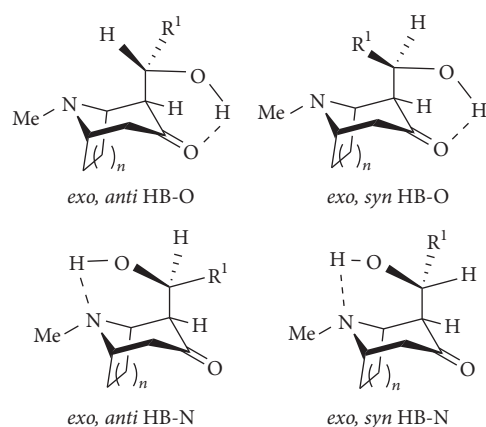


FIGURE 3: Structures of the main H-bond stabilized conformers of the diastereoisomeric aldols of tropinone and granatanone.

**2** are estimated in the range found experimentally for cyclohexanone [49]. Bearing in mind the possibility of hydration of tropinone and granatanone we asked how a hydration, similar to that, observed by us in crystal of granatanone, may affect the  $\Delta G$  of enolization. Calculations showed that the free energies of enolization for **1** and **2** are lowered, if one considers the  $\beta$ -amino ketones hydrated by a molecule of water (Table 4). This tendency is especially noticeable in water (in aqueous solution). For example, the difference in the  $\Delta G$  of enolization of axial N-invertomers of granatanone with and without one molecule of water is 2.1 kcal/mol (Table 4). However, the supposedly more accurate calculations with 6-311++g(3d,3p) basis set did not reproduce lowering of

enolization energy with an explicit water molecule placed close to the oxygen atom of the enolate and ketone (Table 4). Placement of explicit H<sub>2</sub>O molecule bond to N atom resulted in higher enolization energy than enolization energy of species with H<sub>2</sub>O bound to oxygen by ca. 1 kcal/mol for B3LYP/6-31g(d) theory level.

Since the lower level results properly predict disparity in enolization of **2** and **1**, which should be expected on grounds of differences in the bicyclic structures (the steric interactions of the carbonyl group and the C-7 atom in **2** versus the C6-C7 bridge in **1**), they are likely more accurate in this case. This further confirms our using the B3LYP/6-31g(d) as the method of choice. Based on chemical intuition and inspection of models one could expect that the relief of the steric congestion (Figure 6) may stabilize the flattened structure of granatanone enol (**6**) more than that of tropinone (**5**), compared to the parent ketone. The difference in the  $\Delta G$  of enolization could also account for different rate of protium-deuterium exchange (exchange of the axial hydrogens in the  $\alpha$ -position in granatanone is faster (ca. 90% exchange for deuterium in 2 h), then in tropinone (ca. 70% deuteration in 2 h) as observed by <sup>1</sup>H-NMR spectroscopy). Computations of the free energy of enolization that are more relevant to our reaction, that is, for ketones associated with benzaldehyde molecule in water using B3LYP/6-31g(d) CPCM method, provided smaller values: 5.9 for tropinone and 4.3 kcal/mol for granatanone [24]. The respective values for the gas-phase enolization were 6.2 and 4.6 kcal/mol. Thus, assuming the prior enolization step in the presence of water or benzaldehyde (with  $\Delta G$  ca. 4.3–6.2 kcal/mol; see Table 4), we were in a position to explore the key step—the addition of the enol

TABLE 2: Calculated (method A: B3LYP/6-31g(d) CPCM and method B: B3LYP/6-311++g(3d,3p) CPCM) distributions of products (for terminology see Figure 3) and experimental results for the aldol reaction of tropinone with aldehydes at 25 °C.

R <sup>1</sup> (Aldol)	Reaction medium <sup>a</sup>	Method	Anti HB-O (%)	Syn HB-O (%)	Anti HB-N (%)	Syn HB-N (%)	Calculated <sup>b,c</sup> dr anti: syn	Experimental dr anti: syn (yield [%] <sup>d</sup> )	Deviation of calculated from experimental dr <sup>e</sup> [%]
Ph ( <b>3a</b> )	Gas/neat	A	1.87	0.02	8.65	89.46	11:89	10:90 (84)	11
		B	9.06	0.03	8.34	82.57	17:83		84
	Water	A	0.38	0.01	40.20	59.41	41:59	41:59 (55) <sup>f</sup>	0
		B	2.67	0.01	43.84	53.47	46:54		23
<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> ( <b>3b</b> )	Gas/neat	A	1.11	0.02	17.51	81.36	19:81	22:78 (76)	17
		B	4.91	0.04	19.19	75.85	24:76		12
	Water	A	0.16	0.01	50.70	49.13	51:49	64:36 (95)	39
		B	0.55	0.01	54.82	44.63	56:44		25
<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> ( <b>3c</b> )	Gas/neat	A	2.15	0.02	11.16	86.68	14:86	20:80 (75)	35
		B	11.29	0.04	13.24	75.42	24:76		26
	Water	A	0.33	0.01	38.55	61.11	39:61	46:54 (43)	25
		B	2.11	0.02	44.82	53.05	47:53		4
<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> ( <b>3d</b> )	Gas/neat	A	1.39	0.03	9.87	88.72	12:88	14:86 (90)	16
		B	8.55	0.07	13.44	77.94	22:78		73
	Water	A	0.27	0.01	37.92	61.81	38:62	45:55 (69)	25
		B	1.74	0.02	43.35	54.89	45:55		0
<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> ( <b>3e</b> )	Gas/neat	A	2.05	0.07	14.94	82.93	17:83	17:83 (92)	0
		B	7.48	0.01	11.52	80.99	19:81		15
	Water	A	0.17	0.01	66.10	33.72	66:34	55:46 (77)	62
		B	1.00	0.02	47.29	51.70	48:52		23
<i>m</i> -MeO-C <sub>6</sub> H <sub>4</sub> ( <b>3f</b> )	Gas/neat	A	1.71	0.02	11.61	86.66	13:87	10:90 (73)	34
		B	10.09	0.05	14.20	75.66	24:76		184
	Water	A	0.38	0.01	46.83	52.77	47:53	39:61 (46)	39
		B	2.08	0.02	46.74	51.16	49:51		50
$\alpha$ -Naphth ( <b>3g</b> )	Gas/neat	A	0.52	0.00	8.81	90.67	9:91	5:95 (51)	88
		B	1.65	0.00	9.16	89.19	10:90		111
	Water	A	0.06	0.00	32.62	67.32	33:67	33:67 (34)	0
		B	0.54	0.00	46.22	53.24	46:54		73
MAD 6-31g(d)									<b>28</b>
MAD 6-311++g(3d,3p)									<b>50</b>

<sup>a</sup>Reaction [23]: gas/neat (2 mmol aldehyde, 1 mmol tropinone, and 18  $\mu$ L H<sub>2</sub>O); water (2 mmol aldehyde, 1 mmol tropinone, and 2.5 mL H<sub>2</sub>O). <sup>b</sup>Calculated and experimental data in part taken from the literature [24]. <sup>c</sup>Diastereoisomer ratio given as a ratio of the sum of both *anti* forms to both *syn* forms. <sup>d</sup>Calculated in the gas phase for the neat reaction. <sup>e</sup>The progress of reactions were monitored by <sup>1</sup>H NMR spectroscopy (reaction time: 1–14 days). Yield of all aldols (amount of *anti* and *syn* aldols). <sup>f</sup>Calculated as 100% · |dr<sub>expt</sub> - dr<sub>calcd</sub>|/dr<sub>expt</sub>. <sup>g</sup>No solid product precipitated under these conditions. When formation of solid was observed the selectivity *anti*:*syn* rose to >95:5 and yield to 75%.

TABLE 3: Calculated (method A: B3LYP/6-31g(d) CPCM and method B: B3LYP/6-311++g(3d,3p) CPCM) distributions of products (for terminology see Figure 3) and experimental results for the aldol reaction of granatone with aldehydes at 25°C.

R <sup>1</sup> (Aldol)	Reaction medium <sup>a</sup>	Method	Anti HB-O (%)	Syn HB-O (%)	Anti HB-N (%)	Syn HB-N (%)	Calculated <sup>b,c</sup> dr anti: syn	Experimental <sup>b,c</sup> dr anti: syn (yield [%] <sup>d</sup> )	Deviation of calculated from experimental dr <sup>e</sup> [%]
Ph (4a)	Gas/neat	A	4.27	0.08	6.58	89.07	11:89	11:89 (45)	0
		B	9.41	0.11	6.52	83.97	16:84		54
	Water	A	0.67	0.03	37.13	62.17	38:62	39:61 (21)	4
		B	2.52	0.03	33.44	64.01	36:64		12
<i>p</i> -NO <sub>2</sub> - C <sub>6</sub> H <sub>4</sub> (4b)	Gas/neat	A	2.98	0.15	14.36	82.51	17:83	20:80 (90)	18
		B	12.13	0.11	0.00	87.76	12:88		45
	Water	A	0.23	0.02	40.75	59.01	41:59	49:51 (n.d. 2 h) <sup>f</sup>	28
		B	1.33	0.03	38.80	59.84	40:60		31
<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> (4c)	Gas/neat	A	2.59	0.05	10.92	86.45	14:86	18:82 (48) <sup>g</sup>	26
		B	6.27	0.06	49.29	44.37	56:44		480
	Water	A	0.00	0.01	37.73	62.26	38:62	45:55 (27) <sup>g</sup>	25
		B	2.75	0.03	39.62	57.60	42:58		11
<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> (4d)	Gas/neat	A	1.92	0.04	22.21	75.82	24:76	17:83 (29) <sup>g</sup>	54
		B	5.82	0.14	16.16	77.88	22:78		38
	Water	A	0.23	0.02	54.27	45.48	55:45	45:55 (46) <sup>g</sup>	49
		B	1.96	0.03	48.28	49.74	50:50		22
<i>p</i> -CF <sub>3</sub> - C <sub>6</sub> H <sub>4</sub> (4e)	Gas/neat	A	1.27	0.06	13.94	84.73	15:85	20:80 (61)	29
		B	23.12	0.40	57.94	18.54	81:19		1605
	Water	A	0.06	0.01	27.08	72.85	27:73	17:83 (58)	81
		B	0.87	0.01	70.17	28.95	71:29		1095
<i>m</i> -MeO- C <sub>6</sub> H <sub>4</sub> (4f)	Gas/neat	A	2.51	0.04	11.90	85.55	14:86	10:90 (17) <sup>g</sup>	47
		B	12.55	0.10	11.79	75.56	24:76		184
	Water	A	0.31	0.02	49.90	49.77	50:50	39:61 (22) <sup>g</sup>	56
		B	3.37	0.05	54.03	42.55	57:43		107
$\alpha$ -Naphth (4g)	Gas/neat	A	0.24	0.00	3.80	95.96	4:96	2:98 (8) <sup>g</sup>	104
		B	1.53	0.00	4.44	94.02	6:94		213
	Water	A	0.06	0.00	24.81	75.13	25:75	35:65 (12) <sup>g</sup>	38
		B	0.38	0.00	34.48	65.13	35:65		0
MAD 6-31g(d)									40
MAD 6-311++g(3d,3p)									278

<sup>a</sup>Reaction [23]: gas/neat (2 mmol aldehyde, 1 mmol granatone, and 18  $\mu$ L H<sub>2</sub>O); water (2 mmol aldehyde, 1 mmol granatone, and 2.5 mL H<sub>2</sub>O). <sup>b</sup>Diastereoisomer ratio given as a ratio of the sum of both *anti* forms to both *syn* forms. <sup>c</sup>Calculated in the gas phase for the neat reaction. <sup>d</sup>The progress of reactions was monitored by <sup>1</sup>H NMR spectroscopy; reaction time: up to 4 days (over 4 days significant amounts of elimination products were formed). Isolated yield of all aldols (amount of *anti* and *syn* aldols). <sup>e</sup>Calculated as 100% · |dr<sub>expt</sub> - dr<sub>calcd</sub>|/dr<sub>expt</sub>. <sup>f</sup>No solid product precipitated under these conditions in 2 h. Extension of the reaction time to 24 h resulted in formation of solid and change in selectivity *anti/syn* 5:95 and yield (93%). <sup>g</sup>Conversion determined by <sup>1</sup>H NMR spectroscopy. Pure product was not isolated because of low conversion.

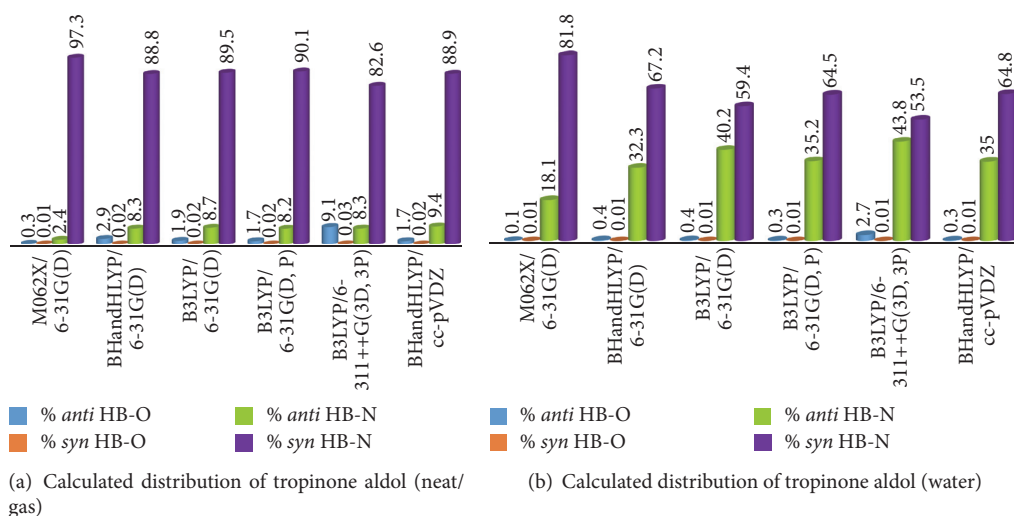


FIGURE 4: Calculated distributions of tropinone aldol **3a** (with benzaldehyde) forms for gas/neat reaction (a) and for reaction in water (b). Charts prepared with numerical data from Table 1.

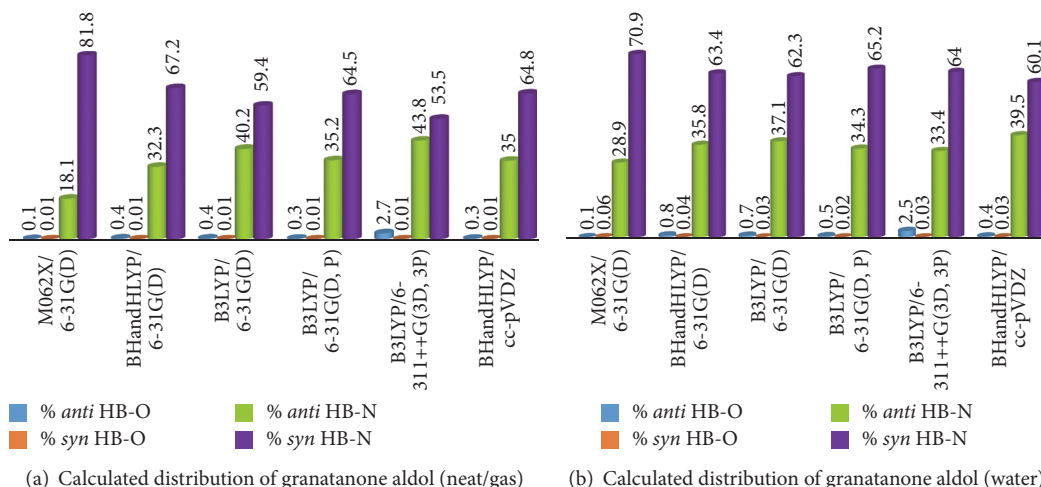


FIGURE 5: Calculated distributions of granatanone aldol **4a** (with benzaldehyde) forms for gas/neat reaction (a) and for reaction in water (b). Charts prepared with numerical data from Table 1.

to an aldehyde—and possibly rationalize the outcome of the whole aldol process.

At first glance, the reaction parameters obtained from our computational approach, at 6-31g(d) level (but also at 6-311++g(3d,3p) *vide infra*), calculated along the lines used for aldol reaction of acetone by Zhang and Houk [26], that is, the reaction of tropinone and granatanone enols with benzaldehyde, totally disagreed with experiment. Representative (for benzaldehyde) energy versus reaction coordinate (IRC) plots is shown in Figure 7.

The free energies obtained (Figure 7, Tables 5 and 6) for the hydrogen bond stabilized conformer of the addition product (marked HB-O, Figure 3) did not show any relationship to the experimental observations; the experimentally observed selectivity disagreed qualitatively with both the kinetic and the thermodynamic parameters calculated for the reactions.

According to these calculations in all reactions (Tables 5 and 6) the *exo,anti*-product should be favoured both kinetically [ $k(anti)/k(syn)$ ] and thermodynamically ( $K_{anti/syn}$  for HB-O). As can be seen in Figures 3 and 7, the initially formed HB-O form may undergo conformational change forming another stable structure with hydrogen bond to the nitrogen atom (marked HB-N conformer, Figure 3). The HB-N form does not result directly from the aldol addition but is stabilized by formation of a hydrogen bond to the tertiary nitrogen atom. Structures with such internal hydrogen bond have been observed for this type of aldols in crystals [18, 22, 51–53].

In a preliminary report we showed that the neat/solventless reaction conditions were most accurately reproduced by the gas-phase DFT calculations which integrated such (HB-N) structures [24]. As can be seen in Tables 5 and 6, for



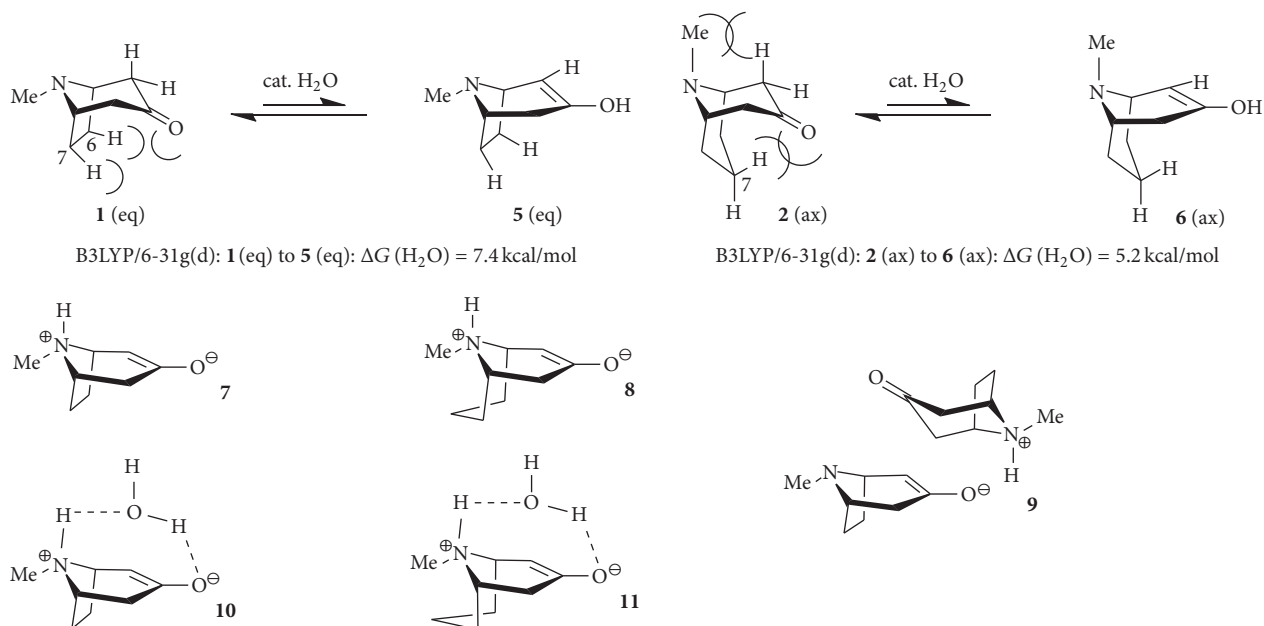


FIGURE 6: Considered possible forms of reacting donor species and steric interaction relieved during enolization of tropinone and granatanone (numerical data from Table 4).

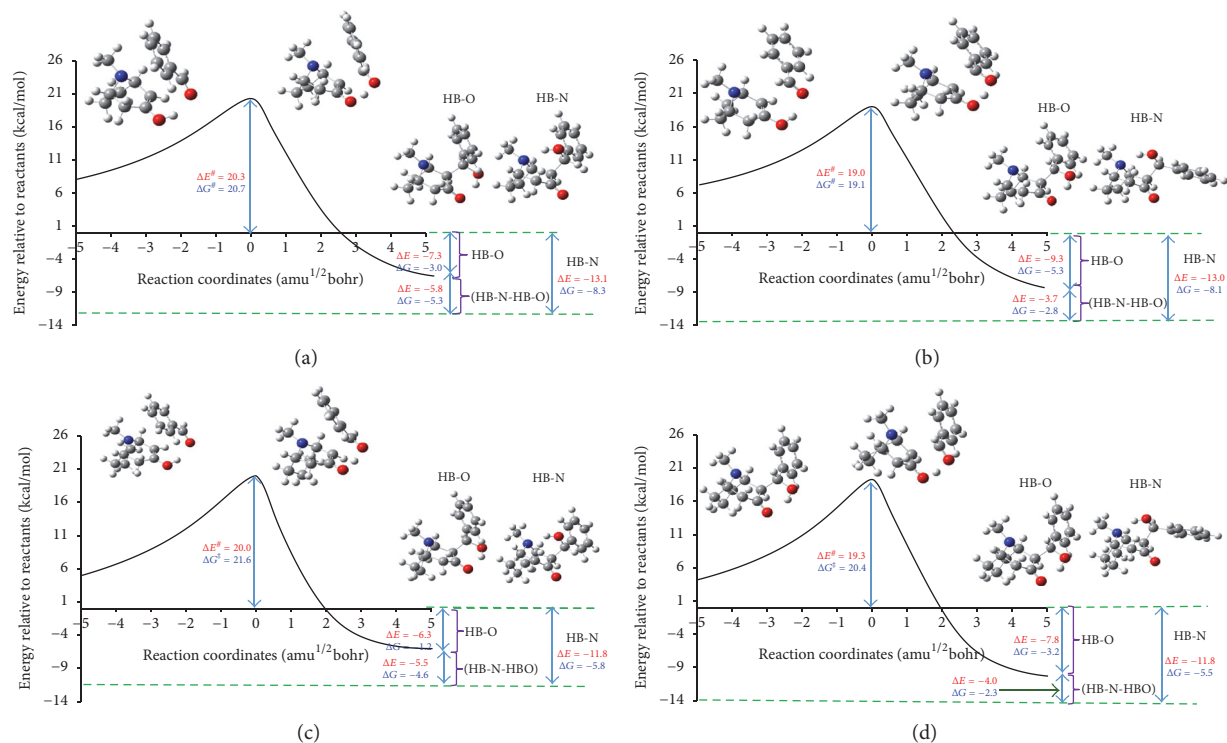


FIGURE 7: The classical adiabatic ground state ( $V_C$ ) potential energy curve along the reaction coordinates of the aldol addition of tropinone enol (a, b) and granatanone enol (c, d) to benzaldehyde proceeding to the *exo,syn* (a, c) and the *exo,anti* (b, d) isomers. The activation energies ( $E_{\text{TS}} - E_{\text{reactants}}$ ), reaction energies ( $E_{\text{product}} - E_{\text{reactants}}$ ), and differences of energies ( $\Delta E$ ) of the HB-N and HB-O forms of the isomeric products are shown in red. For the sake of comparison, the corresponding free energies differences ( $\Delta G$ ) are given in blue. Note that the ordinates correspond to the energies ( $E$ ) not free energies ( $G$ ), so the blue values cannot be figured out from the chart.

TABLE 4: Free energies of enolization of tropinone and granatanone computed at the B3LYP/6-31g(d) and B3LYP/6-311++g(3d,3p) (*in parenthesis, italics*) levels.

Ketone	Reaction medium	$\Delta G$ of enolization ( $G_{\text{enol}} - G_{\text{ketone}}$ )						With explicit molecule of PhCHO [24]
		Without explicit H <sub>2</sub> O		With explicit molecule of H <sub>2</sub> O		Zwitterionic form	Hydrated zwitterionic form	
		ax <sup>a</sup>	eq <sup>a</sup>	ax <sup>a</sup>	eq <sup>a</sup>	<i>The most stable N-invertomer</i>		
Tropinone	Gas	5.6 (4.9)	7.4 (6.5)	4.3 (5.4)	7.3 (6.6)	—	—	6.2
	Water (CPCM)	6.4 (6.2)	7.4 (7.2)	4.7 (6.8)	6.0 (7.5)	18.6 (14.4)	21.7 (20.2)	5.9
Granatanone	Gas	4.7 (3.5)	6.2 (5.4)	4.5 (4.1)	6.2 (7.6)	—	—	4.6
	Water (CPCM)	5.2 (5.2)	6.4 (6.3)	3.1 (5.7)	4.9 (6.0)	18.4 (15.9)	21.3 (22.0)	4.3

<sup>a</sup>N-Me group position.

reactions taking place both in water and in the absence of solvent, there exists correspondence between the experimental ratio (*dr*) of *exo,anti/exo,syn* isomers ( $dr_{\text{exp}} \text{ anti/syn}$ ) and the equilibrium constant for the interconversion of the HB-N conformers (*Kanti/syn* for HB-N) of these isomers. This correspondence combined with the observed equilibration suggests the thermodynamic control of the reaction and involvement of the interconversion of the competing product conformers in the equilibrium. Because of the bicyclic structure (*endo* and *exo* faces) of tropane and granatane derivatives, we propose that the *syn-anti* isomerization of the aldols takes place through retroaldolization (observed in several instances) [19, 22, 54] and not by enolization mechanism reported, for example, in the imidazole catalysed isomerization [55, 56].

Assuming thermodynamic control, it is reasonable to expect that the experimentally observed *dr*'s should result from weighted contributions of the forms involved in the equilibrium. Consequently, the question arises as to whether taking into account the contributions of the other, less stable, forms (the HB-O) would give even better agreement of theory with experiment. To test it, we converted free energies of formation of both (HB-O and HB-N) forms of competing diastereoisomers to percentage distribution.

Results calculated with two basis sets, 6-31g(d) and 6-311++g(3d,3p), for tropinone and granatanone are presented in Tables 2 and 3, respectively. In these tables MAD (mean average deviations of the calculated and experimental *dr*'s) for basis set 6-31g(d) are smaller than the MAD in Tables 5 and 6, where the other conformers were ignored, thus validating this approach. For several aldehydes (Tables 2 and 3,  $R_1 = \text{Ph}$ ,  $p\text{-NO}_2\text{-C}_6\text{H}_4$ ,  $p\text{-F-C}_6\text{H}_4$ , and  $p\text{-CF}_3\text{-C}_6\text{H}_4$ ) excellent agreement (deviation below 30%) was found. Interestingly, the results obtained with the B3LYP/6-311++g(3d,3p) showed, in general, worse agreement with experiment. However, it must be noted that in some instances this high-end and more computationally demanding basis set gave slightly better agreement with experiment (e.g.,  $p\text{-F-C}_6\text{H}_4$ ,  $p\text{-Cl-C}_6\text{H}_4$ , and

$\alpha\text{-Napht}$ ), but no clear rules with regard to neither medium nor reactant may be drawn here. The calculated  $\Delta G$  values for the HB-O and HB-N forms (Tables 5 and 6) can also explain observed low conversions and, consequently, low yields (or failed isolation of products in extreme cases). In theory, given sufficient reaction rate, sum of the free energies of formation of the HB-O or the HB-N forms of products and  $\Delta G$  of enolization for the ketone used could be used to determine conversion of the reaction for particular reactants.

Indeed, the calculated  $\Delta G$ 's for the HB-O and the HB-N isomers are somehow related to the conversions and yields found experimentally (compare Tables 2 and 3 with Tables 5 and 6). Assuming the enolization free energy for tropinone and granatanone ca. 5.9 and 4.3 kcal/mol, respectively, the calculated  $\Delta G$ 's predicted poor results found later on with some aldehydes (e.g., products **3h**, **4g**, and **4h**). Experimentally, several of the granatanone reactions gave poor outcome. In general, reactions with granatanone gave lower yields (or showed lower conversion) than those with tropinone. This was expected based on calculated lower thermodynamic drive for the addition step of the granatanone enol (average  $\Delta G -2.8$  for the HB-O and  $-6.2$  kcal/mol for the HB-N) than for the tropinone enol (average  $\Delta G -4.1$  for the HB-O and  $-7.8$  kcal/mol for the HB-N). Calculations for reactions of some aldehydes, for example,  $\alpha$ -naphthaldehyde and notably *p*-methoxybenzaldehyde, gave very small (as compared to the estimated  $\Delta G$  for the ketones enolization, that is, 4.3–6.2 kcal/mol) negative or even positive  $\Delta G$  values (Tables 5 and 6, **3h**, **4g**, and **4h**). In all such cases experiments confirmed correctness of the prediction and showed low conversions. Expansion of aldehyde range in this work to include *p*-methoxybenzaldehyde gave result so poor that neither conversion nor isomers ratio could be measured (n.d. in Tables 5 and 6). This failure was predicted based on calculations. Because rotation of C-C bond and formation of the HB-N form follow formation of the HB-O product, the positive or not sufficiently negative  $\Delta G$  for formation of the initial addition product—the HB-O form—hinders the

TABLE 5: Calculated (B3LYP/6-31g(d) CPCM) reaction parameters for tropinone enol addition to aldehydes.

R <sup>1</sup>	Reaction medium	Aldol isomer	$\Delta G^\ddagger$ HB-O	k(anti)/k(syn)	$\Delta G$ HB-O	K anti/syn HB-O	$\Delta G$ HB-N	K anti/syn HB-N	dr <sub>exp</sub> anti/syn
Ph	Gas/neat	<i>exo,syn-3a</i>	20.1	41.3	-2.0	133.9	-7.2	0.1	0.11
		<i>exo,anti-3a</i>	18.9		-4.9		-5.8		
	Water	<i>exo,syn-3a</i>	20.7	15.2	-3.0	48.6	-8.3	0.7	0.69
		<i>exo,anti-3a</i>	19.1		-5.3		-8.1		
<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Gas/net	<i>exo,syn-3b</i>	17.8	14.4	-6.1	48.6	-10.9	0.2	0.28
		<i>exo,anti-3b</i>	16.2		-8.4		-10.0		
	Water	<i>exo,syn-3b</i>	18.2	6.1	-6.5	29.3	-11.9	1.0	1.78
		<i>exo,anti-3b</i>	17.1		-8.5		-11.9		
<i>p</i> -F-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-3c</i>	21.3	31.3	-1.7	113.1	-6.7	0.1	0.25
		<i>exo,anti-3c</i>	19.3		-4.5		-5.5		
	Water	<i>exo,syn-3c</i>	21.7	14.9	-2.0	48.6	-7.4	0.6	0.85
		<i>exo,anti-3c</i>	20.1		-4.3		-7.1		
<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-3d</i>	20.1	21.3	-3.3	48.6	-8.1	0.1	0.16
		<i>exo,anti-3d</i>	18.3		-5.6		-6.8		
	Water	<i>exo,syn-3d</i>	21.4	14.9	-2.8	41.1	-8.2	0.6	0.82
		<i>exo,anti-3d</i>	19.8		-5.0		-7.9		
<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-3e</i>	18.9	40.2	-5.1	29.3	-9.3	0.2	0.20
		<i>exo,anti-3e</i>	16.7		-7.1		-8.3		
	Water	<i>exo,syn-3e</i>	20.4	45.1	-4.2	24.7	-9.3	1.7	1.22
		<i>exo,anti-3e</i>	18.2		-6.1		-9.6		
<i>m</i> -MeO-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-3f</i>	20.3	46.2	-3.0	95.5	-8.0	0.1	0.11
		<i>exo,anti-3f</i>	18.1		-5.7		-6.8		
	Water	<i>exo,syn-3f</i>	20.6	12.9	-3.3	41.1	-8.0	1.7	0.64
		<i>exo,anti-3f</i>	19.1		-5.5		-8.3		
$\alpha$ -Naphth-	Gas/neat	<i>exo,syn-3g</i>	21.4	38.2	-1.0	311.5	-7.4	0.1	0.05
		<i>exo,anti-3g</i>	19.2		-4.4		-6.0		
	Water	<i>exo,syn-3g</i>	21.8	8.3	-1.2	80.7	-7.9	0.5	0.49
		<i>exo,anti-3g</i>	20.5		-3.8		-7.5		
<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-3h</i>	21.9	35.7	-0.4	96.5	-5.1	0.1	n.d.
		<i>exo,anti-3h</i>	19.8		-3.1		-3.9		
	Water	<i>exo,syn-3h</i>	22.4	43.0	-0.8	65.7	-5.8	1.0	n.d.
		<i>exo,anti-3h</i>	20.2		-3.3		-5.8		
MAD K <sub>anti/syn</sub> HBN								37.5	

entire aldol process, as is evident from data (Table 6) and low yield for  $\alpha$ -naphthaldehyde and granatanone (Table 3). For the sake of prediction of the success of the reactions with other aldehydes one could accept that reactions with  $\Delta G$  for the isomer HB-O ca. -3 kcal/mol and for the HB-N ca. -6 kcal/mol are at the borderline of acceptable yields.

In effect, we found that considering free energies of four hydrogen bond stabilized forms of possible products (including the HB-O and the HB-N forms) gave especially good correlation with experimental results for solventless reaction and also for reactions "diluted" with water, unless formation of solid products was involved [24]. Thus, processes where solid product deposited from the reacting mixture were clearly

controlled by other phenomena; selectivity and conversions did not parallel the calculations and prediction of reaction result under such conditions is not possible. With the caveat that precipitation will affect the reaction equilibrium, the reported correlations of theory and experiment are useful for assessing outcome of new reactions.

### Conclusions

- (i) Two crystal structures of granatanone and its hemihydrate (2-(1/2)H<sub>2</sub>O) have been experimentally determined by single crystal X-ray diffraction. The experiments showed domination of the N-axial forms in the

TABLE 6: Calculated (B3LYP/6-31g(d) CPCM) reaction parameters for granatanone enol addition to aldehydes.

R <sup>1</sup>	Reaction medium	Aldol isomer	$\Delta G^\ddagger$ HB-O	$k(\text{anti})/k(\text{syn})$	$\Delta G$ HB-O	K <i>anti/syn</i> HB-O	$\Delta G$ HB-N	K <i>anti/syn</i> HB-N	$dr_{\text{exp}}$ <i>anti/syn</i>
Ph	Gas/neat	<i>exo,syn-4a</i>	21.0	18.1	-1.3	56.8	-5.5	0.1	0.12
		<i>exo,anti-4a</i>	19.3		-3.7		-4.0		
	Water	<i>exo,syn-4a</i>	21.6	7.5	-1.2	26.6	-5.8	0.6	
		<i>exo,anti-4a</i>	20.4		-3.2		-5.5		
<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-4b</i>	18.1	5.3	-5.2	20.2	-9.0	0.2	0.25
		<i>exo,anti-4b</i>	17.1		-7.0		-7.9		
	Water	<i>exo,syn-4b</i>	18.3	3.0	-5.5	10.6	-10.2	0.7	
		<i>exo,anti-4b</i>	17.7		-6.9		-10.0		
<i>p</i> -F-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-4c</i>	20.8	20.3	-0.9	49.7	-5.3	0.1	0.22
		<i>exo,anti-4c</i>	19.0		-3.3		-4.1		
	Water	<i>exo,syn-4c</i>	20.9	6.8	-1.5	31.7	-6.5	0.6	
		<i>exo,anti-4c</i>	19.8		-3.6		-6.2		
<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-4d</i>	19.9	10.4	-2.1	48.8	-6.6	0.3	0.20
		<i>exo,anti-4d</i>	18.5		-4.4		-5.9		
	Water	<i>exo,syn-4d</i>	20.5	0.7	-2.5	15.2	-7.2	1.2	
		<i>exo,anti-4d</i>	20.7		-4.1		-7.3		
<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-4e</i>	18.9	4.7	-3.4	20.0	-7.6	0.2	0.25
		<i>exo,anti-4e</i>	18.0		-5.1		-6.6		
	Water	<i>exo,syn-4e</i>	19.3	2.8	-3.6	11.4	-9.2	0.4	
		<i>exo,anti-4e</i>	18.6		-5.0		-8.6		
<i>m</i> -MeO-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-4f</i>	20.8	18.3	-1.3	61.4	-5.9	0.1	0.11
		<i>exo,anti-4f</i>	19.1		-3.8		-4.7		
	Water	<i>exo,syn-4f</i>	21.1	6.4	-1.8	14.6	-6.4	1.0	
		<i>exo,anti-4f</i>	20.0		-3.4		-6.4		
$\alpha$ -Naphth-	Gas/neat	<i>exo,syn-4g</i>	21.9	14.2	0.8	135.6	-5.7	0.04	0.02
		<i>exo,anti-4g</i>	20.3		-2.1		-3.8		
	Water	<i>exo,syn-4g</i>	21.1	3.4	-0.4	82.1	-7.2	0.3	
		<i>exo,anti-4g</i>	20.4		-3.0		-6.6		
<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	Gas/neat	<i>exo,syn-4h</i>	22.2	25.7	0.8	47.3	-3.4	0.3	n.d.
		<i>exo,anti-4h</i>	20.3		-1.5		-2.7		
	Water	<i>exo,syn-4h</i>	22.6	14.5	0.4	26.2	-3.9	1.5	
		<i>exo,anti-4h</i>	21.0		-1.5		-4.2		
MAD $K_{\text{anti/syn}}$ HBN								41.3	

solid state and hydration of the nitrogen site of two granatanone molecules.

- (ii) Despite the fairly expanded scope of tested computational methods, including a recently introduced functional (M062X), the B3LYP/6-31g(d) accounting for the orbital relaxation upon immersion in solution (i.e., geometry optimization in liquid state performed with CPCM) is still recommended as the most accurate and additionally cost effective approach, to probe reactivity and selectivity in this specific type of aldol reactions.
- (iii) Presence of basic nitrogen in substrates results in considerable concentration of strong specific base in their aqueous solutions (pH ca. 10). Considering the

most stable forms of hydrated  $\beta$ -amino ketones, our computations indicated lowering of the free energies of enolization, suggesting higher equilibrium concentration of the enol forms in the presence of water. This may be another factor responsible for the beneficial role of water in the process.

- (iv) For the studied range of aldehydes the diastereoselectivities and conversions of the aldol reactions can be computationally reproduced (the *exo,syn* isomers are typically the most stable forms and dominate in the solventless reaction) and even predicted (no product with *p*-methoxybenzaldehyde).
- (v) Yield of the particular reaction can be correlated with the calculated free energies of formation of the

HB-O and the HB-N forms of products and  $\Delta G$  of enolization for the ketone used.

- (vi) The experimental observation that tropinone gives in general better results than granatanone is reflected in calculated thermodynamic parameters ( $\Delta G$ ) for formation of products conformers stabilized by hydrogen bonding.

### 3. Experimental Section

*9-Methyl-9-azabicyclo[3.3.1]nonan-3-one (2)*. Crystals suitable for X-ray diffraction study were obtained at 255 K from a mixture of *n*-hexane-ethyl ether (ratio 5:1) and molecular sieves 4 Å. The X-ray diffraction data were collected at 100(2) K on SuperNova diffractometer (Agilent) with a CCD detector and Cu- $K_{\alpha}$  radiation. The crystal data were processed with *CrysAlisPro* (data collection, cell refinement, and data reduction) [57]. The crystal structure was solved using direct methods with *SHELXD* and refined with *SHELXL* [58]. All H atoms were located in electron density difference maps. C-bonded hydrogen atoms were constrained to idealized positions with C-H distances fixed at 0.98–1.00 Å and with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$  for methyl hydrogen atoms and  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$  for others. *PLATON* software [59] was used to validate the crystallographic data.

*Crystal Data.*  $\text{C}_9\text{H}_{15}\text{NO}$ ,  $M_r = 153.22$ , colourless prism,  $0.46 \times 0.28 \times 0.21 \text{ mm}^3$ , monoclinic, space group  $P2_1/c$ ,  $a = 20.8638(2) \text{ \AA}$ ,  $b = 7.24526(8) \text{ \AA}$ ,  $c = 11.47997(13) \text{ \AA}$ ,  $\beta = 105.3447(12)^\circ$ ,  $V = 1673.49(3) \text{ \AA}^3$ ,  $Z = 8$ ,  $\rho_{\text{calcd}} = 1.216 \text{ g}\cdot\text{cm}^{-3}$ ,  $\mu = 0.62 \text{ mm}^{-1}$ ,  $F(000) = 672$ ,  $R_1 = 0.037$ ,  $wR^2 = 0.092$ , 3382 independent reflections,  $\theta_{\text{max}} = 74.5^\circ$ ,  $\theta_{\text{min}} = 4.4^\circ$ , and 201 parameters are included. CCDC-1014754 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [https://www.ccdc.cam.ac.uk/data\\_request/cif](https://www.ccdc.cam.ac.uk/data_request/cif).

*9-Methyl-9-azabicyclo[3.3.1]nonan-3-one hemihydrate (2·(1/2)H<sub>2</sub>O)*. Crystals suitable for X-ray diffraction study were obtained at 255 K by slow evaporation from a mixture of *n*-hexane-ethyl ether (ratio 5:1). The X-ray diffraction data were collected at 100(2) K on SuperNova diffractometer (Agilent) with a CCD detector and Mo- $K_{\alpha}$  radiation. The crystal data were processed with *CrysAlisPro* (data collection, cell refinement, and data reduction) [57]. The crystal structure was solved using direct methods with *SHELXD* and refined with *SHELXL* [58]. All H atoms were located in electron density difference maps. C-bonded hydrogen atoms were constrained to idealized positions with C-H distances fixed at 0.98–1.00 Å and with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$  for methyl hydrogen atoms and  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$  for others. The positions and atomic displacement parameters of water hydrogen atoms were freely refined. *PLATON* software [59] was used to validate the crystallographic data.

*Crystal Data.*  $(\text{C}_9\text{H}_{15}\text{NO})_2\cdot\text{H}_2\text{O}$ ,  $M_r = 324.46$ , colourless prism,  $0.34 \times 0.19 \times 0.09 \text{ mm}^3$ , orthorhombic space group  $P2_12_12_1$ ,  $a = 6.77816(14) \text{ \AA}$ ,  $b = 10.1532(3) \text{ \AA}$ ,  $c = 25.8827(4) \text{ \AA}$ ,

$V = 1781.25(7) \text{ \AA}^3$ ,  $Z = 4$ ,  $\rho_{\text{calcd}} = 1.210 \text{ g}\cdot\text{cm}^{-3}$ ,  $\mu = 0.08 \text{ mm}^{-1}$ ,  $F(000) = 712$ ,  $R_1 = 0.038$ ,  $wR^2 = 0.098$ , 2542 independent reflections,  $\theta_{\text{max}} = 28.3^\circ$ ,  $\theta_{\text{min}} = 3.1^\circ$ , and 218 parameters are included. CCDC-1012809 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [https://www.ccdc.cam.ac.uk/data\\_request/cif](https://www.ccdc.cam.ac.uk/data_request/cif).

*Computational Methods.* Electronic structure calculations were carried out using the GAUSSIAN 09 (G09) [60] suite of programs. To account for the solvent effect, the polarizable continuum model (CPCM [61]) was applied as implemented in the Gaussian 09 package. All reported results for stable molecules and transition states were obtained for the lowest energy conformer of a given species. Normal mode analysis was performed at each stationary point to ensure that the stable structure had zero imaginary vibrational frequency whereas the transition state (TS) structure had one imaginary vibrational frequency, whose mode corresponds to the reaction coordinate. Intrinsic Reaction Coordinate (IRC) calculations have been systematically performed at the B3LYP/6-31G(d) level to ensure that the computed TSs connect the desired reactants and products. A self-consistent reaction field (SCRF) approach using CPCM [61, 62] settings with the solvent explicitly set to water was used to model the influence of implicit solvation.

### Competing Interests

The authors declare that they have no competing interests.

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