The *gem*-disubstituent effect—a computational study that exposes the relevance of existing theoretical models

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A B S T R A C T

The DFT B3LYP/6-31G (d, p) and HF/6-31G calculation results for the cyclization reactions of six different di-substituted 4-bromobutylamines (Brown's system) reveal that the driving force for accelerations in the rate for intramolecular cyclization compared to the linear unsubstituted compound is due to strain effects (difference in strain energy in the ground state and in the transition state) and not to proximity in the ground state stemming from the distribution of rotational conformations 'near attack conformation' (time of residence at a reactive distance). Further, the results indicate that the reaction rate (log k_{rel}) for the intramolecular cyclization process is strongly correlated with the distance between the two reacting centers (r) and the attack angle (α). The latter result is the first to correlate strain and reaction rate with geometrical parameters (r and α).

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Alkyl substitution is considered to be an important factor in promoting cyclization reactions and in stabilizing cyclic compounds. However, many theories and experimental studies have been presented to attempt to understand the source of the driving force(s) behind such increases in rate and equilibrium constants. Among the theories advocated are (a) the Thorpe-Ingold effect (theory of valency deviation) in which the substitution of the methylene hydrogens with more sterically demanding alkyl groups results in the compression of the internal angle. As a result, the two reactive centers move closer together, and this facilitates the cyclization;[1] (b) Allinger and Zalkow's thermodynamic analysis. Allinger and Zalkow concluded from their study on the effect of dimethyl substitution on a set of ring-closing reactions leading to substituted cyclohexane systems, that rate enhancement in the dialkyl-substituted derivatives compared to the unsubstituted reactants originates from a decrease in the non-bonding interactions and rotational entropy which results in more favorable values of either $\Delta H°$ or $\Delta S°$ or both;[2] and (c) Bruice's 'reactive-rotamer hypothesis'. Bruice and Pandit studied the cyclization reactions of a number of dicarboxylic semi-esters and they concluded that increasing the steric bulk of the substituent leads to rate acceleration due to the greater statistical proximity of the carboxylate and the ester groups. In other words, the cyclization of the substituted compound (Bruice's monophenyl esters) is facilitated by a higher population of the reactive rotamer.[3]

Despite the many studies that have been carried out to prove or disprove one or more of the above-mentioned hypotheses, the ori-

gin of the *gem*-dialkyl effect is still an object of debate in the scientific community.[4]

Recently, we have been extensively investigating the origin of the driving force(s) for the remarkable enhancements in the rate of some intramolecular reactions.[5] Exploiting the HF and DFT molecular orbital at different levels, molecular mechanics, and AM1 molecular orbital methods, we have studied the kinetic behavior of the acid-catalyzed lactonizations of hydroxy-acids as studied by Cohen[6] and Menger,[7] the cyclization reactions of di-carboxylic semi-esters as studied by Bruice,[3] the intramolecular proton-transfers in rigid systems as studied by Menger,[7] and S_N2-based cyclization as reported by Mandolini.[8] The results of these studies revealed the following salient conclusions: (1) the rate accelerations in intramolecular processes can be due to proximity orientation that stems from strain effects or due to proximity that is unrelated to strain effects of a starting material and/or a corresponding transition state. (2) The nature of the reaction (inter- or intramolecular) is largely dependent on the distance between the electrophile and the nucleophile. (3) Both enthalpic and entropic effects are important factors for the accelerations of the rates of intramolecular processes.[9] This is in contrast to Bruice's proposal that enthalpic effects are the main driving force for such enhancements.[3]

In 1956, Brown and Van Gulick reported a kinetic study on the cyclization of a number of substituted bromobutylamines (Chart 1).[10] They observed an increase in the rate of up to 10^4. These data indicate that both the position and the size of the *gem*-disubstituent have a profound effect on the rate of ring closure of the 4-bromobutylamines **1**–**6** to the corresponding pyrrolidines (Chart 1). The authors proposed that alkyl substitution strongly affects the distribution of rotational conformations due to non-bonding

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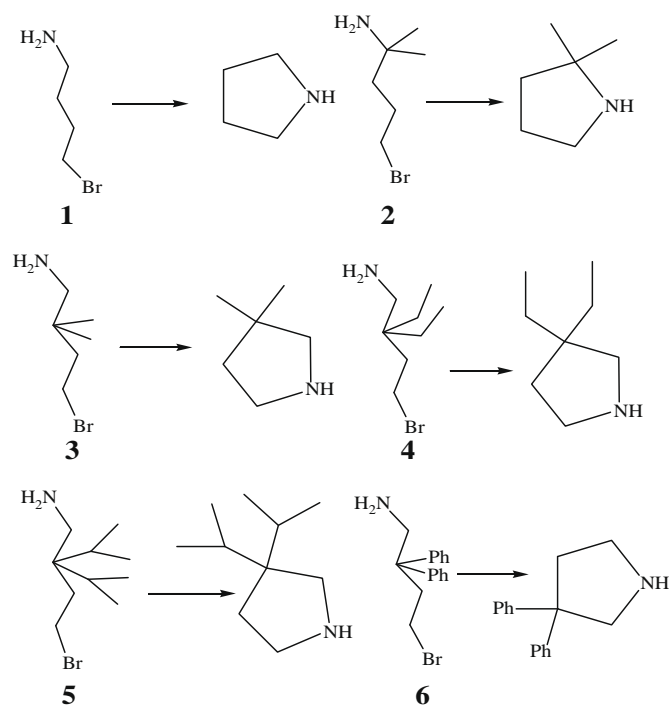*E-mail address:* dr_karaman@yahoo.com

Chart 1. Ring-closing reactions of **1–6**.

interactions within the chain. Thus, compounds with *gem*-disubstitution (the 'coiled' configurations) are preferred over the extended corresponding non-substituted molecules, and this consequently increases the probability of cyclization.

Later von Ragué Schleyer pointed out that the change in bond angle observed upon substitution is too small (2–3°) to explain the large rate enhancement during cyclization.[11]

In this Letter, we report a computational study which tests the validity of the three theories described above. The findings of this study indicate that the main driving force for the *gem*-disubstituent effect in Brown's system is the strain energy that is linearly correlated with the activation energies and with the geometrical parameters (distance, r and attack angle, α).

Using the quantum chemical package GAUSSIAN-98[12] we have calculated the HF/6-31G and DFT B3LYP/6-31G (d, p) kinetic and thermodynamic properties for ring closure of 4-bromobutyl-amines **1–6** to the corresponding pyrrolidines (Chart 1). The calculated energy profiles for processes **1–6** indicate that there are two transition states along the reaction pathway. The lower is around 2.2 Å (TS$_1$) and the higher is around 2.0 Å (TS$_2$). The details of this surprising finding, two transition states for the S$_N$2

process, observed in this system and other related systems will be discussed elsewhere.[13] The calculated HF and DFT enthalpies and entropies for the global minimum structures (GM) of **1–6** and the derived higher transition states (TS$_2$) are summarized in Table S1 (Supplementary data). Figures S1a–c (Supplementary data) illustrate the DFT-optimized calculated structures of GM, TS$_1$, and TS$_2$ for processes **1–6**.

Using the calculated enthalpic and entropic energies for the GM and the second-derived transition states (TS$_2$) of **1–6** (Table S1), we have calculated enthalpic activation energies ($\Delta\Delta H^{\ddagger}$), entropic activation energies ($T\Delta S^{\ddagger}$), and free activation energies in the gas phase ($\Delta\Delta G^{\ddagger}$) and in water ($\Delta\Delta G_S^{\ddagger}$) for the corresponding ring-closing reactions (Table 1). The calculated HF and DFT values in Table 1 were examined for linear correlations with the experimental relative intramolecular ring closure rate (log k_{rel})[10] and the resulting equations along with their correlation coefficients are summarized in the equations illustrated in Figure 1a.
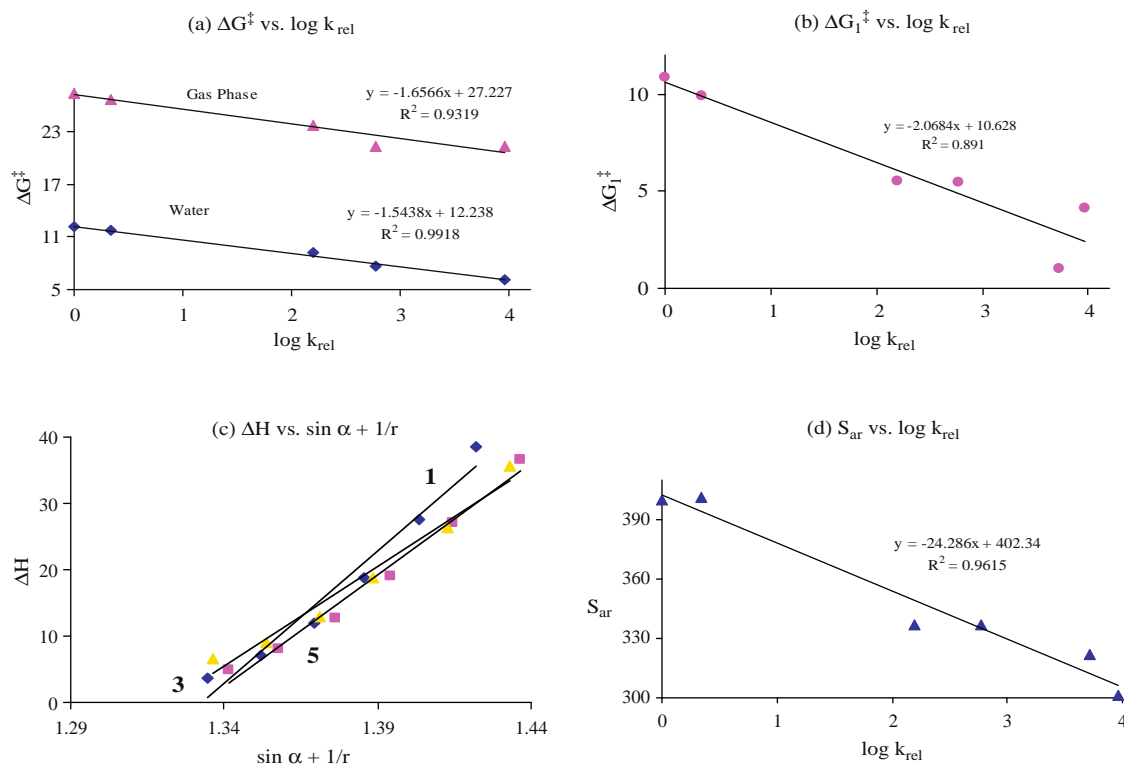
The results delineated in Figure 1a show good agreement between the calculated HF and DFT activation energies ($\Delta\Delta G_S^{\ddagger}$) and the experimental log k_{rel}. However, the correlation coefficient (R) value obtained from the calculated B3LYP/6-31G (d, p) energies is better than that obtained from the HF/6-31G calculated values (0.98 vs 0.95).

The 'reactive-rotamer theory' proposes that conformers having a short distance between their two reactive centers (near attack conformations, NACs) are more accessible to undergo reaction than those with a larger distance. Further, the theory suggests that the reaction rate for a system is dependent on the ratio between the number of rotamers with a relatively short distance between their two reactive centers and those with a larger distance.[3]

To test the validity of the 'reactive-rotamer hypothesis', two different approaches were examined: (a) calculations of the energies for a pool of conformers created upon rotation of the amino group around the C2–C3 bond in the starting geometries of amines **1–6**, and (b) calculation of the energy profiles for the approach of the amino nitrogen (N1) toward the carbon attached to bromine (C5–Br) in **1–6**.

(a) 360° rotation of the amino group around C2–C3 bond was accomplished by changing the dihedral angle N1C2C3C4 in increments of 10° (for the numbering, see Chart 2) while optimizing all other variables. The calculated HF enthalpic energies along with the dihedral angle values are listed in Table S2 (Supplementary data).

Examination of Table S2 reveals (1) The barrier for rotation in **1–6** varies and ranges from 5.01 to 11.31 kcal/mol, with the lowest being in system **5** and the highest in system **2**. (2) The C5–N1 distance for the most stable conformer among the possible conformers is 4.14 Å for **1**, 4.06 Å for **2**, 3.74 Å for **3**, 3.71 Å for **4**, 3.01 Å for

Table 1
DFT and MM2-calculated kinetic and thermodynamic properties for the cyclization reactions of **1–6**.

Compound	Log k_{rel}	MM2 ΔE_s	B3LYP $\Delta H^{\ddagger}$	B3LYP $T\Delta S^{\ddagger}$	B3LYP $\Delta G^{\ddagger}$	B3LYP $\Delta H_S^{\ddagger}$	B3LYP $\Delta G_S^{\ddagger}$	MM2 ΔG_1
1	0	7.67	26.11	−1.35	27.46	10.79	12.14	10.83
2	0.340444	7.68	25.27	−1.45	26.71	10.29	11.74	9.91
3	2.198657	3.83	23.22	−0.59	23.81	8.61	9.20	5.54
4	2.773786	2.23	20.52	−0.86	21.38	6.81	7.67	5.46
5	3.962843	2.82	19.71	−1.70	21.41	4.42	6.12	4.15
6	3.720159	−0.79	20.32	−0.85	21.17	5.71	6.56	1.01

B3LYP and MM2 refer to values calculated using B3LYP/6-31G (d, p) and Allinger's MM2 methods, respectively. Log k_{rel} is the logarithm of the relative reactivity (see Ref. 10). ΔE_s is the MM2 difference in strain energies of the products and the reactants in kcal/mol. $\Delta H^{\ddagger}$ is the activation enthalpic energy calculated in the gas phase (kcal/mol). $\Delta G^{\ddagger}$ is the activation free energy calculated in the gas phase (kcal/mol). $\Delta H_S^{\ddagger}$ is the activation enthalpic energy calculated in water (kcal/mol). $\Delta G_S^{\ddagger}$ is the activation free energy calculated in water (kcal/mol). $T\Delta S^{\ddagger}$ is the entropic energy in kcal/mol. MM2 ΔG_1 is the free energy (in kcal/mol) calculated from the MM2 enthalpic energy (ΔE_s) and the B3LYP/6-31G (d, p) entropic energy with correction for the effect of water on the strain (enthalpic energy).

Figure 1. (a) Plot of the DFT-calculated free activation energy in the gas phase ($\Delta G^{\ddagger}$) and in water ($\Delta G_S^{\ddagger}$) versus the rate of ring-closing ($\log k_{rel}$) in **1–6**. (b) Plot of MM2-calculated free energy ($\Delta G_1 = \Delta E_s - T\Delta S^{\ddagger}$) versus ring-closing rate ($\log k_{rel}$) in **1–6**. (c) Plot of the HF-calculated enthalpic energy (ΔH) versus $\sin \alpha + 1/r$, where α is the attack angle and r is the C5–N1 distance in ring-closing reactions of **1–6**. (d) Plot of the slope S_{ar} versus the ring-closing rate ($\log k_{rel}$) in **1–6**, where S_{ar} is the slope of (ΔH) versus $\sin \alpha + 1/r$.
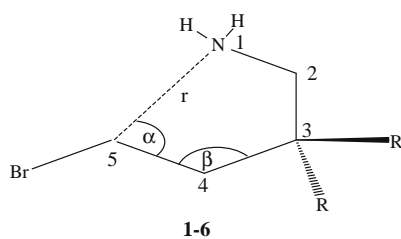
Chart 2. Representation of the attack angle α and the C5–N1 distance, r, in the ring-closing reactions of **1–6**.

5, and 3.82 Å for **6**. Attempts to correlate these distances with $\log k_{rel}$ gave a very poor correlation coefficient ($R^2 = 0.67$). Similarly, correlation of the B3LYP/6-31G(d, p) calculated C5–N1 distances of the global minimum structures in **1–6** (4.39 Å, 4.32 Å, 4.17 Å, 4.01 Å, 3.06 Å, and 3.82 Å, respectively) with $\log k_{rel}$ resulted in a poor correlation coefficient, $R^2 = 0.68$.

(b) In the HF calculations for the approach of a nucleophile (N-1) toward an electrophile (C-5), the distance between N1 and C5 in processes **1–6** was changed in increments of 0.1 Å until the zone of the first transition state (2.2 Å) was reached. The calculated derived enthalpic energies along with the C5–N1 distance and the attack angle α (see Chart 2) values are depicted in Table S3 (Supplementary data).

Inspection of Table S3 (Supplementary data) reveals that the enthalpic energy needed to shorten the distance between the electrophilic (C5) and the nucleophilic (N1) centers from $\sim$4.3 Å (the C5–N1 distance in systems **1** and **2**) to $\sim$3.0 Å (the C5–N1 distance in system **5**) is less than 0.5 kcal/mol.

The combined results described in (a) and (b) exclude the notion that the distance between a nucleophile (N1) and an electrophile (C5) is a crucial factor in determining the rate of the cyclization reaction. Thus, the 'reactive-rotamer theory' is not applicable for explaining the discrepancy in rates for the different di-substituted 4-bromobutylamines.

Further, if diffusion processes are not rate-limiting, the rate constant will only be determined by the free energy levels of the ground state and the transition state. Then, the fact that the reaction pathways involve more or less stable reactive conformers would not influence the rate. Moreover, any relationship between the probability of reactive conformers and rate constant would only depend on the similarity of these conformers to the transition state. In the system studied herein, two possibilities may be found: (i) strain is already released in the NACs, or (ii) there is a difference in strain energy between NACs and the TS. The DFT calculations of the six different bromobutyl amines indicate clearly that the global minimum structures calculated for these systems are in a *syn* orientation by which the nucleophile (–NH$_2$) is pointing toward the electrophile (–CH$_2$–Br) resembling that for the NACs (see Fig. S1a, Supplementary data). Thus, there is no release of strain energy in the NAC and the only difference between the six systems **1–6** is in the strain energy of the transition state and NACs. This observation is in conflict with Bruice's theory thereby negating its general application.

Brown and Van Gulick studied the kinetic behavior of the cyclization reactions of **1–6** and found that both the position and the size of the *gem*-disubstituent have a profound effect on the rate of ring closure. This result led them to conclude that *gem*-nonsubstituted systems, such as **1–2** with a relatively low cyclization rate, prefer to be engaged in an extended form while the *gem*-substituted systems, such as **4–6** with a relatively high reaction rate, are most likely engaged in the coiled form.[10]

In order to test the validity of Brown's proposal we have calculated the kinetic and thermodynamic properties for the cyclization processes of **1–6**.

The calculated HF and DFT global minimum structures (GM) for **1–6** (Fig. S1a, Supplementary data) and the N1C2C3C4 dihedral angle values for these optimized structures (Table S4, Supplementary data) indicate clearly that the reactants in systems **1–6** are engaged in the coiled form and the orientation of the amino group (the nucleophile) to C5–Br (electrophilic center) is similar in all the systems. For example, the difference in values of both the HF and DFT N1C2C3C4 dihedral angles **1** and **5** is only 3–4° (Table S4, Supplementary data).

In the 'Thorpe-Ingold effect', the substitution of the methylene hydrogens with more bulky alkyl groups results in compression of the internal angle. Consequently, the two reactive centers move closer together, and this enhances the cyclization rate.[1]

To test the validity of the 'Thorpe-Ingold effect'[1] on Brown's system, we attempted to correlate both the calculated HF and DFT C2C3C4 bond angle values (angle β in Chart 2) for the reactants in **1–6** with log k_{rel}. Although a qualitative relationship exists between the two parameters, the R value for their linear correlation was very poor, $R^2 = 0.58$ (for the calculated β values, see Table S4, Supplementary data).

To examine whether the discrepancy in the rates for processes **1–6** stems from proximity orientation (difference in the distance between the two reacting centers) or due to steric effects (strain energy) we calculated, using Allinger's MM2 method,[14] the strain energy values for the reactants and the products in systems **1–6**. The difference in values between the MM2 strain energies of the products and the reactants (ΔE_s) are listed in Table 1. The MM2-calculated activation energies ($\Delta\Delta G_1$) for **1–6** were obtained using the following equation:

$$(\Delta\Delta G_1) = \Delta E_s - T\Delta S^{\ddagger}$$

where $T\Delta S^{\ddagger}$ is the B3LYP/6-31G (d, p)-calculated entropic energy.

The calculated MM2 $\Delta\Delta G_1$ (ΔE_s) values were examined for the correlation with the experimental (log k_{rel}) values and the correlation results are illustrated graphically in Figure 1b which reveals that there is a good correlation between the experimental log k_{rel} and the MM2-calculated free energy values ($\Delta\Delta G_1$). The results shown in Figures 1a and b indicate that for systems that have small differences in strain energy values between the products and the reactants (such as **5**), the corresponding activation energies ($\Delta\Delta G_S^{\ddagger}$) are small and vice versa.

In order to better understand which constituent factors are affected by the strain effect, we calculated the change in the value of the attack angle α (N/C5/ < α > –C4, Chart 2) and the change in the distance between the two reacting centers (r = N1–C5 distance) as a function of ΔH (enthalpic energy) since both parameters (r and α) are reported to play an important role in the reaction rates of intramolecular systems.[3,7]

It should be noted that the values of ΔH, r, and α were obtained from the HF calculations of the approach of the amine group, –NH$_2$, toward the electrophilic center, C5–Br, in each of the reactants **1–6**. The calculation results for the approach are summarized in Table S3 (Supplementary data).

The data in Table S3 (Supplementary data) were examined for linear correlations, and a strong correlation was observed between the energy ΔH (enthalpic energy) and sin α and $1/r$, as shown in Eqs. 1–6 in Table S5 (Supplementary data). Eqs. 1, 3, and 5 are shown graphically in Figure 1c. Careful examination of Eqs. 1–6 indicates that the energy needed to increase the value of angle α to reach the optimal value for the formation of a stable transition state is less for **5** than for **1**. This suggests that the approach of N1 to C5 in system **5** is much easier than in system **1**. Further, it

was found that the order of the slope values (S_{ar}) of the curves ΔH versus sin $\alpha + 1/r$ in systems **1–6** is: S_{ar} (**2**) > S_{ar} (**1**) > S_{ar} (**3**) > S_{ar} (**4**) > S_{ar} (**6**) > S_{ar} (**5**), and when the (S_{ar}) values were plotted against log k_{rel} values, very strong correlations were obtained (see Fig. 1d). Since $\Delta\Delta G_1$ (ΔE_s) correlates strongly with log k_{rel}, the slope value (S_{ar}) can be used as a good indicator for predicting the strain energy of a ring-closing reaction.

The combined results exclude the notion that accelerations in the rate for *gem*-disubstituted systems are driven by the 'reactive-rotamer effect'.[3] In addition, our HF and DFT calculations show that the global minimum structures for **1–6** have the same conformational pattern (coiled form, see Fig. S1, Supplementary data). This is in contrast to that suggested by Brown and Van Gulick that *gem*-non-substituted systems, such as **1–2**, prefer to be engaged in an extended form while the *gem*-substituted systems such as **4–6**, most likely exist in coiled form.[10]

In summary, we have introduced a new equation that correlates strain and activation energies with geometrical parameters (r and α).[15] Using this equation, we have proved that the driving force for accelerations in rate for Brown's *gem*-di-substituted system is due to the strain energy and not proximity orientation, and neither due to 'the reactive-rotamer effect', as suggested by Bruice et al.,[3] nor due to a coiled conformation preference as proposed by Brown and Van Gulick.[10]

Acknowledgments

Supplementary data

Supplementary data (Table S1, HF and DFT calculated properties for the reactions of **1–6**. Table S2, HF calculated energies and C–N bond distances as a function of the change in the dihedral angle C2C3C4C5 of **1–6**. Table S3, HF calculated enthalpic energies (ΔH), attack angles (α) and bond distances (r) in the energy profiles for the cyclization reactions of **1–6**. Table S4, HF and DFT calculated bond distances (r) and bond angles (β and α) for the entities involved in the ring-closing reactions of **1–6**. Table S5, correlation equations for the HF/6-31G calculated properties for the ring-closing reactions of **1–6**. Figures S1a–1c, B3LYP/6-31G (d, p) optimized structures of the global minimum (GM), the first transition state (TS1) and the second transition state structures for **1–6**.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.072.

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