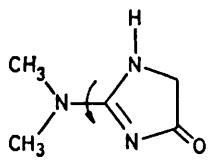
Barriers to Rotation in Acylguanidines and Acylguanidinium Ions

By **Robert F. Dietrich, George L. Kenyon,* John E. Douglas,** and **Peter A. Kollman,** Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143, U.S.A.

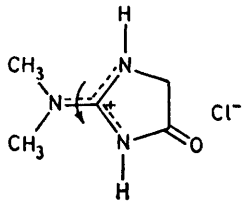
Using both ^1H and ^{13}C n.m.r. spectroscopy, the free energies of activation ($\Delta G_c^{\ddagger}$) values for barriers to rotation in 2-dimethylamino-2-imidazolin-4-one (1a), an acylguanidine, and its hydrochloride salt (1b), an acylguanidinium ion, have been determined to be 15.6 ± 0.1 and 17.6 ± 0.2 kcal mol^{-1}, respectively. In both cases, the rotational barrier about the exocyclic carbon–nitrogen bond was involved. Resonance arguments are used to rationalize these experimental results, and *ab initio* theoretical calculations are presented that successfully reproduce the relative order of experimentally determined barriers to rotation in guanidinium ions, acylguanidines, and acylguanidinium ions.

WHILE extensive investigations of both barriers to rotation and barriers to inversion have been carried out on guanidines and guanidinum ions,[1-4] acylguanidines and acylguanidinium ions have received relatively little attention. This is in spite of the fact that there are numerous examples of biologically important molecules containing acylguanidine moieties (*e.g.*, creatinine, some purines, some pyrimidines, biopterin, and tetrahydrofolate).

The specific molecules we have chosen to examine, 2-dimethylamino-2-imidazolin-4-one (1a) and its hydrochloride salt (1b), provide ideal models for examining rotational barriers about a particular carbon–nitrogen bond in an acylguanidine molecule and the corresponding acylguanidinium ion. Although Kessler and Leibfritz [1-4] have compared 'isomerization' barriers in guanidines and guanidinium ions using n.m.r. spectroscopy, they concluded that the particular guanidines they examined 'isomerize' by an inversion mechanism, while the



(1a)

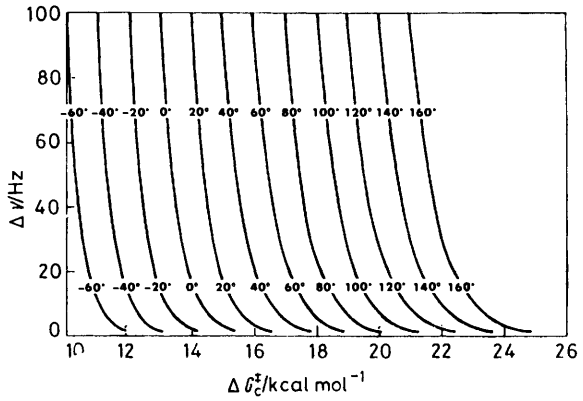


(1b)

guanidinium ions 'isomerize' by a rotational mechanism.[4] Since an inversion mechanism is not possible for either (1a or b), we can be assured that we are observing only the barrier to rotation about one particular bond in each case, namely that between the ring C-2 atom and the nitrogen of the dimethylamino substituent.

The proton-decoupled ^{13}C n.m.r. spectrum at 30 °C of the acylguanidine (1a) showed the two methyl peaks of the dimethylamino group to be nonequivalent and to be separated by 46 Hz, and so, in principle, the barrier to rotation could have been examined by ^{13}C n.m.r. spectroscopy. For reasons of convenience, however, we chose variable temperature ^1H n.m.r. spectroscopy to evaluate the barrier to rotation about the bond in question.

The Figure is a representation of the relationships among Δν [the difference in frequency (in Hz) in an n.m.r spectrum of the signals due to two exchangeable species], T_c (the coalescence temperature), and $\Delta G_c^{\ddagger}$ [the free energy of activation (in kcal mol^{-1}) for the coalescence process]. It was constructed by substituting various



Plot of the free energy of activation at the coalescence temperature ($\Delta G_c^{\ddagger}$) *versus* the difference in frequencies of the n.m.r. absorption singlets for two exchangeable species (Δν) for various coalescence temperatures T_c

values of Δν and T_c into equation (1) and the Eyring equation (2) where k_c is the rate constant for exchange at

$$k_c = \pi (\nu_a - \nu_b)/\sqrt{2} \qquad (1)$$

coalescence and k is Boltzmann's constant and h Planck's constant.

$$k_c = kT/h \cdot e^{-\Delta G^{\ddagger}/RT} \qquad (2)$$

The Figure serves as a simple graphic device for quickly determining any one of the three parameters when the other two are known, and is applicable to many exchange phenomena observable by n.m.r. spectroscopy.[5] Even though equations (1) and (2) are both well known and have been widely applied, such a graphical representation as shown in the Figure has not to our knowledge been presented before.

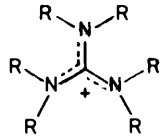
At 1.4 °C, the ^1H n.m.r. spectrum of acylguanidine (1a) showed two sharp singlets separated by 11 ± 1 Hz (0.11 p.p.m.) indicating a rate constant at coalescence of 24.4 s^{-1}. Substitution of both this value and the observed coalescence temperature of 25.5 ± 0.5 °C into the Eyring

equation yields a free energy for the barrier to rotation ($\Delta G_c^{\ddagger}$) of 15.6 ± 0.1 kcal mol^{-1}.*

The rotational barrier in the corresponding acylguanidinium ion (1b) was obtained utilizing both ^{1}H and ^{13}C n.m.r. spectroscopy. The ^{1}H n.m.r. spectrum (25.4 °C) showed a pair of well resolved singlets (Δν 2.6 ± 0.2 Hz or 0.026 p.p.m.) which coalesce at 47 ± 0.5 °C, indicating a $\Delta G_c^{\ddagger}$ of 17.7 ± 0.1 kcal mol^{-1}.

This barrier was confirmed using proton-decoupled ^{13}C n.m.r. spectroscopy. The two methyl peaks were found to be separated by 34 ± 2 Hz (1.35 p.p.m.) at 30 °C, and these peaks coalesced at 75 ± 2 °C, indicating a $\Delta G_c^{\ddagger}$ value of 17.5 ± 0.2 kcal mol^{-1}. This rotational barrier is significantly higher than the barrier for a guanidinium ion reported previously by Kenyon *et al.*[6] (see Table). Much closer agreement is found by comparing this value to the rotational barrier in 4-acetylphenyl(pentamethyl)guanidinium iodide (3), which can be considered a phenylogous analogue of an acylguanidinium ion. The barrier in this molecule was found to be 16.5 kcal mol^{-1} by Kessler and Leibfritz.[4]

The unusually high barrier in (1b) can be rationalized using arguments similar to those of Kessler and Leibfritz[4] for 4-substituted aromatic guanidinium ions. Comparison of the three potential resonance structures for guanidinium ion show them all to be equivalent, implying equal delocalization of the double bond over the three carbon–nitrogen bonds [structure (A)].



(A)

A comparison of the three similar resonance structures for an acylguanidinium ion shows two equivalent resonance structures (11a and b) plus a more energetically unfavourable structure (11c) in which a formal positive charge is on the nitrogen atom adjacent to the partially

* In this paper, 1 kcal = 4.184 kJ.

Barriers to rotation in guanidines, guanidinium ions, acylguanidines, acylguanidinium ions, and related compounds

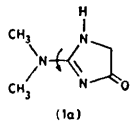
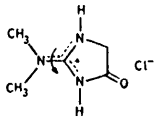
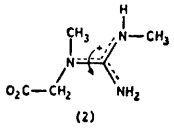
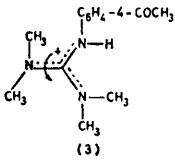
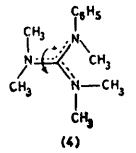
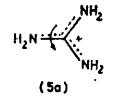
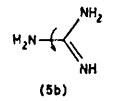
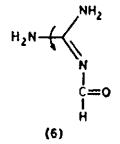
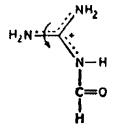
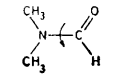
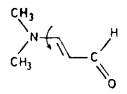
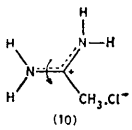
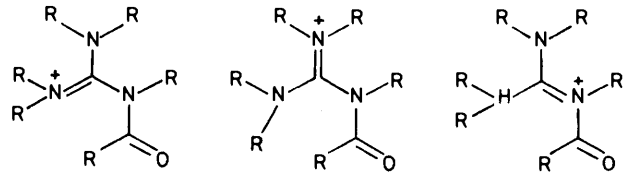
Structure	Barriers to rotation (kcal mol^{-1}) Experimental	Calculated (ΔE) [a] STO–3G	4–31G
 (1a)	15.6 ± 0.1 ($\Delta G_c^{\ddagger}$)	15.5	
 (1b)	17.6 ± 0.2 ($\Delta G_c^{\ddagger}$)	23.7	
 (2)	13.6 ± 1.9 ($\Delta H_c^{\ddagger}$) [b] 11.1 ± 3.8 ($\Delta G_c^{\ddagger}$) [b]		
 (3)	16.5 ± 0.2 ($\Delta G_c^{\ddagger}$) [c]		
 (4)	15.5 ± 0.2 ($\Delta G_c^{\ddagger}$) [c]		
 (5a)		22.1	15.5 [d]
 (5b)			12.2
 (6)			17.0
 (7)		23.4	17.7

TABLE (*Continued*)

Structure	Barriers to rotation (kcal mol^{-1}) Experimental	Calculated (ΔE) [a] STO–3G	4–31G
 (8)	20.9 ± 0.2 [e] 21.0 ± 0.4 [f] ($\Delta G_c^{\ddagger}$) 20.2 ± 0.2, [e] 20.5 ± 0.1 [f] ($\Delta H_c^{\ddagger}$) −1.7 cal mol^{-1} K^{-1}; [e] −1.4 ± 1 cal mol^{-1} K^{-1} [f] ($\Delta S^{\ddagger}$)		
 (9)	15.6 ± 0.2 ($\Delta G_c^{\ddagger}$) [g]		
 (10)	18—19 ($\Delta G_c^{\ddagger}$) [h]		

[a] The calculated ΔE between the planar and perpendicular conformations. [b] Ref. 6. [c] Ref. 4. [d] Ref. 7; the calculated barrier when the carbon–nitrogen bonds were both optimized in planar and perpendicular geometries was 14.1 kcal mol^{-1}. [e] Ref. 8. [f] Ref. 9. [g] Ref. 10. [h] Ref. 11.

positively charged carbonyl carbon. These considerations lead to the prediction of a higher contribution from resonance structures (11a and b), with more double-bond character in those carbon–nitrogen bonds and a higher



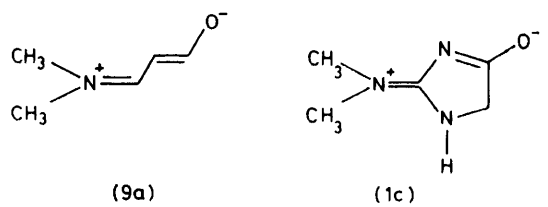
(11a) (11b) (11c)

rotational barrier about those bonds. The slightly lower barrier in the phenylogous compound can be explained by the insulating effect of the phenylene ring.

While the comparison between (1b) and the acylphenylguanidinium ion (3) shows fairly good agreement, there is more than likely a larger steric contribution to the energy barrier in the phenyl-substituted compound. Pentamethylphenylguanidinium ion (4) has a rotational barrier of 15.5 kcal mol^{-1}, only 1.1 kcal mol^{-1} lower than the 4-acetylphenyl compound. Compound (1b), on the other hand, has a barrier *ca.* 4 kcal mol^{-1} higher than a similar guanidinium ion.[6] Thus, the effect of the acetyl group on the phenylguanidinium ion may be dampened not only the insulating property of the phenylene group, but also by steric effects present in both (3) and (4).

The resonance arguments for the relatively high rotational barrier in (1b) indicate that the barrier to rotation in acylguanidinium ions (17.6 $\pm$ 0.2 kcal mol^{-1}) ions might more closely agree with amidinium ions than with similar guanidinium ions. This indeed appears to be the case. Using the data of Hammond and Neuman,[11] one can estimate a $\Delta G_c^{\ddagger}$ value for acetamidinium chloride (10) in dimethyl sulphoxide of 18—19 kcal mol^{-1}.

The rotational barrier of 15.6 kcal mol^{-1} in (1a) can be put into perspective by considering it as being analogous to a vinylogous amide. The well studied amide, dimethylformamide (8), has been shown to have a rotational barrier ($\Delta G_c^{\ddagger}$) of 21.0 kcal mol^{-1},[8,9] while the corresponding vinylogous compound (9) has a $\Delta G_c^{\ddagger}$ value of 15.6 kcal mol^{-1}.[10] Thus, just as the resonance hybrid of compound (9) has an important contribution from resonance structure (9a), so the resonance hybrid of compound (1a) has an important contribution from resonance structure (1c).



(9a) (1c)

The possibility exists that rotation about the carbon–nitrogen bond in (1b) might occur by a mechanism involving deprotonation, rotation, followed by reprotonation. In order to explore this possibility, the barriers to rotation were determined at two different acidic pD values. If deprotonation is necessary for rotation to occur, then a higher pD value, with a correspondingly higher proportion of the unprotonated species, should lead to a lower observed rotational barrier. In DCl (pD — 1), the observed barrier was 17.5 $\pm$ 0.1 kcal mol^{-1}, while at pD 2.0, the barrier was found to be 17.4 $\pm$ 0.1 kcal mol^{-1}. [The value of pD 2.0 was chosen to be within *ca.* 2 pK units of the known pK_a value of (1b) (4.45)].[12] These results imply that it is not likely that the unprotonated species is necessary for the rotational process to occur.

A referee has raised two important points *vis-à-vis* these experiments. First, he questioned whether one should consider *O*-protonation of (1a) when the HCl salt is formed. We consider this very unlikely, considering the relative pK_a values of guanidines (*ca.* 13) and amides (*ca.* —1). Even if both pK_a values are perturbed significantly, it is extremely unlikely they will reverse.

Secondly, he pointed out to us the uncertainties in using equations (1) and (2) rather than full line shape analysis in our determinations of $\Delta G^{\ddagger}$ (see ref. 13 for a more complete discussion). In fact, the Figure shows clearly that the uncertainties in $\Delta G^{\ddagger}$ go up dramatically at small $\Delta\nu$ values. However, our results for (1a) ($\Delta\nu$ 11 Hz) and (1b) (the ^{1}H $\Delta\nu$ value of 2.6 Hz was confirmed by the ^{13}C $\Delta\nu$ value of 34 Hz) should be at least qualitatively correct in determining the relative rotational barriers of (1a and b) and (2).

In conjunction with these experiments, we carried out *ab initio* calculations on the barrier to rotation about the exocyclic carbon–nitrogen bonds of compounds (1a and b) as well as calculations on the simpler guanidinium ions (5a and b), (6) and (7) (see Table).

With the STO-3G basis set, the acylguanidinium ion (6) has a calculated barrier 1.3 kcal mol^{-1} higher than that for guanidinium ion (5a); with the 4-31G basis set this difference was calculated to be 2.2 kcal mol^{-1}. This result with the more extended basis set is in reasonably good agreement with the experimentally determined difference in barriers of *ca.* 2.1 kcal mol^{-1} between a highly substituted guanidinium ion (4) and acylguanidinium ion (1b). It was considered to be too expensive to carry out calculations at the 4-31G level on (1b) itself, but calculations at the STO-3G level on this molecule led to a ' predicted ' barrier 1.6 kcal mol^{-1} higher than that for guanidinium ion (5a).

The *ab initio* calculated bond orders in compound (1b) for both the exocyclic carbon–nitrogen bond and the carbon–nitrogen bond not conjugated with the carbonyl (0.446 and 0.441, respectively) were significantly higher than that of the carbon nitrogen bond which is conjugated with the carbonyl (0.415). Similar relative bond orders were also found in model compound (6). These results are in accord with the resonance arguments presented above in which resonance forms (11a and b) were favoured over resonance form (11c).

For the corresponding acylguanidine (1a), the *ab initio* calculations find a lower barrier than that for the acyl-

guanidinium ion (1b), again consistent with the experimental results, although the calculated difference in the barriers is exaggerated. As expected, the calculated bond orders for the exocyclic and endocyclic C–N bonds (both 0.394) are significantly smaller than that for the conjugated C=N bond (0.438). The STO-3G basis set does not correctly reproduce the fact that acylguanidine should have a higher barrier than guanidinium [using (2) as a model for (5a)]. However, the 4-31G basis set is able to calculate the barriers in (5a), (6), and (7) in the same order as found experimentally for compounds (2), and (1a and b).

The calculations at the 4-31G level on model compounds (5b) and (6) illustrate the important role of the acyl group in raising the rotational barrier of the guanidine. Assuming that compounds (6) and (7) are faithful models of (1a and b), respectively, the 4-31G calculations are successful in reproducing the relative experimental barriers to rotation in (1a and b), although the observed difference ($\Delta\Delta G_c^{\ddagger}$) is 2 kcal mol^{-1} and the calculated difference between (6) and (7) is only 0.7 kcal mol^{-1}. The barriers are, of course, quite sensitive to the carbon–nitrogen bond distances employed, and the use of a somewhat longer C–N distance in (6) would improve the agreement [calculations on compound (5b) suggest, for example, that the barrier to rotation decreases by *ca.* 0.5 kcal mol^{-1} for every 0.01 Å the rotatable C–N bond is lengthened]. However, complete geometry optimizations of these structures were considered to be too expensive and no sufficiently accurate *X*-ray crystal structures of related compounds are available. In view of these uncertainties in the bond lengths involved, we feel that the calculations using the extended 4-31G basis set adequately represent the rotational barriers in these molecules.

EXPERIMENTAL

Materials.—Compound (1a) was prepared according to the procedure of Kenyon and Rowley.[12]

The pD 2.0 buffer solution was prepared by exchanging 85% phosphoric acid three times with 99.8% D_2O, diluting with 99.8% D_2O to 1.0M-D_3PO_4, and adjusting the pD to 2.0 by the addition of anhydrous, powdered K_2CO_3.

N.m.r. Spectroscopy.—Both ^1H and ^{13}C spectra were obtained with a Varian XL-100 spectrometer in the pulse mode interfaced with a Nicolet Instrument Corporation model NIC-80 data processer. For the ^{13}C spectra, a Nicolet Multi Observe Nuclei Accessory (MONA) was utilized, and the spectra obtained at 25.158 MHz with broadband proton decoupling for a *ca.* 1.2M solution in 70% D_2O–H_2O. The ^1H n.m.r. spectra were obtained from *ca.* 0.1M solutions in 99.8% D_2O at 100.1 MHz. Temperatures were measured by direct insertion of a Doric Trendicator 412-A copper–constantan thermocouple into the sample. The spectra may be seen elsewhere.[14]

Computational Details.—We used the program GAUSSIAN 70 [15] in the *ab initio* calculations with STO-3G [16] and 4-31G [17] basic sets. In the STO-3G calculations on guanidinium ion (5a) and acylguanidinium ion (6) standard geometries were used and the energies evaluated at planar and perpendicular structures.

Since no *X*-ray crystal structures were available for either compounds (1a or b), we used the QCFF-PI [18] program to calculate reasonable geometries for (1b). For (1a), we used the same geometry as for (1b), except that the proton was removed. In order to simplify comparisons among calculations of barriers using the STO-3G basis set, the exocyclic carbon–nitrogen bond around which rotation occurs was kept at a bond distance *R* of 1.37 Å for all calculations at this level. This value was the STO-3G optimized value found earlier for guanidinium ion.[7]

For the 4-31G calculations on (6), we used the minimum energy C–N distance (1.33 Å) found for compound (5a).[7] In the 4-31G calculations on (5b) and (7) we used *R*(C=N) 1.26 and *R*(C–N) 1.365 Å; the former was taken from the calculated C=N bond length for methyleneimine; [19] the latter was chosen so that the sum of the three carbon–nitrogen bond lengths would be the same as the sum of the three carbon–nitrogen bond lengths in the guanidinium ion (1a).

We thank the United States Public Health Service and the National Science Foundation for financial support. This project was also supported by the Division of Research Resources, National Institutes of Health, to the UCSF Magnetic Resonance Laboratory. G. L. K. is a United States Public Health Service Research Career Development Awardee. P. A. K. is a United States Public Health Service Research Development Awardee. R. F. D. was a National Institutes of Health Predoctoral Trainee. We also thank Dr. N. Oppenheimer for helpful discussions.

[0/036 *Received*, 9*th January*, 1980]

REFERENCES

[1] H. Kessler and D. Leibfritz, *Tetrahedron Letters*, 1969, 427.
[2] H. Kessler and D. Leibfritz, *Tetrahedron*, 1969, **25**, 5127.
[3] H. Kessler and D. Leibfritz, *Tetrahedron*, 1970, **26**, 1805.
[4] H. Kessler and D. Leibfritz, *Chem. Ber.*, 1971, **104**, 2158.
[5] F. A. Bovey, ' Nuclear Magnetic Resonance Spectroscopy,' Academic Press, New York, 1969.
[6] G. L. Kenyon, G. E. Struve, P. A. Kollman, and T. I. Moder, *J. Amer. Chem. Soc.*, 1976, **98**, 3695.
[7] P. A. Kollman, P. Gund, and S. Rothenberg, *J. Amer. Chem. Soc.*, 1975, **97**, 1640.
[8] K. Rabinovitz and A. Pines, *J. Amer. Chem. Soc.*, 1969, **91**, 1585.
[9] T. Drakenberg, K. J. Dahlquist, and S. Forsen, *J. Phys. Chem.*, 1972, **76**, 2178.
[10] M. L. Blanchard, A. Chevallier, and G. J. Martin, *Tetrahedron Letters*, 1967, 5057.
[11] G. S. Hammond and R. C. Neuman, jun., *J. Phys. Chem.*, 1963, **67**, 1655.
[12] G. L. Kenyon and G. L. Rowley, *J. Amer. Chem. Soc.*, 1971, **93**, 5552.
[13] G. Binsch, ' Topics in Stereochemistry,' eds. E. Eliel and N. Allinger, Wiley–Interscience, New York, 1968.
[14] R. F. Dietrich, Ph.D. Thesis, University of California, San Francisco, 1979.
[15] W. Hehre, W. Latham, R. Ditchfield, M. Newton, and J. A. Pople, QCPE No. 236.
[16] W. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, 1969, **51**, 2657.
[17] R. Ditchfield, W. Hehre, and J. A. Pople, *J. Chem. Phys.*, 1971, **54**, 7241.
[18] A. Warshel and M. Levitt, QCPE No. 247.
[19] J. M. Lehn, *Theor. Chim. Acta*, 1970, **16**, 351.