Influence of Compression upon Kinetic Isotope Effects for S_N2 Methyl Transfer: A Computational Reappraisal

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Abstract: Secondary α-D_3 kinetic isotope effects (KIEs) have been calculated using ab initio HF and B3LYP methods with 6-31G and 6-31G* bases for four methyl transfer reactions of the general type $R_3N + CH_3NR_3^+$. Comparison of $R = CH_3$ (B) with $R = H$ (A) serves to investigate the effect of varying the nucleophile and nucleofuge by alkylation of the entering and leaving amine moieties. The changes in KIE, transition-structure (TS) looseness, and energy barrier do not accord with the generalization of Wolfe and co-workers (*J. Am. Chem. Soc.* **1993**, *115*, 10147). Reactions C and D are intramolecular methyl transfers between the bridgeheads of inside-methylated [1.1.1]cryptand and 1,7-diazabicyclo[5.5.5]heptadecane, respectively, in which the N···N distances are significantly smaller than in B. Comparison of B with either C or D serves to investigate the effect of compression along the N−C−N axis. The energy barriers for C and D are markedly lower than for B, and, although their TS's are tighter than for B, their reactant complexes (RC's) are even tighter. Progress from RC to TS in the compressed systems is accompanied by a decrease in strain. The inverse α-D_3 KIEs for C and D are dominated by zero-point energy changes, but the contribution from the CH stretching modes is *less* inverse than that for B. The more inverse B3LYP KIEs for C and D arise because there is a significant increase in the relaxed valence force constant for bending the $H{-}C_\alpha{-}N_{lg}$ angle in going from RC to TS. These calculated results are consistent with Schowen's compression hypothesis for enzymatic methyl transfer.

Introduction

Methyl-group transfer from an electrophile to a nucleophile by an S_N2 mechanism is an archetypal reaction in organic chemistry and still the subject of much experimental and theoretical study.[1] Transmethylation is an important process in biochemistry[2] and the mechanism of its enzymic catalysis is of great interest.[3] Some years ago one of us performed a theoretical investigation[4] to test the validity of Schowen's[5] "compression hypothesis" for enzymic methyl transfer. Experimentally, the secondary kinetic isotope effect (2° KIE) $k(CH_3)/k(CD_3)$ is large and inverse for methyl transfer catalyzed by catechol-*O*-methyltransferase (COMT), much more inverse than for an uncatalyzed reaction in solution, suggesting a very tight transition state for the enzymic reaction. Theoretically, a very simple model displayed the same result.[4] However, the idea has since been criticized.[6]

We now present results from ab initio Hartree−Fock (HF) and density-functional theoretical (DFT) calculations of 2° KIEs for the model reactions A to D depicted in Scheme 1, designed with the aim of providing a better system with which to assess the validity of the compression hypothesis. These identity reactions are of the general type $R_3N + CH_3NR_3^+$ and occur either within acyclic complexes (A and B) or within bicyclic cage structures (C and D). We consider two computational tests. The first is provided by comparison of reactions A and B and serves to investigate the effect of varying the nucleophile and nucleofuge by alkylation of the entering and leaving amine moieties. The second is provided by comparison of B with either reaction C or D and serves to investigate the effect of compression along the N−C−N axis.

Critique of the Compression Hypothesis. The power of any catalyst derives fundamentally from its ability to stabilize the transition state relative to the reactant state, as compared with the uncatalyzed reaction. This requires effective discrimination between the reactant state and the transition state. In the case of methyl transfer, stabilizing enzyme−substrate interactions (1 in Scheme 2) probably do not provide any significant degree of discrimination, since the geometrical and electronic changes occurring do not provide sufficient differences; thus

$$|\Delta E^{R}_{\text{stabilize}}| \approx |\Delta E^{T}_{\text{stabilize}}| \qquad (1)$$

The key proposal of the compression hypothesis is this: if the transition state for S_N2 methyl transfer is more plastic than the reactant state for the catalyzed process, then mechanical compression by the enzyme (2 in Scheme 2) might destabilize the reactants more than the transition state. In other words, the

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(1) Shaik, S. S.; Schlegel, H. B.; Wolfe, S. *Theoretical Aspects of Physical Organic Chemistry. The S_N2 Mechanism*; Wiley: New York, 1992.

(2) (a) Takusagawa, F.; Fujioka, M.; Spies, M. A.; Schowen, R. L. In *Comprehensive Biological Catalysis*; Sinnott, M. L., Ed.; Academic Press: London, 1998; Vol. 1. (b) Jost, J. P.; Saluz, H. P. *DNA Methylation: Molecular Biology and Biological Significance*; Birkhauser Verlag: Boston, 1993.

(3) (a) Zheng, Y.-J.; Bruice, T. C. *J. Am. Chem. Soc.* **1997**, *119*, 8137. (b) Lau, E. Y.; Bruice, T. C. *J. Am. Chem. Soc.* **1998**, *120*, 12387. (c) Kuhn, B.; Kollman, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 2586.

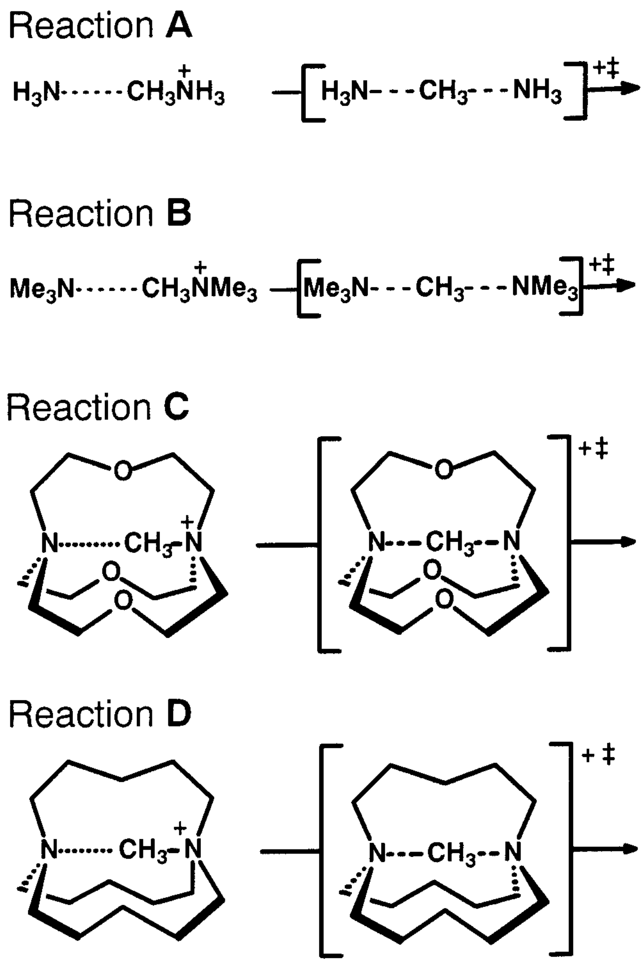
(4) Williams, I. H. *J. Am. Chem. Soc.* **1984**, *106*, 7206.

(5) Olsen, J.; Wu. Y.-S.; Borchardt, R. T.; Schowen, R. L. In *Transmethylation*; Usdin, E., Borchardt, R. T., Creveling, C. R., Eds.; Elsevier: New York, 1979.

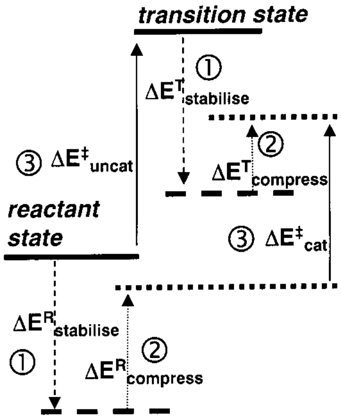
(6) Boyd, R. J.; Kim, C.-K.; Shi, Z.; Weinberg, N.; Wolfe, S. *J. Am. Chem. Soc.* **1993**, *115*, 10147.

10.1021/ja001170e CCC: $19.00

Scheme 1



Scheme 2



energetic penalty for deforming the structure to a given degree is greater for the reactant state than for the transition state.

$$|\Delta E^{\mathrm{R}}_{\mathrm{compression}}| > |\Delta E^{\mathrm{T}}_{\mathrm{compression}}| \tag{2}$$

The net effect (3 in Scheme 2) is reduction of the barrier for the catalyzed reaction as compared with that for the uncatalyzed process.

$$\Delta \mathrm{E}^{\ddagger}_{\mathrm{cat}} < \Delta E^{\ddagger}_{\mathrm{uncat}} \tag{3}$$

As a consequence of (intrinsically unfavorable) compression of the S_N2 transition state in the enzymic reaction, the enzyme is able to distinguish the transition state structurally from the preceding reactant state and the succeeding product state in order to stabilize the transition state specifically. Thus compression may serve to achieve efficient catalysis, with a large $V_{\max}$ at the expense of a slight reduction in $V_{\max}/K_{\mathrm{m}}$. The evidence in support of this idea comes from 2° α-D KIEs, but it depends on how the values of these experimental observations should be interpreted in terms of the "tightness" or "looseness" of the transition state. The isotope effect $V^{\mathrm{CH_3}}/V^{\mathrm{CD_3}} = 0.83 \pm 0.05$ for methylation of 3,4-dihydroxyacetophenone with *S*-adenosylmethionine at 37 °C catalyzed by COMT was found[7] to be more inverse than the value of $k_{\mathrm{CH3}}/k_{\mathrm{CD3}} = 0.97 \pm 0.02$ for methylation of methoxide ion by *S*-methyldibenzothiophenium ion at 25 °C in methanol.[8] According to the orthodox view, Schowen and co-workers interpreted[7] these observations in terms of a tighter S_N2 transition state for the COMT-catalyzed reaction than for the nonenzymic reaction.

Computational studies of identity[9] (X = Y) and nonidentity[6] (X ≠ Y) gas-phase methyl-transfer reactions $X^- + CH_3Y \rightarrow XCH_3 + Y^-$, at levels up to MP2/6-31+G*, led Wolfe and co-workers to report that energy barriers were directly related to the looseness of the transition structures (TS's) but were inversely related to the 2° α-D KIEs. In other words, in contrast to the prevailing belief, α-D KIEs became more inverse as the TS became looser. According to this view, Schowen's results would imply a looser transition state for the enzymic reaction, but with a higher barrier than for the uncatalyzed process. Consequently, Wolfe and co-workers suggested that the change in the α-D KIE for the COMT-catalyzed reaction must be caused by factors others than changes in TS geometry.

Wolfe and co-workers summarized their suggestion as follows:[6] "When an S_N2 TS is altered by variation of the nature of the entering and leaving groups, a decrease in α-D KIE (i.e., more inverse) reflects a looser geometry and is accompanied by an increase in the barrier." We will subsequently refer to this summary statement as the "BKSWW dictum".

Computational Procedures

All calculations were carried out by means of the GAUSSIAN 94[10] and GAUSSIAN 98[11] programs; employing either *ab initio* Hartree−Fock theory or the hybrid density functional B3LYP[12] both with the

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[7] Hegazi, M. F.; Borchardt, R. T.; Schowen, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 4359.

[8] Gray, C. H.; Coward, J. K.; Schowen, K. B.; Schowen, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 4351.

[9] Wolfe, S.; Kim, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 8056.

[10] *Gaussian 94*, Revision B.3; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Repogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1995.

[11] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. In Gaussian, Inc.: Pittsburgh, PA, 1998.

[12] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

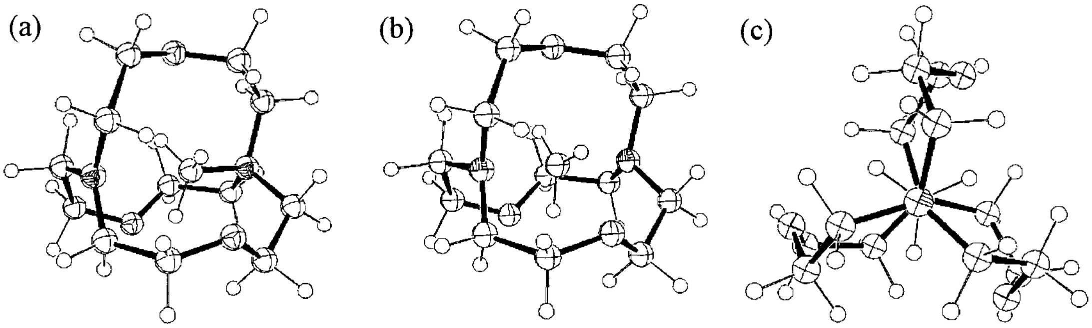

Figure 1. Representative views of B3LYP/6-31G* optimized structures for C: (a) RC; (b) TS; (c) TS view along N−C−N axis.

6-31G and 6-31G* basis sets. Geometry optimization for reactant complexes (RC's) used the Berny routine with analytical gradients, while TS's were obtained by means of the EF algorithm. Termination criteria of 1.8×10^{-3} Å for the maximum displacement and 4.5×10^{-4} hartree bohr^{-1} for the maximum force were employed. The nature of each stationary point was determined by inspection of eigenvalues of the Hessian matrix, computed analytically for HF and numerically for DFT. No symmetry constraints were imposed. Although the cryptand-like species (Figure 1) involved in reactions C and D possess approximate 3-fold symmetry along the N−C−N axis, the optimized geometries do not have exact C_3 or D_3 symmetries. Where small differences in bond lengths, angles, and valence force constants involving the three hydrogen atoms of the transferring methyl group were present, average values were taken.

KIEs k_{CH3}/k_{CD3} at 298.15 K were evaluated from the optimized geometries and computed Hessians using our CAMISO program.[13] Unwanted contamination by spurious translational and rotational contributions, which give rise to small nonzero frequencies for translational and rotational motion, were eliminated by a projection method. The resultant pure vibrational frequencies for isotopomeric species satisfied the Teller−Redlich product rule, being entirely consistent with the masses and moments of inertia obtained from the molecular geometries.[14] This provides a stern and unambiguous test for the correctness of the procedures employed in the isotope-effect calculations. Partition functions were evaluated within the harmonic-oscillator, rigid-rotor, ideal-gas approximations and were utilized within a standard semiclassical transition-state theoretical treatment of isotope effects.[15]

Hessians were transformed from Cartesian coordinates to nonredundant internal coordinates. The latter comprised generally of a subset of bond stretches, angle bends, and torsions, but local symmetry coordinates were constructed for bending about the transferring methyl group, as described previously, to eliminate local redundancies: five independent symmetry coordinates from the six valence coordinates of the distorted tetrahedral RC's[13] and seven from the nine valence coordinates of the trigonal bipyramidal TS's.[16] Inversion of the nonsingular matrix of internal coordinates yielded the compliance constant matrix, the reciprocals of the diagonal elements of which are relaxed force constants. Relaxed valence force constants were obtained by back-transformation of the compliance matrix from nonredundant internal coordinates to redundant valence coordinates.[13] Scaling of force constants was carried out by introducing a scaling factor s_i for each diagonal valence force constant and using the geometric mean $(s_is_j)^{1/2}$ for off-diagonal interaction force constants.[17]

It is known that some DFT methods perform poorly for van der Waals complexes and loose TS's. However, in their study of gas-phase S_N2 identity reactions $X^- + CH_3X$ (X = F, Cl, Br, and I), Ziegler and co-workers found that DFT methods gave overall better geometries and frequencies than the HF and MP2 schemes in comparison with experimental results.[18] Castejon and Wiberg recently concluded that the B3LYP method provided a good description of the Menschutkin reaction of methyl halides with amines in the gas phase, giving calculated activation free energies falling within the accuracy of experimental values.[19] The classical barrier height $\Delta E^\ddagger$ reported by Truong and Stefanovich for X = Cl at the B3LYP/6-31+G(d,p) level *relative to the separated reactants* was negative, in common with many DFT methods but in contrast to positive values for the HF and MP2 methods.[20] However, the barrier height relative to the ion−molecule reactant complex calculated with B3LYP (+36 kJ mol^{-1}) was in as good or better agreement with experiment (50 kJ mol^{-1}) as either the HF (64 kJ mol^{-1}) or MP2 (72 kJ mol^{-1}) results.

Table 1. Optimized Bond Lengths in $(CH_3)_4N^+$ and the TS for Reaction B, Pauling Bond Order Coefficients *c*, and Scaling Factors *s* for Valence Force Constants

method	d^1_{CN}	$d^{0.5}_{CN}$	c	s(CH)	s(rest)
HF/6-31G	1.560	2.032	0.681	0.820	0.825
HF/6-31G*	1.497	2.025	0.762	0.814	0.823
B3LYP/6-31G	1.526	2.031	0.729	0.900	0.965
B3LYP/6-31G*	1.511	2.022	0.737	0.900	0.974

Results and Discussion

Selected geometrical parameters for optimized species are presented in Tables 1 and 2, but complete listings of optimized coordinates and total energies of RC's and TS's obtained at various computational levels are available in the Supporting Information. The acyclic species involved in A and B all adopt perfectly staggered conformations with collinear N−C−N atoms. The cryptand-like species (Figure 1) involved in C and D all possess N−C−N angles of no less than 179.9°, and viewed along this axis the RC's and TS's all appear as slightly twisted Manx emblems. The bridgeheads are twisted by ∼30° away from the eclipsed position, leaving an approximately ∼90° sector between the arms of the cage, within which the transferring methyl group adopts a staggered orientation. A single conformer (essentially C_3) was considered for the purpose of these investigations.

Tightness and Looseness. The looseness parameter $L^\ddagger$, as defined by Wolfe and co-workers,[21] is the percent lengthening of the C−X and C−Y bonds given by eq 4, where d^{RC} and d^{TS} are the C−X (C−Y) bond lengths of CH_3X (CH_3Y) in RC and TS, respectively.

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[13] Williams, I. H. *Chem. Phys. Lett.* **1982**, *88*, 462.

[14] Williams, I. H. *J. Mol. Struct., Theochem.* **1983**, *94*, 275.

[15] Melander L.; Saunders: W. H. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980.

[16] Williams, I. H. *Bull. Soc. Chim. Belg.* **1982**, *91*, 356.

[17] Pulay, P.; Fogarasi, G.; Pongor, G.; Boggs, J. E.; Vargha, A. *J. Am. Chem. Soc.* **1983**, *105*, 7037.

[18] Deng, L.; Branchadell, V.; Ziegler, T. *J. Am. Chem. Soc.* **1994**, *116*, 10 645.

[19] Castejon, H.; Wiberg, K. B. *J. Am. Chem. Soc.* **1999**, *121*, 2139.

[20] Truong, T. N.; Stefanovich, E. V. *J. Phys. Chem.* **1995**, *99*, 14700.

[21] Shaik, S. S.; Schlegel, H. B.; Wolfe, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1322.

Table 2. Selected Bond Lengths (Å), TS Looseness and Tightness Parameters, Barrier Heights (kJ mol^{-1}), and Transition Frequencies (cm^{-1})

method	$(N\cdots N)^{RC}$	$(N\cdots N)^{TS}$	$(C\cdots N_{lg})^{RC}$	$(C\cdots N_{lg})^{TS}$	$(C\cdots H)^{RC}$	$(C\cdots H)^{TS}$	$L^‡$	τ^{RC}	τ^{TS}	$\Delta\tau^‡$	$\Delta E^‡$	$\nu^‡$
Reaction A												
HF/6-31G	4.589	4.180	1.533	2.090	1.074	1.064	73	1.15	0.92	−0.23	83	532*i*
HF/6-31G*	4.556	4.150	1.517	2.075	1.075	1.065	74	1.11	0.94	−0.17	98	580*i*
B3LYP/6-31G	4.496	4.113	1.550	2.057	1.086	1.079	65	1.11	0.97	−0.14	51	429*i*
B3LYP/6-31G*	4.467	4.074	1.532	2.037	1.087	1.078	66	1.12	0.98	−0.14	63	475*i*
Reaction B												
HF/6-31G	4.692	4.063	1.515	2.032	1.076	1.066	68	1.16	1	−0.16	113	647*i*
HF/6-31G*	4.685	4.050	1.501	2.025	1.077	1.066	70	1.10	1	−0.10	130	687*i*
B3LYP/6-31G	4.603	4.061	1.534	2.031	1.088	1.081	65	1.11	1	−0.11	66	459*i*
B3LYP/6-31G*	4.580	4.045	1.518	2.022	1.089	1.081	66	1.11	1	−0.11	76	487*i*
Reaction C												
HF/6-31G	3.833	3.722	1.471	1.861	1.050	1.047	53	1.45	1.29	−0.16	77	788*i*
HF/6-31G*	3.804	3.671	1.453	1.836	1.052	1.047	53	1.39	1.28	−0.11	89	869*i*
B3LYP/6-31G	3.863	3.745	1.491	1.875	1.068	1.065	52	1.36	1.24	−0.12	47	583*i*
B3LYP/6-31G*	3.833	3.704	1.473	1.852	1.068	1.065	52	1.37	1.26	−0.11	54	637*i*
Reaction D												
HF/6-31G	3.817	3.717	1.465	1.858	1.053	1.047	54	1.46	1.29	−0.17	62	813*i*
HF/6-31G*	3.796	3.670	1.453	1.833	1.056	1.052	52	1.39	1.29	−0.10	88	872*i*
B3LYP/6-31G	3.835	3.724	1.450	1.866	1.069	1.066	57	1.42	1.25	−0.17	45	576*i*
B3LYP/6-31G*	3.812	3.699	1.474	1.847	1.071	1.067	51	1.38	1.27	−0.11	51	613*i*

$$L^‡ = \%CX^‡ + \%CY^‡ \tag{4}$$

$$\%CX^‡ = 100(d^{TS}{}_{CX} - d^{RC}{}_{CX})/d^{RC}{}_{CX}$$

$$\%CY^‡ = 100(d^{TS}{}_{CY} - d^{RC}{}_{CY})/d^{RC}{}_{CY}$$

For identity reactions the expression simplifies to eq 5.

$$L^‡ = 200(\mathrm{d}^{TS}{}_{CX} - d^{RC}{}_{CX})/d^{RC}{}_{CX} \tag{5}$$

The definition of L‡ has itself come under criticism. Poirier, Wang, and Westaway concluded[22] that it was not a good measure and suggested that the sum ($CX^‡ + CY^‡$) would be better. Glad and Jensen, however, pointed out[23] that this quantity fails to distinguish between different nucleophiles and nucleofuges and that it would be better to take the size of the entering and leaving groups into account when discussing TS looseness. These authors argued instead that, for identity reactions, the simple bond length elongation ($d^{TS}{}_{CX} - d^{RC}{}_{CX}$) was best or equivalently the Pauling bond order, as indeed we have previously used ourselves in this context.[24] Furthermore, Glad and Jensen presented MP2/6-31++G(d,p) results for identity reactions with anionic nucleophiles X^- ($X = Y = F$, Cl, Br), which indicated that the α-D KIE became *less* inverse as the TS became looser.

Another limitation of L‡ as a measure of TS looseness is that it disregards any interaction between the nucleophile and the electrophile in the RC. While this is not a problem for genuinely bimolecular processes, for which the activation parameters are evaluated with respect to isolated reactants, it may obscure significant features of reactions occurring within encounter complexes, cages, and active sites of catalysts. Albery and Kreevoy defined[25] a tightness parameter τ as the sum of the Pauling bond orders n involving the bonds to the entering group X and leaving group Y (eqs 6 and 7).

$$\tau = n_{CX} + n_{CY} \tag{6}$$

$$n_{CX} = \exp[(d^1{}_{CX} - d^n{}_{CX})/c] \tag{7}$$

In this study we choose to define $d^1{}_{CX} = d^1{}_{CY}$ as the C−N bond length in the tetramethylammonium cation, the isolated electrophile in reaction B, and $d^{0.5}{}_{CX}$ as the bond length $(C\cdots N_{lg})^{TS} = (C\cdots N_{nuc})^{TS}$ for B; accordingly, for each level of calculation $\tau^{TS} = 1$ by definition for B. The value of the coefficient c determined in this way for each theoretical method employed is shown in Table 1. Since barrier heights and KIEs reflect differences between the reactant state and the transition state, we may evaluate tightness parameters τ^{RC} and τ^{TS} and their difference $\Delta\tau^‡$ in order to determine whether they are related to the classical barrier heights ($\Delta E^‡ = E^{TS} - E^{RC}$).

Computational Test 1: Variation of Entering and Leaving Groups. Comparison of reactions A and B (Scheme 1) allows us to assess the influence of alkylation upon the nucleophile and nucleofuge. Reaction B is an acyclic analogue of reactions C and D (see later), in each of which the entering and leaving groups are tertiary amines. Reaction A was the subject of our earlier theoretical study of compression effects[4] and is considered now in order to establish how a tertiary amine nucleophile/nucleofuge pairing compares with ammonia. Selected interatomic distances for these structures are collected in Table 2, along with tightness and looseness parameters, barrier heights, and imaginary transition frequencies $\nu^‡$ for the TS's. Table 3 contains 2° α-D KIEs calculated at 298 K for isotopic substitution of all three hydrogen atoms of the transferring methyl group.

At the HF level it may be seen (Tables 2 and 3) that alkylation of the nucleophile and nucleofuge gives a more inverse α-D KIE and a higher barrier height $\Delta E^‡$ for a *tighter* TS (smaller L‡), contrary to the BKSWW dictum. Comparison of the B3LYP results for B with those for A also shows an increased barrier but with a *less* inverse α-D KIE and with no change in L‡, again contrary to the suggestion of Wolfe and co-workers.

The higher barrier for B as compared with A may be understood in the following way. Trimethylamine has a greater proton affinity than ammonia. The three methyl groups stabilize the positive charge of the protonated base, and may be expected

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[22] Poirier, R. A.; Wang, Y.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 2526.

[23] Glad, S. S.; Jensen, F. *J. Am. Chem. Soc.* **1997**, *119*, 227.

[24] Barnes, J. A.; Wilkie, J.; Williams, I. H. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1709.

[25] Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1978**, *15*, 87.

Table 3. Analysis of Secondary α-D_3 Kinetic Isotope Effects (298 K)

	unscaled						scaled		
method	k_{CH3}/k_{CD3}	MMI	EXC	ZPE	ZPE(CH str)	ZPE(rest)	k_{CH3}/k_{CD3}	EXC	ZPE
Reaction A									
HF/6-31G	0.913	0.990	1.114	0.827	0.788	1.050	0.925	1.109	0.842
HF/6-31G*	0.864	0.991	1.111	0.785	0.776	1.011	0.881	1.106	0.804
B3LYP/6-31G	0.925	0.990	1.120	0.834	0.860	0.970	0.932	1.119	0.841
B3LYP/6-31G*	0.885	0.991	1.117	0.799	0.844	0.946	0.891	1.116	0.806
Reaction B									
HF/6-31G	0.874	0.999	1.068	0.819	0.801	1.023	0.890	1.067	0.835
HF/6-31G*	0.840	0.999	1.058	0.794	0.788	1.008	0.859	1.058	0.813
B3LYP/6-31G	0.952	0.999	1.089	0.875	0.895	0.978	0.957	1.089	0.880
B3LYP/6-31G*	0.926	0.999	1.080	0.858	0.873	0.983	0.932	1.080	0.864
Reaction C									
HF/6-31G	0.918	1.000	1.020	0.900	0.937	0.960	0.929	1.022	0.909
HF/6-31G*	0.861	1.000	1.020	0.844	0.922	0.916	0.877	1.022	0.858
B3LYP/6-31G	0.866	1.000	1.029	0.842	0.974	0.864	0.870	1.030	0.845
B3LYP/6-31G*	0.906	1.000	1.023	0.886	0.971	0.913	0.909	1.024	0.888
Reaction D									
HF/6-31G	0.960	1.000	1.014	0.947	0.929	1.019	0.966	1.016	0.952
HF/6-31G*	0.870	1.000	1.017	0.856	0.921	0.929	0.885	1.019	0.868
B3LYP/6-31G	0.916	1.000	1.023	0.895	0.987	0.907	0.919	1.024	0.897
B3LYP/6-31G*	0.888	1.000	1.022	0.869	0.972	0.894	0.891	1.022	0.872

to do the same in the tetramethylammonium cation. Thus the reactants and products for B are stabilized by alkylation relative to those for A, and the energy required to reach the TS is greater. The curvature of the reaction barrier as measured by the transition frequency $\nu^\ddagger$ is consistently higher for B than for A.

The inverse α-D KIEs each arise as the product of a larger inverse ZPE factor and a smaller normal EXC factor (unscaled data, Table 3). Vibrational analysis permits identification of the three stretching modes for the C−H (C−D) bonds of the transferring methyl group in both RC and TS and allows the contribution to the total ZPE factor from changes in their frequencies to be evaluated; this is denoted as ZPE(CH). Owing to strong vibrational coupling between it and the amine moieties, it is not possible to make unambiguous assignments for the bending modes of the transferring methyl group. Instead this contribution is simply included, along with the minor contributions from all other stretching, bending, and torsional modes, as ZPE(rest). This analysis (Table 3) clearly shows that the inverse values of the α-D KIEs for A and B are dominated by the ZPE(CH) factor.

Glad and Jensen also confirmed[23] the observation, apparently first noted in our original paper,[4] that the (inverse) absolute value of the α-D KIE for methyl transfer is due to changes in CH (CD) stretching frequencies but that the variation with TS looseness is determined by bending modes involving these bonds. We had previously demonstrated that α-alkylation leads to increasingly looser S_N2 TS's with α-D KIEs becoming less inverse and then more normal, as the variable contribution from the bending modes counterbalanced a small, nearly constant, inverse contribution from CH stretching.[26] However, the present result is for alkylation not of the transferring group but of the entering and leaving groups.

The RC's for A and B have similar values of the tightness parameter $\tau^{RC} \approx 1.1$, which reflect the small but significant degree of interaction between the nucleophile and electrophile (Table 2). The TS's are all looser than the RC's; τ^{TS} has slightly smaller values for A than for B, with the consequence that $\Delta\tau^\ddagger$ is more negative for A. There is no obvious relation between $\Delta E^\ddagger$ and either τ^{TS} or $\Delta\tau^\ddagger$.

Computational Test 2: Influence of Compression. Comparison between the data presented in Tables 2 and 3 for reactions B and C or D serves to evaluate the effect of the mechanical constraint provided by a [1.1.1]cryptand or 1,7-diazabicyclo[5.5.5]heptadecane cage structure. Although to our knowledge the "inside" quaternary cations of C and D have not yet been synthesized, this goal may yet be achievable. In contrast, our previous study of compression effects employed[4] a hypothetical (but functional) catalyst constituted from helium atoms and appropriately aligned dipoles; although this system hinted at features of a real cryptand, its credibility suffered from the impossibility of its synthesis. Furthermore, although this bizarre supramolecular device exerted a longitudinal compression by virtue of a fixed separation between rare-gas atoms located on the N−C−N axis, it was incapable of exerting any transverse force to prevent the reacting system from undergoing an off-axis deformation. Consequentially the computed Hessians possessed small negative eigenvalues corresponding to such displacements.

In C and D the methyl transfer occurs between the bridgehead nitrogens: the entering and leaving groups are both tertiary amines, just as for B. The most noticeable structural difference in the RC's is that the interbridgehead N···N distance is very significantly smaller for both C and D as compared with the intracomplex N···N distance in B, at all computational levels. Moreover, the N···N distance is further diminished in each TS. So which is tighter, therefore, RC or TS? The looseness parameter $L^\ddagger$ tells us only that the TS for C is tighter than that for B, but says nothing about RC. The tightness parameter $\tau^{TS} \approx 1.3$ for C is indeed considerably larger than for B, but it is very interesting to note that $\tau^{RC} \approx 1.4$ is even larger. This observation is entirely reasonable from the point of view of the compression hypothesis, described above, a key point of which is that the reactant state suffers a greater energetic penalty from compression than does the transition state. Progress from RC to TS involves a decrease in the tightness and is accompanied by a decrease in strain.

A different aspect of tightness and looseness concerns torsion of the transferring methyl group about the N−C−N axis and lateral deformation away from this axis. In these respects the cage structures of C and D ensure that both RC and TS are

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(26) Barnes, J. A.; Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1993**, 1286.

considerably tighter than for A or B. For example, the transferring methyl torsional frequencies are about 200 cm^{-1} for B but about 800 cm^{-1} for C, in each case being only slightly lower in TS than in RC.

The energy barriers are similar for C and D and are markedly lower than for B according to both HF and B3LYP methods. Compression along the N−C−N axis does indeed reduce the barrier to methyl transfer. Furthermore, the α-D KIEs evaluated with the B3LYP method for C and D are significantly more inverse than for B, in accord with the compression hypothesis. In contrast, the BKSWW dictum would suggest that a reaction with a more inverse KIE should have a looser TS and a higher barrier. Clearly our density functional theoretical results differ from this pattern of behavior. However, to our surprise, the HF method predicts α-D KIEs less inverse for C and D than for B. This is hardly of vindication of the BKSWW dictum since, as already noted, the TS's for C and D are both tighter than for B but involve lower barriers. However, this unexpected method dependence does suggest that any interpretation of these isotope effects should be made with caution.

Why are the B3LYP KIEs for C and D more inverse than for reaction B? The ZPE factor may be further factorized into the contributions from CH stretching modes and from everything else (the "rest"). Consistently, the ZPE(CH) factor is *less* inverse, but the ZPE(rest) factor is *more* inverse, for both C and D than for B, with both HF and B3LYP. The overall ZPE and KIE depends on the balance between these component factors. With the B3LYP method, the change in ZPE(rest) outweighs the change in ZPE(CH), but with the HF method it is the other way around. The important result from all the methods used here is that compression makes the ZPE(CH) factor less inverse but the ZPE(rest) factor more inverse.

Scaling of Force Constants and Frequencies. The isotope effect calculations of Wolfe and co-workers[6,9] and of Poirier et al.[22] employed uniform scaling of calculated harmonic frequencies by a factor of 0.9, equivalent to scaling the force constants by the square of this factor. Similarly our earlier theoretical study of compression effects[4] used a single scaling factor of 0.82 for all force constants computed at the HF/4-31G level. The purpose of scaling is to reduce the error due to overestimation of calculated vibrational frequencies. Scott and Radom[27] have recommended a set of scale factors for uniform scaling of frequencies computed by a range of 19 levels of theory (including HF/6-31G* and B3LYP/6-31G*) that have slightly different values for different properties: fundamental vibrational frequencies, low-frequency vibrations, zero-point vibrational energies, and thermal contributions to enthalpy and entropy. In our experience[28] the value of a scale factor depends on the nature of the molecules for which it is determined. Although Scott and Radom employed sets of up to 122 molecules in their study, these comprised neutral species for which observed fundamentals were available. All of the species involved in the present reactions A−D are cationic, and it is known that stretching frequencies for CH bonds differ significantly upon the charge, for example, in the series CH_3^+, $CH_3^\bullet$, and CH_3^-. To investigate the influence of scaling on KIEs in the present work, we therefore preferred to determine the scale factors for molecular species related to the reactions under consideration.

It seemed appropriate to use the rather complete Raman and infrared spectra of the tetramethylammonium cation in aqueous solution obtained by Berg.[29] Counting degeneracies, but excluding the inactive F_1 modes of this tetrahedral species, there are 33 vibrational modes. In view of the important role of CH stretching modes in determining the value of α-D_3 KIEs, we chose to consider this group of modes separately from the rest of the stretching, bending, and torsional modes. Frequency scale factors were determined by dividing the sum of observed frequencies by the sum of calculated harmonic frequencies for each of the theoretical methods employed in this study; the scale factors *s*(CH) and *s*(rest) for valence force constants (Table 1) are simply the squares of these fractions. Both the HF/6-31G and HF/6-31G* methods yield similar values for *s*(CH) and *s*(rest) of about 0.82, approximately the same as the values recommended by Scott and Radom, and implying that all vibrational frequencies are overestimated to about the same extent at this level of theory. However, the B3LYP method with either basis gives scale factors closer to unity but significantly different for CH stretching and for the rest of the modes: *s*(rest) $\approx$ 0.97 is very similar to Scott and Radom's value for B3LYP/6-31G* zero-point vibrational energies, but *s*(CH) = 0.90 implies that the B3LYP error in the frequencies for these modes in $(CH_3)_4N^+$ is greater than for the rest.

Inspection of the α-D_3 KIE values (Table 3) obtained by using the scaled force constants reveals that each is slightly less inverse than that from the unscaled force constants, as expected. The HF results are brought closer to the B3LYP values, and the change is mainly in the ZPE factor. In view of the role of CH stretching frequencies in determining inverse α-D KIEs in methyl transfer, it was thought that scaling these frequencies might significantly alter the values of the isotope effects. However, there is no qualitative difference between the scaled and unscaled KIEs and, in particular, the HF results for C and D remain less inverse than for B.

Force Constant Analysis. The origin of any KIE is often ascribed to a change in curvature of the potential energy surface as between the reactants and the TS. At first it might appear that the ideal set of coordinates for analysis of these curvature changes would be the normal coordinates, since the curvatures would be simply the vibrational eigenvalues. However, as a consequence of mass weighting and of mechanical coupling between vibrational modes, it is often impossible to make unambiguous correlations between the RC and the TS. For example, the vibrational modes of the transferring methyl group in the RC for B are inseparably coupled with those for the other (essentially equivalent) methyl groups, even though they may be assigned for the TS. The curvature of the surface at a stationary point is therefore often expressed by the values of valence force constants, since these refer to the stiffness of bonds and the resistance to bending of angles between bonds, and provide an appealing basis for chemical discussion. However, as we have pointed out before,[13,30] valence force constants as conventionally used are often without physical meaning. This is the case whenever there is redundancy among the valence coordinates as, for example, when all six angles about carbon are considered to reflect the symmetry of a methyl group. A conventional "rigid" valence force constant is the value of the force engendered in that coordinate by a unit displacement, while all other coordinates remain unchanged. Since this is physically impossible to achieve whenever the coordinates are not independent of each other, the value of a rigid force constant for a particular valence coordinate depends arbitrarily upon the selection of the other coordinates describing the molecule. A relaxed force constant is the force engendered by a unit displacement of a particular coordinate, while the *force* in every

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[27] Scott, A. P., Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

[28] (a) Williams, I. H. *J. Phys. Org. Chem.* **1990**, *3*, 181. (b) Harris, N. J. *J. Phys. Chem.* **1995**, *99*, 14689.

[29] Berg, R. W. *Spectrochim. Acta* **1978**, *34A*, 655.

[30] Francisco, J. S.; Williams, I. H. *Chem. Phys.* **1985**, *95*, 373.

Table 4. Scaled Rigid and Relaxed Valence Force Constants for Selected Coordinates[a]

	rigid valence force constants						relaxed force constants					
	$C_\alpha-H$ stretch		$H-C_\alpha-N_{lg}$ bend		$H-C_\alpha-H$ bend		$C_\alpha-H$ stretch		$H-C_\alpha-N_{lg}$ bend		$H-C_\alpha-H$ bend	
method	RC	TS	RC	TS	RC	TS	RC	TS	RC	TS	RC	TS
						Reaction A						
HF/6-31G	5.14	5.50	0.63	0.43	0.46	0.26	5.08	5.46	0.83	0.73	0.64	0.59
HF/6-31G*	5.13	5.51	0.63	0.43	0.45	0.26	5.07	5.47	0.81	0.69	0.63	0.58
B3LYP/6-31G	5.16	5.39	0.62	0.48	0.48	0.27	5.09	5.74	0.80	0.97	0.64	0.60
B3LYP/6-31G*	5.14	5.41	0.62	0.49	0.47	0.26	5.09	5.37	0.82	0.87	0.64	0.59
						Reaction B						
HF/6-31G	5.06	5.41	0.65	0.71	0.48	0.71	4.99	5.38	0.85	0.66	0.65	0.47
HF/6-31G*	5.05	5.43	0.65	0.71	0.47	0.70	4.99	5.40	0.86	0.65	0.65	0.47
B3LYP/6-31G	5.08	5.27	0.66	0.74	0.49	0.72	5.00	5.24	0.83	0.78	0.66	0.48
B3LYP/6-31G*	5.06	5.27	0.66	0.73	0.48	0.72	5.00	5.69	0.85	0.74	0.66	0.48
						Reaction C						
HF/6-31G	5.88	5.99	0.91	19.5	0.51	2.22	5.81	5.90	0.91	1.12	0.51	0.50
HF/6-31G*	5.88	6.02	0.91	17.9	0.51	2.01	5.70	5.88	1.05	1.12	0.67	0.50
B3LYP/6-31G	5.64	5.70	0.94	18.8	0.50	2.16	5.49	5.59	1.05	1.34	0.67	0.51
B3LYP/6-31G*	5.64	5.72	0.94	18.1	0.50	2.00	5.50	5.60	1.06	1.25	0.66	0.50
						Reaction D						
HF/6-31G	5.82	5.95	0.83	22.9	0.50	1.15	5.66	5.82	0.98	1.13	0.67	0.48
HF/6-31G*	5.75	5.89	0.84	20.8	0.49	1.19	5.61	5.76	0.99	1.11	0.67	0.48
B3LYP/6-31G	5.66	5.70	0.86	21.6	0.50	1.19	5.52	5.57	0.97	1.39	0.66	0.48
B3LYP/6-31G*	5.60	5.65	0.87	21.6	0.50	1.22	5.46	5.54	0.98	1.31	0.65	0.48

[a] Units are md Å^{-1} for stretching and md Å rad^{-2} for bending force constants.

other coordinate remains zero; it is always unambiguous and physically meaningful.

The C−H bonds of the transferring methyl group are shorter and stiffer in the TS's for C and D as compared with the TS for B (Table 4). However, the increase in the CH stretching force constant from the RC to the TS is actually smaller for C and D than for B. This is the reason the ZPE(CH) factors for C and D are consistently less inverse than for B. It is correct to use either rigid or relaxed force constants for CH stretching, since these coordinates are not involved in any redundancy relation.

On the other hand, the $H-C_\alpha-N_{lg}$ and $H-C_\alpha-H$ angles are not independent, and the rigid force constants for bending of these coordinates are therefore not unambiguously defined. Although the values (Table 4) for these force constants in any of the RC's, or in the TS's for A and B, do not appear to be odd, the value of about 20 md Å rad^{-2} found for the $H-C_\alpha-N_{lg}$ bending force constant in the TS's for C and D might seem extraordinary. In fact none of these force constants, even those with smaller, unexceptional values, are meaningful. This is because it is physically impossible to make a displacement in either a $H-C_\alpha-N_{lg}$ or a $H-C_\alpha-H$ bending coordinate without also affecting at least one other coordinate related to it by a redundancy condition. In view of this fact and in order to allow a comparison to be made between RC and TS force constants, it is essential to employ relaxed valence force constants.

The $H-C_\alpha-N_{lg}$ relaxed bending force constant increases considerably from the RC to the TS for C and D, whereas it decreases for B. This analysis indicates that the more inverse ZPE(rest) contribution to the KIE resulting from compression is caused by changes in bending force constants involving the transferring methyl group.

Recently Wolfe and co-workers distinguished two types of compression.[31] They defined longitudinal effects as compression of the S_N2 TS in the X−C−Y plane and transverse effects as compression perpendicular to this plane. In our view these definitions are confusing, especially since the example of longitudinal compression provided is the classical alkyl halide series ethyl, propyl, isobutyl, and neopentyl, in which the off-axis repulsive interactions cause bending of the X−C−Y group away from linearity. We suggest that a clearer distinction would be to restrict the term longitudinal compression to effects operating along the X−C−Y axis and to expand the term transverse compression to any effect perpendicular to this axis. Thus the compression we have discussed above in relation to C and D would be considered as longitudinal. The question now is whether there is also any transverse compression in these systems. Following Wolfe et al.,[31] this would be evidenced by compression of the C−H bonds in the TS's. We have already noted that these bonds are indeed shorter and stiffer than in the TS for B, and this may well be due to transverse compression from the arms of the cryptand cages. However, since the same bonds are also shorter and stiffer in the RC's for the same reason, transverse compression does not contribute significantly to the KIEs being more inverse in these cases. The 3-fold symmetry (Figure 1c) ensures that any transverse compression is felt equally by all three C−H bonds.

Conclusions

We have performed calculations for the methyl transfer reactions A, B, C, and D using HF and B3LYP methods. Although the use of a larger basis set would have been desirable, the computational resources available to us meant that it was not practical to perform geometry optimizations and force constant evaluations for C or D (45 and 51 atoms, respectively) at any calculational level better than B3LYP/6-31G*. Nonetheless, this method should be considered as reliable for the present purposes.

Neither the HF nor the B3LYP calculated results for the effect of alkylation of the nucleophile and nucleofuge (B vs A) are in accord with the pattern of behavior, summarized herein as the BKSWW dictum. That is, "when an S_N2 TS is altered by variation of the nature of the entering and leaving groups, a decrease in α-D KIE (i.e., more inverse) reflects a looser geometry and is accompanied by an increase in the barrier."[6] It may be pertinent to note two points. First, our model reactions

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(31) Wolfe, S.; Kim, C.-K.; Yang. K.; Weinberg, N.; Shi, Z. *Can. J. Chem.* **1998**, *76*, 102.

are all cationic in nature (neutral nucleophile and positively charged electrophile) whereas those studied by Wolfe and co-workers[6,9] are all anionic (negative nucleophile and neutral electrophile). Second, the variation of the nucleophile and nucleofuge we have considered preserves the identity of the atom directly involved in bond making or breaking, whereas the variations studied by Wolfe and co-workers involved atoms of six different elements.

The inverse α-D KIEs calculated at all levels of theory for the acyclic reactions A and B are dominated by the change in zero-point energy of the CH(CD) stretching modes. This arises from a significant increase in the CH stretching force constant in going from RC to TS.

Incorporation of the methyl transfer within a cryptand or diazabicycloheptadecane cage (C or D) causes an increase in the tightness of the TS as compared with that for B, in which the entering and leaving groups are also tertiary amines. However, the tightness of the RC for either C or D is even greater than for the TS. Thus for these compressed systems, progress from RC to TS is accompanied by a decrease in strain.

The energy barriers for C and D are markedly lower than for B. Compression along the N−C−N axis reduces the barrier to methyl transfer. The inverse α-D KIEs calculated at all levels of theory for C and D are dominated by the zero-point energy changes. Scaling of force constants does not alter this result. The effect of compression (C or D vs B) is to make ZPE(CH) less inverse but ZPE(rest) more inverse. This is because the increase in CH stretching force constant in going from RC to TS is smaller for C and D than for B. On the other hand the relaxed force constant for $H-C_\alpha-N_{lg}$ angle bending increases significantly in going from RC to TS for C and D but decreases for B. With the B3LYP method, the balance between the contributions of the CH stretching modes and the rest is such that compression leads to a more inverse α-D KIE.

Schowen's compression hypothesis[5] should not be discarded prematurely.[6] It may apply to certain specifically designed molecular systems, such as those modeled in the present theoretical study. Whether it applies in any enzyme-catalyzed reactions remains an open question. Work is in progress in our laboratories to investigate this issue by means of computational determination of the α-D KIE for a COMT-catalyzed methyl transfer; KIEs have so far not been computed by the other groups studying this enzyme.[3]

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Supporting Information Available: Tables of total energies and Cartesian coordinates of optimized structures of reactions A−D. This material is available free of charge via the Internet at http://pubs.acs.org.

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