The Contribution of Ion-pairing to 'Memory Effects'*

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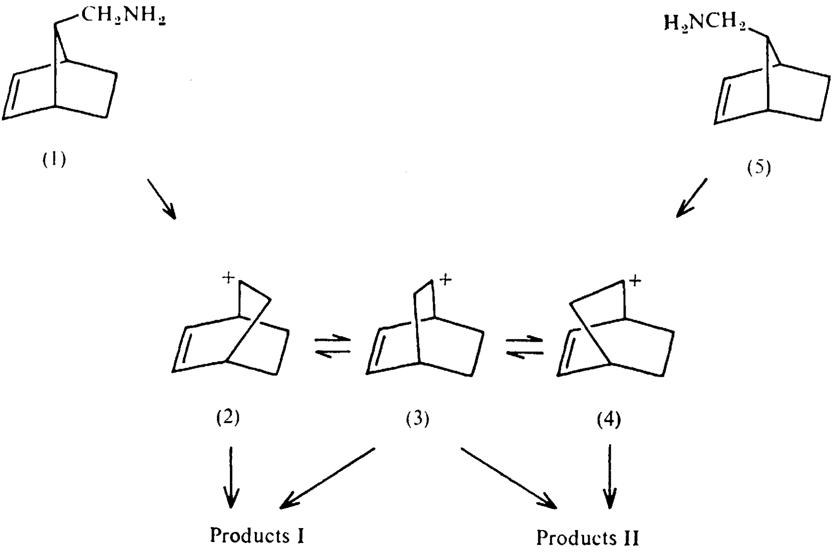
In 1961, Silver[1] reported that the 2-methylbutyl cation formed from different reactants through deamination[2] gave different yields of products, and commented upon this 'transference of unusual behaviour' from reactant to intermediate. Berson and co-workers,[3,4] beginning in 1962, published a series of papers dealing with the same phenomenon for both solvolytic and deamination (amine–nitrous acid) reactions. The phenomenon was relabelled a 'Memory Effect', and its origin was ascribed to 'twisted ions' (2) and (4). Thus reactants (1) and (5), when treated with nitrous acid, were visualized as going to the ions (2) and (4), respectively, which differed from each other only in the direction of the 'twist'. The 'twisted' ions (2) and (4) presumably react with the entering group faster than they go to the normal ion (3), explaining potentially, at least, why the compounds produced in the product mixtures I and II should occur in



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*Dedicated to Prof. Dr. Eugen Müller on the occasion of his 70th birthday.

[1] M. Silver, *J. Amer. Chem. Soc.*, 1961, **83**, 3482.

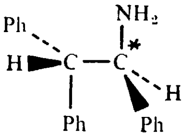
[2] For an excellent review see H. Söll, in Houben-Weyl, 'Methoden der organischen Chemie', ed. E. Müller, George Thieme, Stuttgart, XI/2, 1958, pp. 133—181.

[3] J. A. Berson and P. Reynolds-Warnhoff, *J. Amer. Chem. Soc.*, 1962, **84**, 682; 1964, **86**, 595; J. A. Berson and D. Willner, *ibid.*, 1962, **84**, 575; 1964, **86**, 609.

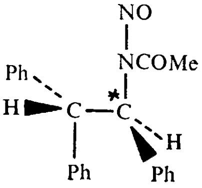
[4] J. A. Berson, *Angew. Chem.*, 1968, **80**, 765.

different proportions. Berson[4] states 'The "twisted" cations therefore are true metastable intermediates occupying minima in the potential energy surface of the reaction'. The possibility that ion-pairing might be responsible for the 'memory effect' was considered by Berson, but was dismissed—particularly for the amine–nitrous acid reaction,[4] since 'The return process in deamination would involve molecular nitrogen . . .'.

We believe, contrary to Berson's explanation, that ion pairs play an important role in 'memory effects', and especially so in the amine–nitrous acid reaction. Huisgen[5] and White[6] demonstrated beyond doubt that ion pairs are present during thermal decompositions of *N*-nitrosoacylamines, and we showed[7,8] in 1960—61 that the thermal decompositions and nitrous acid deaminations are mechanistically related when the two reactions are carried out in acetic acid–sodium acetate solution. In these experiments,[7,8] optically active, labelled isomers both of (6) and of (7) were subjected, respectively, to deamination with



(6)



(7)

nitrous acid or to thermal decomposition (acetic acid–sodium acetate solution). The distributions of ^{14}C (*) in the re-resolved products, as well as the fractions of racemization, indicated[7,8] the similarity in mechanism of the two reactions.[9] The involvement of ion pairs in the thermal decomposition of (7) was established by the experiment with optically active, acetate-labelled reactant (7a), in which 1,2,2-triphenylethyl [^{14}C]acetate (10) of retained configuration was formed predominantly by cation–anion collapse of ion pair (9) whereas the product (11) of inverted configuration was formed principally through reaction of the cation of (9) with unlabelled acetate from the solvent.

That ion pairs (9) should also be involved during the deamination of (6) is understandable, for the nitrosating agent in the solvent employed is undoubtedly acetyl nitrite, leading to the formation of diazonium acetate by the following, or similar, reactions (1)—(5):

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[5] R. Huisgen and Ch. Rüchardt, *Annalen*, 1956, **601**, 21; R. Huisgen and H. Reimlinger, *ibid.*, 1956, **599**, 161, 183.

[6] E. H. White, *J. Amer. Chem. Soc.*, 1955, **77**, 6011, 6014; E. H. White and C. A. Aufdermarsh, *ibid.*, 1958, **80**, 2597. See particularly the discussion by E. H. White and D. J. Woodcock, in 'The Chemistry of the Amino Group,' ed. S. Patai, Interscience, New York, 1968, Chapter 8.

[7] C. J. Collins and J. B. Christie, *J. Amer. Chem. Soc.*, 1960, **82**, 1255; C. J. Collins, J. B. Christie, and V. F. Raaen, *ibid.*, 1961, **83**, 4267.

[8] C. J. Collins, W. A. Bonner, and C. T. Lester, *J. Amer. Chem. Soc.*, 1959, **81**, 466.

[9] C. J. Collins and B. M. Benjamin, *J. Amer. Chem. Soc.*, 1963, **85**, 2519.

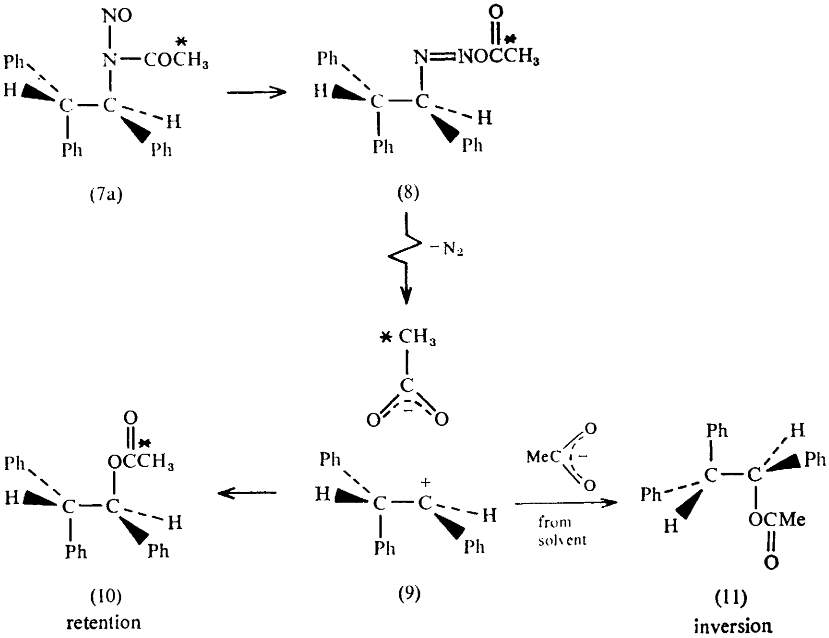
$$2HNO_2 \rightarrow H_2O + N_2O_3 \qquad (1)$$

$$N_2O_3 + MeCO_2H \rightarrow MeCO_2NO + NO_2^- + H^+ \qquad (2)$$

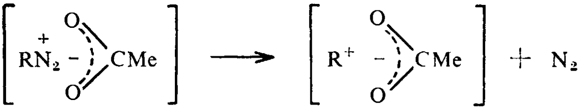
$$RNH_2 + MeCO_2NO \rightarrow [R\overset{+}{N}H_2NO\ MeCO_2^-] \qquad (3)$$

$$[R\overset{+}{N}H_2NO\ MeCO_2^-] \rightarrow [R\overset{+}{N}H{=}NOH\ MeCO_2^-] \qquad (4)$$

$$[R\overset{+}{N}H{=}NOH\ MeCO_2^-] \rightarrow [R\overset{+}{N}_2\ MeCO_2^-] + H_2O \qquad (5)$$



It is, therefore, not the nitrogen, as assumed by Berson,[5] which would be responsible for controlling the stereospecificity of product formation, but rather the counter-ion formed on decomposition of the diazonium acetate, reaction (6):


(6)

The counter-ions [reaction (6)] must be 'oriented' as originally suggested by Huisgen[5] and by White.[10] The question we must now answer is whether these

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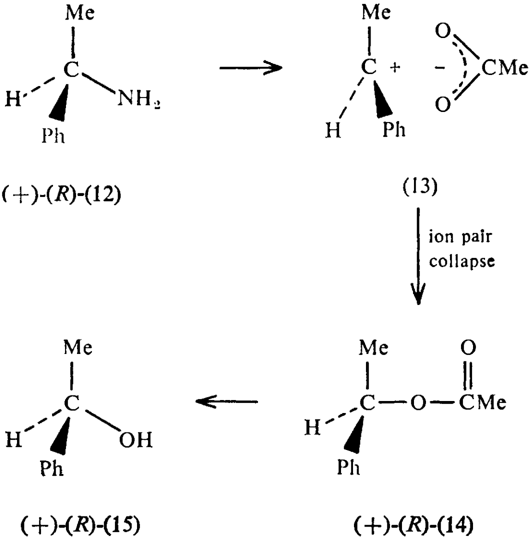
[10] E. H. White, H. P. Tiwari, and M. J. Todd, *J. Amer. Chem. Soc.*, 1968, **90**, 4734.

oriented ion pairs can also be *responsible* for the retention of optical configuration. In the case of reactants (6)[7,9] and (7)[8,9] the steric properties of 1,2,2-triphenylethyl cation appeared dominant, and it was not possible to recognize any contribution by the ion pair to configurational retention, although such a possibility could not be denied.

There are several indications, however, that oriented ion pairs are capable of influencing the steric outcome of a reaction. Ott,[11] for example, noted that treatment of optically active α-phenylethylamine (12) in acetic acid solution with sodium nitrite yielded the carbinol (15) of like sign of rotation (retention[12]),



(+)-(*R*)-(12)

(13)

(+)-(*R*)-(15)

(+)-(*R*)-(14)

whereas when very dilute (0.6% by weight) aqueous acetic acid was used as the solvent, α-phenylethanol of opposite sign of rotation (inversion[12]) was obtained. Partial racemization accompanied both reactions. Ion pairs (13) must be responsible for the retention of configuration observed by Ott.[11]

The data of Lee and Lam[13] for the acetolysis of 1-(Δ^3-cyclopentenyl)[2-^{14}C]-ethyl nosylate (16) (nosylate = *p*-nitrobenzenesulphonate) are also strongly presumptive evidence that the counter-ion can be influential in product control. Thus (16), on acetolysis, is presumed[14] to yield a non-classical ion (17) which can react with acetate anion to produce [5-^{14}C]norbornyl acetate (19) or undergo 6,2-hydride shift to yield the non-classical ion (18). The cation (18) should react

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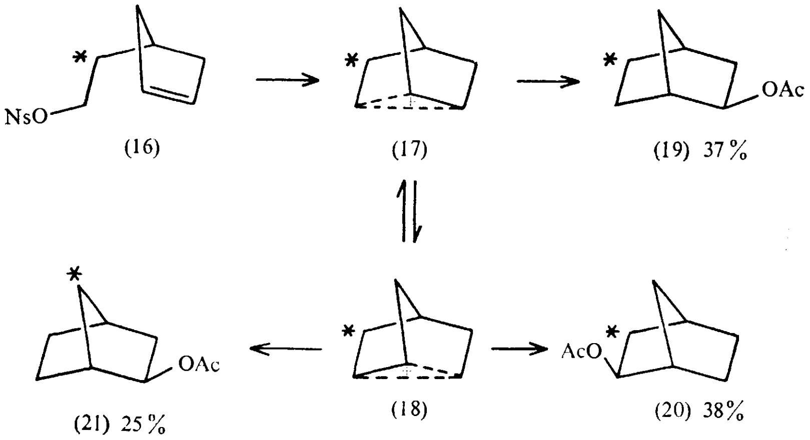
[11] E. Ott, *Annalen*, 1931, **488**, 186.

[12] Beilstein's 'Handbuch der organischen Chemie', Band VI, Drittes Ergänzungswerke (System Nummer 475), pp. 1671—1672.

[13] C. C. Lee and L. K. M. Lam, *J. Amer. Chem. Soc.*, 1966, **88**, 2834.

[14] R. G. Lawton, *J. Amer. Chem. Soc.*, 1961, **83**, 2399; J. D. Roberts, C. C. Lee, and W. H. Saunders, jun., *ibid.*, 1954, **76**, 4501.

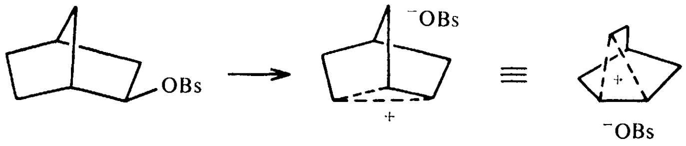
with solvent to yield *equal amounts* of [3-^{14}C]norbornyl (20) and [7-^{14}C]norbornyl (21) acetates. Surprisingly, the results[13] [38 % (20), 25 % (21)] cannot be rationalized with the non-classical ion (18), which should be (except for ^{14}C labelling)



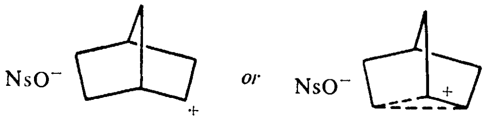
(16) (17) (19) 37 %

(21) 25 % (18) (20) 38 %

a symmetrical intermediate. The observations[13] of Lee and Lam are explainable[15] as follows: the non-classical ion[14] (23) formed directly from norbornyl brosylate (22) (brosylate = *p*-bromobenzenesulphonate) is associated with a counter-ion ($^{-}$OBs) which is oriented symmetrically across the charge-bearing C-1 and C-2 positions.[16] We believe that the counter-ion is responsible for the symmetrical properties usually associated with the norbornyl cation. In the solvolysis of (16), the counter-ion cannot be oriented as in (23), but must approximate the situation shown in (24). Although the ion pair (24) may undergo several Wagner–Meerwein



(22) (23)



(24)

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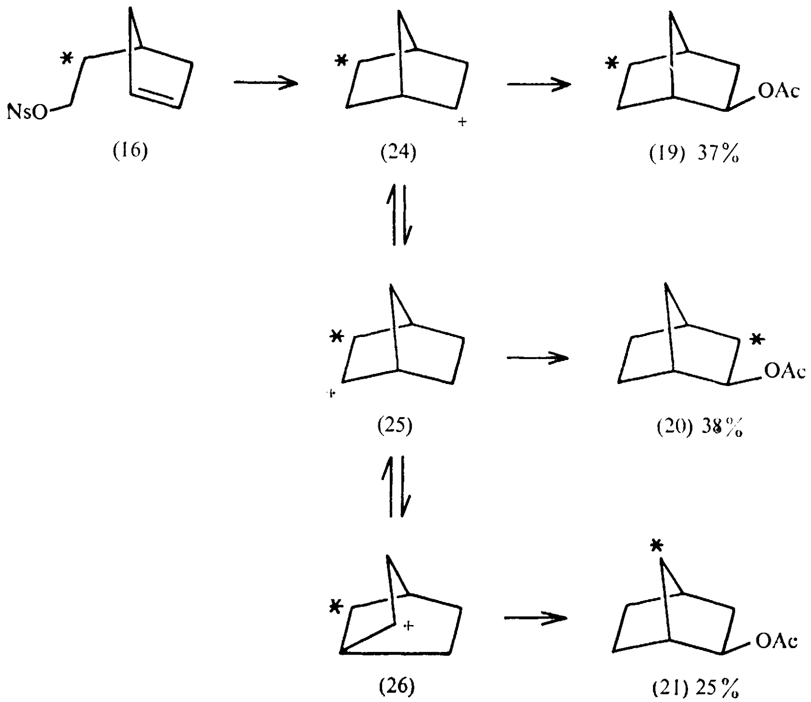
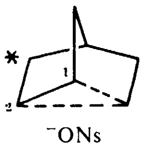
[15] C. J. Collins and M. H. Lietzke, *J. Amer. Chem. Soc.*, 1967, **89**, 6570.

[16] C. J. Collins and C. E. Harding, *Annalen*, 1971, **745**, 124.

or 6,2-hydride shifts, there will never be in any of the subsequent species a substantial contribution of structure (23). One explanation, therefore, for the data of Lee and Lam[13] is that owing to the almost random orientation of the counter-ion, the cations themselves are classical in character. The cation (25) can then react with solvent to yield 2-*exo*-[3-^{14}C]norbornyl acetate (20; 38%) faster than it reaches equilibrium with the cation (26), which itself collapses with

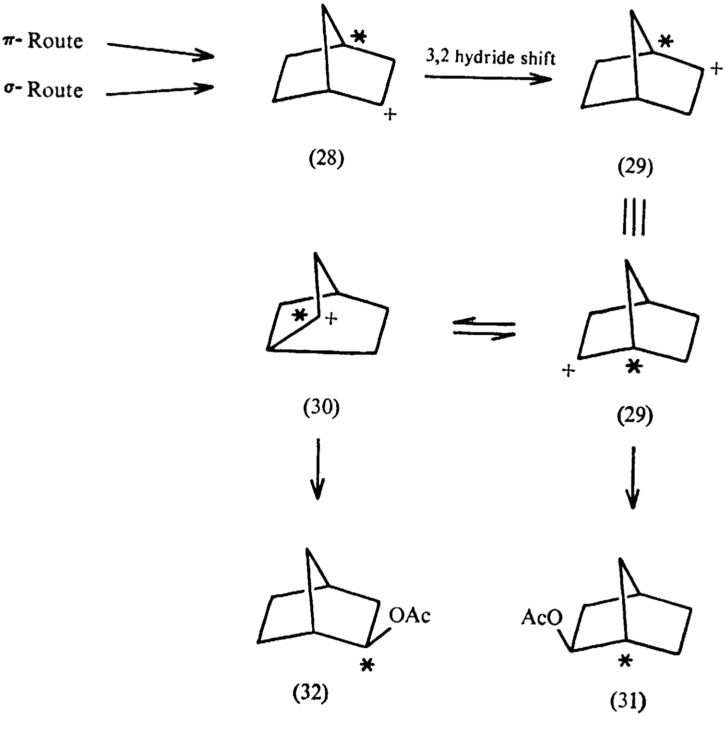


solvent to produce 2-*exo*-[7-^{14}C]norbornyl acetate (21; 25%). An alternative possibility is that the cation of an oriented ion pair such as (27) will not possess an equal charge distribution between C-1 and C-2 and will react with acetate anion at those two positions with different rates to yield more (20) than (21).



(27)

Finally, the results of my co-worker, Dr. C. E. Harding,[16] should be mentioned. The [4-^{14}C]norbornyl cation (28), formed through either the 'sigma' or 'pi' routes[14] underwent 3,2-hydride shift to yield the Wagner–Meerwein cation pair (29) $\rightleftharpoons$ (30). This cation pair did not act like a non-classical norbornyl cation since the two products, (31) and (32), were not formed in equal amounts. Again the possibility must be considered that oriented ion pairs are responsible for these results.



Because of the facts given in the foregoing discussion, we devised a series of experiments to allow us to test further the role of ion pairs in 'memory effects', under conditions which preclude the intervention either of normal conformational effects or of abnormal effects of the type which might lead to 'twisted ions'.

In the first experiment, the reactions with nitrous acid (in acetic acid–sodium acetate) of the two *endo*-amines (33) and (34) were investigated.[17–20] It was established through isotopic labelling[18] for both reactions that the ion (35) was

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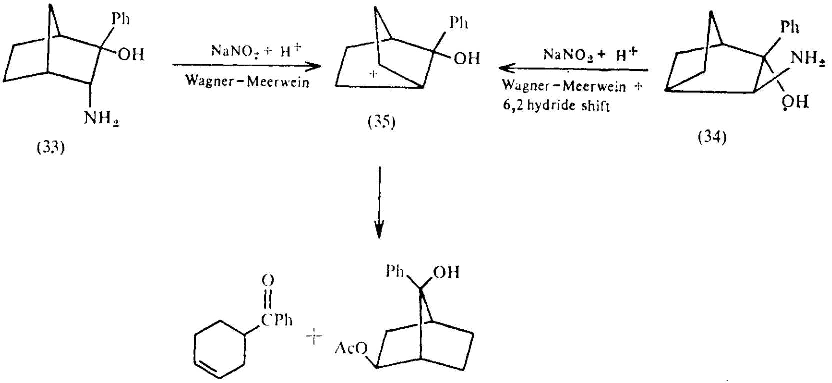
[17] C. J. Collins, V. F. Raaen, and M. D. Eckart, *J. Amer. Chem. Soc.*, 1970, **92**, 1787.

[18] C. J. Collins, B. M. Benjamin, V. F. Raaen, I. T. Glover, and M. D. Eckart, *Annalen*, 1970, **739**, 7.

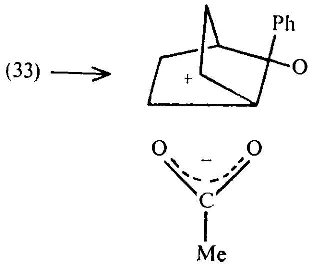
[19] C. J. Collins, *Accounts Chem. Res.*, 1971, **4**, 315.

[20] C. J. Collins, I. T. Glover, M. D. Eckart, V. F. Raaen, B. M. Benjamin, and B. S. Benjaminov, *J. Amer. Chem. Soc.*, 1972, **94**, 899.

the precursor of the two products, Δ^3-cyclohexenyl phenyl ketone (36) and *syn*-7-phenyl-7-hydroxy-2-*exo*-norbornyl acetate (37). Yet from (33), after a single Wagner–Meerwein rearrangement, the cation (35) yields two products in nearly equal amounts, whereas from (34), after Wagner–Meerwein and 6,2-hydride shifts, only one product, (37), was formed. We ascribe these results to ion-pairing, in which the amine (33) yields the ion pair (38) whereas the amine (34) yields the ion pair (39). In these two structures the cations are written as if they were identical, but the anions are in different relative positions. The *exo*-anion in (39) is situated for easy *exo*-collapse to product (37), whereas the acetate anion in (38) is unavailable for *exo*-product formation; here reaction of the cation with acetate anion from the solvent (instead of with the counter-ion) is necessary, and must compete with ring-opening. Thus, from (38), both products (36) and (37) result. This is a true 'memory effect',[4] yet twisted ions are not possible here. We conclude that the oriented ion pairs (38) and (39) are responsible for the results.



(36)	(37)	
18.5	22.1	[Percent yield from (33)]
0	29.2	[Percent yield from (34)]



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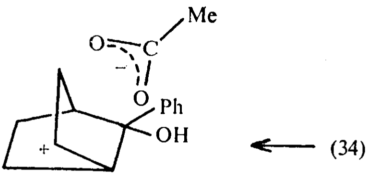
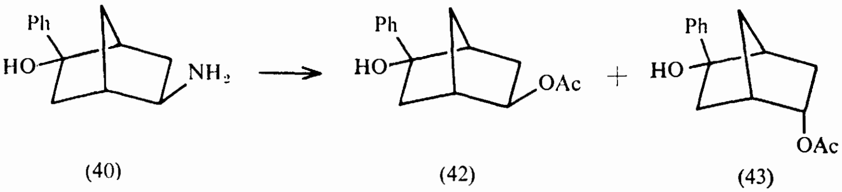
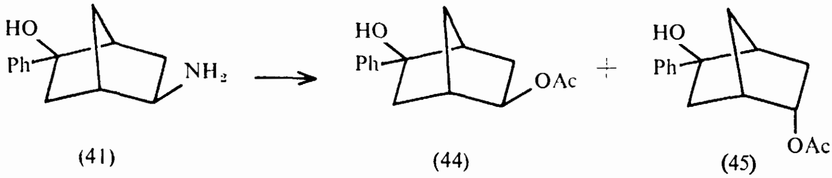


(39)

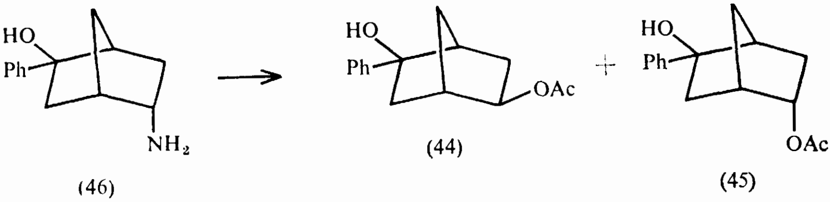


Ratio (42:43) = 18:1



Ratio (44:45) = 18 : 1

The *exo*:*endo* stereospecificities in the deaminations, in acetic acid–sodium acetate solution, of the *exo*-amines (40) and (41) were determined[21–23] to be 18:1 for both reactants. In the deamination, under identical conditions, of the *endo*-amine (46), however, the yield of *endo*-product (45) was greater than that of *exo*-product (44) [ratio of yields (44):(45) = 1:1.2]. These results are clear evidence, we think, that the ion pairs from (40) and (41) must resemble structures (47) and (48), respectively, in which the *exo*-counter-ions dictate collapse from the *exo*-direction. In the case of the *endo*-amine (46), the ion pair must resemble structure (49), and the *endo*-counter-ion here dictates a preponderance of collapse with the cation from the *endo*-direction.



Ratio (44:45) = 1:1.2

A final example of the importance of ion-pairing in controlling product formation will be given. In the Scheme are portrayed portions of the deamination

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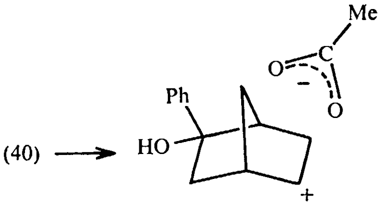
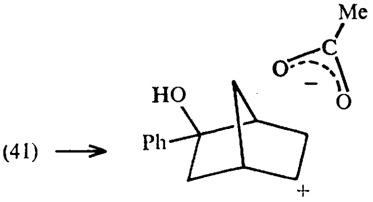
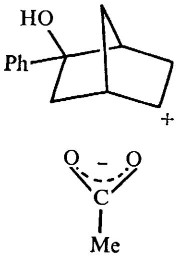
[21] C. J. Collins and B. M. Benjamin, *J. Amer. Chem. Soc.*, 1970, **92**, 3182.
[22] B. M. Benjamin and C. J. Collins, *J. Amer. Chem. Soc.*, 1970, **92**, 3183.
[23] C. J. Collins and B. M. Benjamin, *J. Org. Chem.*, 1972, **37**, 4358.



(47)



(48)



(49)

reactions of the two amines (41) and (46), which differ only in the *exo versus endo* placement of amino-groups. The stereospecificities for *exo- versus endo*-attack of acetate ions on the respective cations formed from the reactants after Wagner–Meerwein rearrangement are also shown. The cation in each of the two ion pairs (47) and (50) is the same: the only difference we have assumed is that the counter-acetate anions are oriented in the same relative positions as were the amino-groups in the two reactants.

As is clear from the experimental results shown in the Scheme, there is only a trace (0.04%) of *endo*-product (43) from the *exo*-amine (41) (*exo*:*endo* product ratio = 640). From the *endo*-amine (46), 1.8% of the *endo*-acetate (43) was isolated, and the ratio of *exo*- to *endo*-products formed [(42):(43)] is 8. The differences in *exo*:*endo* stereospecificities for attack on the two identical cations of the ion pairs (47) and (50) we ascribe to the orientations of the counter-acetate ions as follows: ion pair (47) is well situated for collapse from the *exo*-direction to yield the *exo*-product (42). The *endo*-acetate (43) must be formed by *endo*-attack from solvent, a process which cannot successfully compete with collapse of an intimate ion pair. The *exo*-orientation of acetate anion in (47) imparts a serious bias in favour of *exo*-attack which, when combined with the strong steric factor[24] inhibiting *endo*-attack, results in overwhelming production of the *exo*-product (42). In structure (50), however, ion-pair collapse is severely restricted, and the

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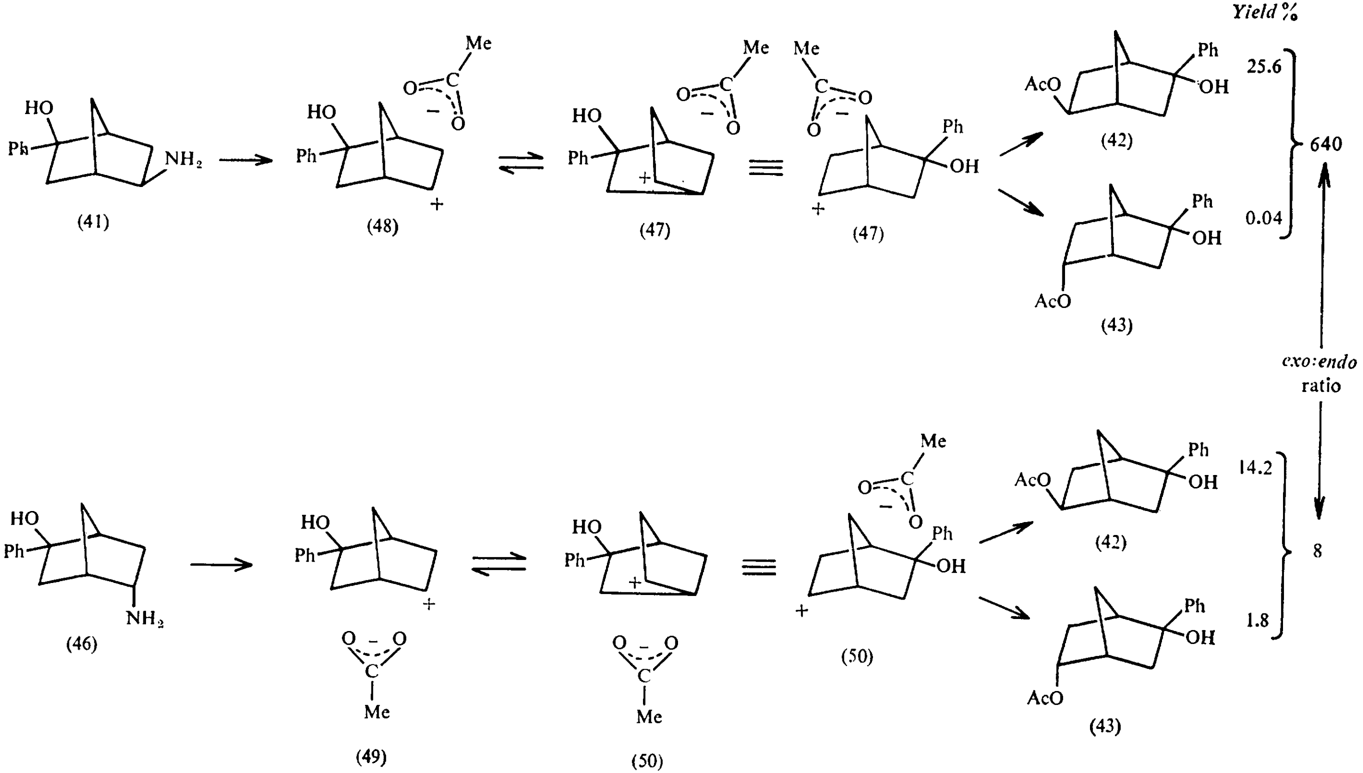
[24] H. C. Brown and K. T. Liu, *J. Amer. Chem. Soc.*, 1970, **92**, 200; *ibid.*, 1971, **93**, 7335; H. C. Brown and J. H. Kawakami, *ibid.*, 1970, **92**, 201, 1990; H. C. Brown, J. H. Kawakami, and S. Igekami, *ibid.*, 1971, **93**, 7335.


Yield %
(41)
(48)
(47)
(47)
(42)
(43)
25.6
0.04
640
exo:endo
ratio
8
14.2
1.8
(46)
(49)
(50)
(50)
(42)
(43)
Me
HO
Ph
NH₂
OH
AcO
+
–

Scheme

cation must react with acetate from the solvent, rather than with the counter-ion. The solvent, however, is free to attack the cation from either direction, subject only to the steric[24] hindrance to approach from the *endo*-direction. There is no serious external bias in favour of *exo*-product, so the cation reacts with its normal[24] 8:1 steric preference.

In conclusion, the evidence for ion-pairing during the amine–nitrous acid reaction of aliphatic amines has been partially reviewed, and the experimental evidence, primarily from our own research at Oak Ridge National Laboratory, that these ion pairs are responsible for stereochemical control or 'memory effects' has been presented.We believe that the weight of evidence is against 'twisted' ions and strongly in favour of counter-ion control as the cause of these 'memory effects' during aliphatic deaminations.