

The Convulsant and Anesthetic Properties of *Cis-Trans* Isomers of 1,2-Dichlorohexafluorocyclobutane and 1,2-Dichloroethylene

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The differences in potencies of optical isomers of anesthetics support the hypothesis that anesthetics act by specific receptor interactions. Diastereoisomerism and geometrical isomerism offer further tests of this hypothesis but have not been explored. They are the subject of this report. We quantified the nonimmobilizing and convulsant properties of the *cis* and *trans* diastereomers of the nonimmobilizer 2N (1,2-dichlorohexafluorocyclobutane). Although the lipophilicity of the diastereomers predicts complete anesthesia at the partial pressures applied, neither diastereomer had anesthetic activity alone, and the *cis* form may have a small (10%) capacity to antagonize anesthesia, as defined by additive effects on the MAC (the minimum alveolar concentration required to suppress movement to a noxious stimulus in 50% of rats) of desflurane. Both diastereomers produced convulsions, the *cis* form being nearly twice as potent as the *trans* form: convulsant

50% effective dose (mean \pm SD) was 0.039 ± 0.009 atmospheres (atm) for the purified *cis* and 0.064 ± 0.009 atm for the purified *trans* isomer. The MAC value for *cis*-1,2-dichloroethylene equaled 0.0071 ± 0.0006 atm, and MAC for *trans*-1,2-dichloroethylene equaled 0.0183 ± 0.0031 atm. In qualitative accord with the Meyer-Overton hypothesis, the greater *cis* potency was associated with a greater lipophilicity. However, the product of MAC \times solubility differed between the *cis* and *trans* isomers by 40%–50%. We conclude that neither the *cis* nor *trans* isomers of 2N have anesthetic properties, but isomerism does influence 2N's convulsant properties and the anesthetic properties of dichloroethylene. These isomeric effects may be as useful in defining receptor-anesthetic interactions as those found with optical isomers.

(Anesth Analg 2001;93:922–7)

Chiral dependence of isoflurane's actions has been demonstrated *in vitro* (1). *In vivo* and *in vitro* tests for chiral dependency suggest that isomers can differ in anesthetic potency (2,3) but that the difference may not be large (4). Potency may be defined by MAC, the minimum alveolar concentration required to produce immobility in response to a noxious stimulus in 50% of subjects. Chiral dependency may be important because it suggests that anesthetics act by sterically influencing specific receptors.

Supported in part by National Institutes of Health Grant 1P01GM47818 and by the Medical Research Council. Dr. Eger is a paid consultant to Baxter Healthcare Corp.; Baxter Healthcare Corp. donated the desflurane used in these studies but otherwise did not contribute to their conduct.

Accepted for publication May 15, 2001.

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Nonanesthetic compounds (5), subsequently termed "nonimmobilizers" (6) and "transitional compounds," provide alternative tools for elucidation of structural dependencies. Transitional compounds have MAC values far greater than might be predicted from their lipophilicities and the Meyer-Overton hypothesis (7,8), and nonimmobilizers do not produce immobility in response to a noxious stimulus despite a lipophilicity that would suggest they should have anesthetic effects. Such compounds have found application in the study of anesthetic mechanisms, as illustrated by their use in demonstrating that different mechanisms underlie the capacities of anesthetics to produce immobility (MAC) and amnesia (6).

Like other nonimmobilizers, 2N [1,2-dichlorohexafluorocyclobutane; c(CClFCClFCF₂CF₂)] has convulsive properties (5). Unlike most anesthetics and nonimmobilizers, 2N has two stereoisomers: the *cis* isomer is *meso* because of its plane of symmetry (it has symmetrical chiral centers with

superimposable mirror images), and it has no optical activity; the *trans* isomer is a racemic mixture of the (+) and (−) enantiomers (Fig. 1). This investigation probed whether the convulsant and nonimmobilizing effects of 2N could be separated from an anesthetic effect and whether the diastereomers of 2N differed in either convulsant or nonimmobilizing properties. Other studies (9,10) gave reason to believe that these types of stereoisomers might differ in their anesthetic potential, convulsive properties, or both of these.

We also determined the effect of *cis-trans* isomerism in a compound (1,2-dichloroethylene) known to have anesthetic properties (11). For both 1,2-dichloroethylene and 2N, we investigated the correlation of convulsant and anesthetic properties with lipophilicity.

Methods

With approval from the University of California–San Francisco Committee on Animal Research, we studied adult specific-pathogen-free Sprague-Dawley male rats (300–500 g; Charles River Laboratories). Before study, each animal was caged individually in a room with 12-h light/dark cycles and had continuous access to standard rat chow and tap water.

Commercially available 2N from PCR Incorporated (Gainesville, FL) was a mixture of 54% *cis* and 46% *trans* isomers. TH's laboratory provided enriched samples of the diastereomers. Purification of the *cis* isomer was achieved by repeated distillation of the commercial mixture by using a 36-in. spinning-band column (model 36T; BR Instruments, Easton, MD). The final *cis/trans* ratio of the 1,2-isomers was 93.6:6.4 for one batch and 91:9 for a second batch. ^{19}F nuclear magnetic resonance spectroscopy and gas chromatography of the final sample revealed that the purified mixtures contained 3.2% of the 1,3-isomers but otherwise were at least 99.8% pure.

Enrichment of the *trans* isomer could not be accomplished by distillation, and we turned to chemical synthesis. Hexafluorocyclobutene was chlorinated at room temperature in a sealed tube, with excess chlorine removed by distillation. After washing with aqueous NaHSO_3 and drying over MgSO_4 , distillation produced a colorless liquid in 79% yield with a *cis/trans* 1,2-isomeric ratio of 7.8:92.2. There was no significant contamination with 1,3-isomers, and the overall purity exceeded 99.8%. These purified or synthesized isomers, or mixtures of the isomers (to obtain intervening proportions), were applied in this study. *Cis* (97% pure) and *trans* (98% pure) geometric isomers of 1,2-dichloroethylene were obtained from Aldrich (Milwaukee, WI).

Each rat was placed in an individual plastic cylinder that had a rubber stopper with two holes at the "tail" end of the chamber. The tail and a rectal temperature probe passed through these holes, and the tail was

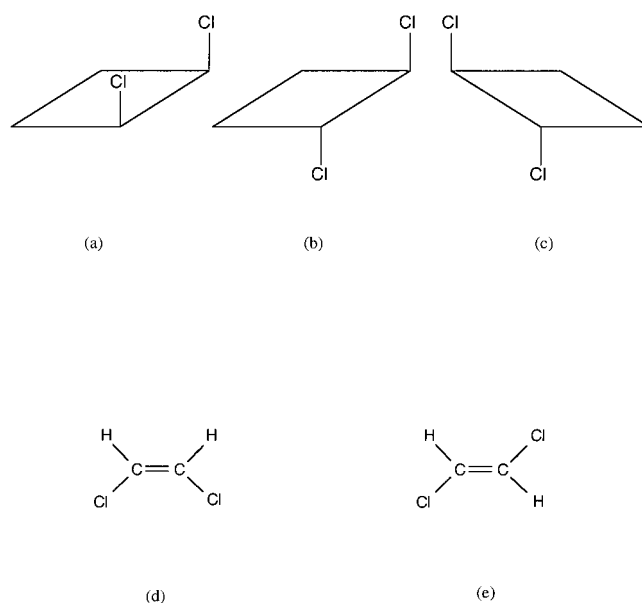


Figure 1. (a) and (b) are the structural formulae of the diastereomers, *cis*- and *trans*-1,2-dichlorohexafluorocyclobutane (2N). The *trans* isomer could potentially be further separated into its two mirror image enantiomers, (b) and (c). The mixtures used in the study were the *cis* and racemic *trans* isomers, but because the enantiomers (b) and (c) were not separated, the distinctions between the different types of *trans* isomers have not been discussed. The two isomers of 1,2-dichloroethylene—(d) and (e)—are geometric *cis-trans* isomers. They do not have mirror images that are enantiomers.

secured with tape to a plastic extension of the cylinder. Three pairs of subcutaneous stimulating platinum needle electrodes were placed under the skin of the tail (approximately 2 cm apart beginning 3 cm from the base of the tail), and the electrodes were taped to the tail and the cylinder extension. The rat was free to move, but the secured tail prevented it from exiting through the "head" end of the cylinder.

Pairs of rats prepared in this manner were placed into a 3.4-L pressure chamber. The pressure chamber was a clear plastic cylinder (permitting full visualization of each rat) with metal ends that contained O-rings and clamps to provide a seal that precluded loss of gas. Electrical connections through the metal ends allowed for tail stimulation, permitted monitoring of rectal temperatures, and provided a power source for a circulation fan that mixed gases through a CO_2 absorber located in the middle of the chamber. Throughout the study, rectal temperatures were maintained from 36.5°C to 39.5°C by application of ice bags or heat from a lamp to the outside of the pressure chamber. The metal ends of the chamber also had ports to allow the introduction of gaseous or liquid agents, the sampling of chamber gases, and the measurement of chamber pressure. The port used for injection of agents always differed from that used for sampling. The chamber was flushed with oxygen for

10 min (chamber concentration exceeded 98% oxygen) before introduction of test compounds.

Animals exposed to the isomers of 2N and 1,2-dichloroethylene were observed for excitatory behavior (increased movement, tremors, and myoclonia) and for convulsions (a sustained tonic-clonic extension of the limbs for 5–10 s, often followed by a period of central nervous system depression). Observations at a given concentration of test compound were made for at least 20 min. The average of the largest and smallest concentrations at which convulsions were and were not observed was taken as the value for the convulsion threshold for an individual animal.

All compounds were tested for their anesthetic effects as defined by MAC (in this case, the minimum alveolar concentration of anesthetic required to produce an absence of motor response to electrical stimulation of the tail in 50% of test rats) (12). 2N isomers were also tested for any partial anesthetic effect by "additivity" studies (i.e., we determined whether they decreased the MAC for desflurane). Control MAC values for desflurane were determined approximately 1 wk before additivity studies. MAC values for desflurane were then redetermined in the presence of 2N: desflurane was initially added to the chamber at approximately 60% of the MAC value, and after a 20- to 30-min equilibration, 2N was introduced to produce a partial pressure of approximately 0.05 atmospheres (atm). The anesthetic end point was the presence versus absence of purposeful movement of the rat in response to an electrical stimulus (15 V, 50 Hz, biphasic, 6.5 ms per pulse) applied for up to 1 min to the tail. Stimulation was first applied to the most distal pair of electrodes. If the animal responded (as all did to the initial desflurane/2N mixtures), the desflurane partial pressure was increased approximately 20%. More 2N was added to keep its partial pressure nearly constant during MAC determinations. Each rat was retested after a 20-min equilibration period. After a negative response and a 60-s minimum rest interval, we applied the electrical stimulus via the next more proximal pair of electrodes (to exclude a false-negative response caused by tissue damage or displacement of the distal electrodes). This approach produces results indistinguishable from those obtained by using the tail clamp as the noxious stimulus (12).

After each electrical stimulation, a chamber gas sample was obtained for analysis of oxygen (Beckman E-2 paramagnetic meter; Fullerton, CA), which was controlled at 0.8–1.0 atm, and for analysis of CO₂ (infrared analysis), which was maintained at <0.005 atm. Desflurane and the concomitantly administered 2N were separated and quantified by gas chromatography.

The anesthetic effect of 2N in the additivity studies was estimated for each rat by taking the ratio of the desflurane MAC in the presence and absence of 2N

[abbreviated, respectively, as MAC(des + 2N) and MACdes]. A value of MAC(des + 2N)/MACdes = 1 indicated an absence of an anesthetic effect of the 2N isomer. A paired *t*-test was used to examine whether MACdes differed significantly ($P < 0.05$) from MAC(des + 2N). Values are given as means \pm SD. With rare exceptions, the animals survived the MAC tests with or without 2N and appeared healthy 24 h after the test.

The anesthetic potencies of the isomers of 1,2-dichloroethylene were determined (eight animals in each group, tested in batches of four). Animals were prepared in cylinders as described previously and inserted into larger chambers connected to a rebreathing circuit. These studies were conducted at ambient pressure. After flushing the circuit with high flows of oxygen to achieve oxygen concentrations exceeding 95%, the system was closed and the isomer injected in amounts estimated to achieve inspired concentrations of approximately 60% of predicted MAC. After 20 min equilibration, the animals were tested as described previously, and a gas sample was taken for analysis. All rats moved when tested the first time; additional compound was then injected to achieve a 20%–30% increase in the concentration, followed by equilibration and retesting. The process was repeated until all the rats were immobile in response to the stimulus.

Because the saline/gas and oil/gas partition coefficients of the 1,2-dichloroethylene were appreciable and differed significantly for the *cis* and *trans* isomers, we anticipated that we would need to correct the inspired gas concentrations to accurately reflect the alveolar (i.e., the arterial) partial pressure. Accordingly, three rats were anesthetized and catheters placed in their femoral arteries. Anesthesia with a 57% *trans*/43% *cis* mixture of 1,2-dichloroethylene was provided for a duration approximating the duration used to determine MAC (100 min). At the end of this period, inspired gas and arterial blood samples were drawn concurrently and analyzed for the concentrations of the *cis* and *trans* isomers by extracting the ethylenes from an aliquot of blood into an aliquot of gas, analyzing the resulting gas concentrations, and correcting for the respective blood/gas partition coefficients (determined separately as 16.3 ± 0.5 for the *cis* isomer [$n = 3$] and 6.26 ± 0.18 for the *trans* isomer [$n = 3$]). The resulting ratios for the arterial/inspired gas values were 0.68 for the *cis* isomer and 0.80 for the *trans* isomer.

The overall concentrations of the 2N isomeric mixtures were analyzed by using a Gow Mac model 580E gas chromatograph (Gow-Mac Instrument Corp., Bridgewater, NJ) equipped with a 40-foot-long SF-96 column at 100°C, through which flowed a nitrogen carrier gas stream (10 mL/min). The flame ionization detector (at 192°C) was maintained with hydrogen (40 mL/min) and air (300 mL/min). Gas samples were injected into a 0.2-mL sample loop.

For the dichloroethylene determinations, we used a Carbowax column at 72°C with a carrier gas flow of 7 mL/min. The detector (at 126°C) received hydrogen and air flows of 37 and 180 mL/min, respectively. Calibrations were with primary standards produced by injection of liquid aliquots of the original compounds into a flask of known volume.

Olive oil/gas, octanol/gas, and saline/gas partition coefficients of 2N and 1,2-dichloroethylene isomers and the blood/gas partition coefficients of the 1,2-dichloroethylene isomers at 37°C were measured by using standard techniques (13). The vapor pressure of the commercial mixture of 2N (at room temperature) was measured.

Results

The desflurane MAC ratio in the presence of various combinations of *cis-trans* mixtures of 2N did not differ significantly from unity, suggesting that neither diastereomer had anesthetic activity (Table 1). However, at the extremes (i.e., >90% pure *cis* versus *trans* 2N), the deviation from 1.0 for the *cis* form exceeded that for the *trans* form by 10% (i.e., it suggested a small increase in MAC; $P < 0.05$). The convulsive 50% effective dose (ED_{50}) values of the *cis-trans* mixtures of 2N differed by a far larger amount; the predominantly *cis* form was a more potent convulsant than the *trans* form (Table 2). The relationship between convulsant ED_{50} and isomeric composition was linear (Fig. 2). The physical properties of the diastereomers were nearly identical (Table 3). Other features of excitatory behavior (increased motor activity, tremors, and myoclonia) were observed, but the partial pressures at which these occurred were not sufficiently consistent to allow quantitative analysis. Consistent with other investigations (14), there was no evidence of impaired oxygenation or ventilation during the study.

Neither isomer of 1,2-dichloroethylene had excitatory or convulsant properties. Anesthetic determinations indicated that the *cis* isomer was more than twice as potent as the *trans* isomer (Table 4). The initial MAC values based on the inspired concentrations for these isomers were corrected to arterial (alveolar) partial pressures by multiplying by the arterial/inspired partial pressure ratio (Table 4). Predictions of the Meyer-Overton hypothesis were tested by determining the product of $MAC \times$ solubility for both olive oil and octanol as solvents modeling potential lipophilic sites of action (Table 4). Differences between the *cis* and *trans* isomers for these products were approximately 40%–50% and were significant ($P < 0.01$).

Discussion

Anesthetics depress the central nervous system, whereas nonimmobilizers and transitional compounds with similar physical properties (particularly their solubility in lipids) do not produce anesthesia (nonimmobilizers) as defined by MAC, or they are less potent anesthetics than might be predicted from their lipophilicity (transitional compounds). Possible explanations for the absent or decreased anesthetic effects of nonimmobilizer and transitional compounds include two thoughts: 1) that the nonimmobilizers are devoid of anesthetic effect and that transitional compounds have a decreased capacity to produce anesthesia or 2) that anesthesia, or lack thereof, results from a balance between depression and excitation (anesthetics cause depression, whereas nonimmobilizer and transitional compounds produce convulsions).

The latter thought has been examined by testing the effect of various multiples of the convulsive ED_{50} of three nonimmobilizers and one transitional compound on the MAC of desflurane in rats (15). Of particular relevance to this study, 2N did not change MAC at concentrations up to its convulsant ED_{50} , although it increased MAC by 25% and 36% at 1.3 and 1.7 times its convulsant ED_{50} , respectively. Similarly, in this study, neither the *cis* nor the *trans* 2N isomer decreased the MAC of desflurane at the concentrations applied in this study (albeit at the extremes, the *cis* isomer was associated with an 8% increase and the *trans* isomer with a 2% decrease, the difference being significant; $P < 0.05$), and all changes were small. These results suggest that the excitation produced by transitional compounds or nonimmobilizers does not explain their limited ability or inability to produce anesthesia. The data are consistent with a decreased anesthetic efficacy of transitional compounds and a lack of efficacy of nonimmobilizers. We conclude that a trivial explanation, such as canceling stimulatory and depressant effects, does not explain the absence of anesthesia associated with 2N.

Consistent with earlier investigations with 2N as a mixture of isomers (5,15), this study found the diastereomers to be nonimmobilizers despite olive oil/gas partition coefficients that would predict a MAC of approximately 0.04 atm (16). The partial pressures predicted for MAC are roughly those found to be associated with convulsions and are well below the saturated vapor pressure (approximately 0.24 atm). The nonimmobilizing properties of this compound are the same for the diastereomers and for the different combinations.

In contrast to the absent or minimal effect of either diastereomer on the anesthetic potency of desflurane, the convulsant potency of the *cis* isomer of 2N exceeds that of the *trans* isomer by 67%, on the basis of the extrapolated values of the "pure" isomers (see Fig. 2). This is consistent with studies of other compounds showing differences in the stimulating and depressive properties

Table 1. Anesthetic Determinations with 2N (1,2-dichlorohexafluorocyclobutane)

Isomeric composition		Pressure (atm) ^a	n	Desflurane MAC with 2N* Desflurane MAC without 2N (MACdes + 2N)/MACdes ^a
<i>Cis</i>	<i>Trans</i>			
93.6	6.4	0.052 ± 0.004	8	1.06 ± 0.12
91	9	0.052 ± 0.002	8	1.10 ± 0.11
33.5	66.5	0.050 ± 0.08	8	1.05 ± 0.08
30	70	0.062 ± 0.002	4	0.96 ± 0.28
7.8	92.2	0.052 ± 0.003	7	0.98 ± 0.08

MAC = the minimum alveolar concentration of anesthetic (desflurane) required to prevent movement in response to a noxious stimulus in 50% of subjects.
^a Data are presented as mean ± sd.

Table 2. Convulsion ED₅₀ Values for *Cis-Trans* Mixtures of 2N (1,2-dichlorohexafluorocyclobutane)

Isomeric composition		Convulsion ED ₅₀ (atm) ^a
<i>Cis</i>	<i>Trans</i>	
93.6	6.4	0.039 ± 0.009
91	9	0.043 ± 0.005
33.5	66.5	0.052 ± 0.008
30	70	0.054 ± 0.007
7.8	92.2	0.064 ± 0.010

ED₅₀ = 50% effective dose.

^a Data are mean ± sd; n = 8 rats in each group.

of enantiomers. For example, the δ isomer of hexachlorocyclohexane has sedative properties, whereas the γ isomer (lindane) is a convulsant (9,10). This study is the first to document a difference in the convulsive, but not the predicted anesthetic, potencies of *cis* and *trans* pairs of isomers. A caveat to our conclusions is the belief that the 3.2% contamination with 1,3-dichlorohexafluorocyclobutane did not alter the results.

A potential interaction between convulsant and anesthetic potencies has been postulated for enflurane versus isoflurane, as well as for other examples of structural isomerism (17). In qualitative agreement with this earlier postulate, the more potent convulsant (the *cis* isomer) caused a small increase in desflurane requirement when given at the same partial pressure as the *trans* isomer (Table 1).

Simple solvent properties do not explain the differential convulsant effects of the *cis* versus *trans* isomers of 2N. This was unexpected because of the correlation of the convulsant potencies of other nonimmobilizers with their oil/gas partition coefficients (18).

Consistent with an earlier report (11), we found 1,2-dichloroethylene to produce anesthesia. In addition, we demonstrated a *cis-trans* dependency in anesthetic potencies. The partition coefficients of the isomers also differed and did so qualitatively, in proportion to the anesthetic potencies of the isomers. The *trans* isomers would be expected to be more lipophilic than *cis* isomers because they are closer to linearity than *cis* isomers and therefore more readily align themselves with the long fatty methylene chains

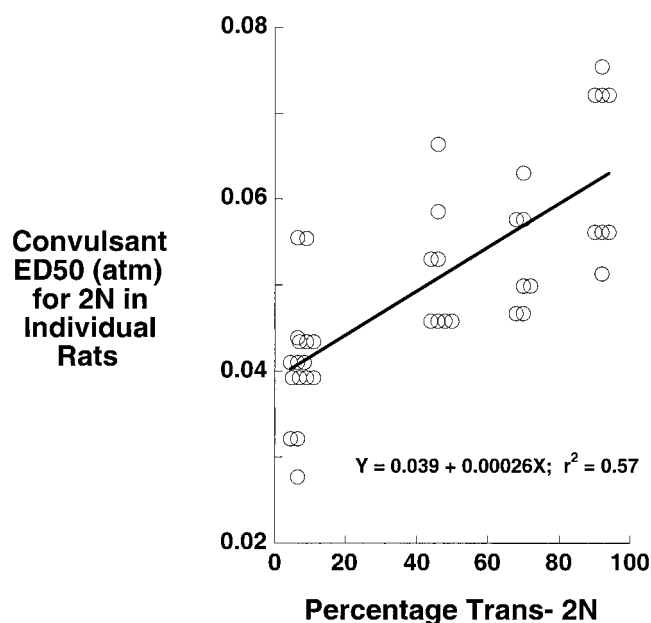


Figure 2. The 2N (1,2-dichlorohexafluorocyclobutane) convulsant values for individual rats (in atmospheres; atm) correlate directly with the proportion of *trans* isomer (expressed as percentage of *trans*) in the 2N. Some data points overlie others, and these have been offset slightly so that they might be seen. The regression line based on the individual data points is $y = (0.039 + 0.00026x)$ atm. For this relationship, $r = 0.75$ ($P < 0.01$). The correlation predicts convulsant 50% effective dose (ED₅₀) values for the "pure" isomers, giving 0.039 and 0.065 atm, respectively, for *cis*- and *trans*-2N.

in olive oil or octanol. If either olive oil or octanol provides a model for the anesthetic site of action, the traditional Meyer-Overton hypothesis (7,8) would predict differences in potencies of the *cis* and *trans* isomers. However, the product of MAC × solubility differed between the *cis* and *trans* isomers by 40% to 50% ($P < 0.01$). This suggests that solubility differences alone do not explain the differences in potencies, thereby implying a small degree of structure-activity dependency. It is curious that the differences in the product of MAC × lipid solubility and the differences in convulsive ED₅₀ × lipid solubility both equal 40% to 70%. This magnitude of difference is the same as that found by Lysko et al. (2) for the potency differences of the enantiomers of isoflurane.

Table 3. Partition Coefficients of *Cis* and *Trans* Isomers of 2N (1,2-dichlorohexafluorocyclobutane) and of 1,2-dichloroethylene at 37°C

2N (1,2-dichlorohexafluorocyclobutane)	<i>Cis</i> (94%) ^a	<i>Trans</i> (92%) ^a
Olive oil/gas	44.4 ± 0.6	43.1 ± 0.6
Octanol/gas	58.7 ± 1.1	56.7 ± 1.0
Saline/gas	0.0114 ± 0.0003	0.0124 ± 0.0005
1,2-dichloroethylene	<i>Cis</i> (97%) ^a	<i>Trans</i> (98%) ^a
Olive oil/gas	349 ± 13	202 ± 4
Octanol/gas	322 ± 13	174 ± 2
Saline/gas	5.43 ± 0.38	1.67 ± 0.03

Data are presented as means ± SD; n = 4 for each partition coefficient.

^a Isomeric purity.

Table 4. Anesthetic Values for *Cis*- and *Trans*-1,2-Dichloroethylene

1,2-Dichloroethylene	<i>Cis</i> (94%) ^a	<i>Trans</i> (92%) ^a
MAC*	0.0104 ± 0.0009	0.0229 ± 0.0039
Corrected MAC	0.0071 ± 0.0006	0.0183 ± 0.0031
MAC × olive oil/gas partition coefficient (atm)	2.47 ± 0.74	3.70 ± 0.63*
MAC × octanol/gas partition coefficient (atm)	2.28 ± 0.20	3.19 ± 0.54*

Values are given as means ± SD in atmospheres; n = 8 for each determination of MAC.

MAC = minimum alveolar concentration (actually, the fraction of 1 atm) of anesthetic (desflurane) required to prevent movement in response to a noxious stimulus in 50% of subjects. The corrected MAC multiplies the MAC by the ratios for the arterial/inspired gas values determined as part of the control experiments (0.68 for the *cis* isomer and 0.80 for the *trans* isomer).

^a Isomeric purity.

* Values for the *cis* and *trans* isomers differed significantly (*P* < 0.01).

We conclude that the *cis-trans* isomerism of 2N does not affect its nonimmobilizer properties (i.e., neither the *cis* nor *trans* isomer has anesthetic effects) but does influence its convulsive properties. The absence of an immobilizing effect of the isomers of 2N is not caused by a counterbalancing of stimulatory and inhibitory effects. We also conclude that *cis-trans* isomerism of 1,2-dichloroethylene does affect anesthetic properties, both determined directly and as predicted from lipophilicity. These significant differences are relatively small, ranging from 40% to 70%. The differences in convulsant and anesthetic potency consequent to isomerism as found in this study may be as useful in defining the importance of receptor-anesthetic interactions as the differences in anesthetic potency found with optical isomers.

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